NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Contents:

The following documents are made available to consultees and commentators

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from Albireo AB

2. **Company PAS submission** from Albireo AB

3. **Clarification questions and company responses**
   a. **Company clarification response**
   b. **Addendum A**
   c. **Addendum B**
   d. **Addendum C**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Children's Liver Disease Foundation *(endorsed by patient expert Rachel Nealson)*
   b. British Association for the Study of the Liver *(endorsed by Royal College of Physicians)*
   c. NHS England

5. **Expert personal perspectives** from:
   a. Prof D Kelly– clinical expert, nominated by Albireo AB
   b. Claire Brinkley – patient expert, nominated by Children's Liver Disease Foundation
   c. Penny North-Lewis - clinical expert, nominated by Royal College of Paediatrics and Child Health

6. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

7. **Evidence Review Group report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Specification for company submission of Odevixibat for progressive familial intrahepatic cholestasis ID1570

10th May 2021

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Glossary of terms

A4250	drug substance code for odevixibat
AASLD	American Association for the Study of Liver Diseases
AE(s)	adverse event(s)
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	alkaline phosphatase
ASBT	apical sodium bile transporter
AST	aspartate aminotransferase
AUC	total area under the plasma concentration versus time curve
BA	biliary atresia
BID	twice per day
BRIC	benign recurrent intrahepatic cholestasis
BSEP	bile salt export pump
CHMP	Committee for Medicinal Products for Human Use
CC	casemix companion
CEAC	cost-effectiveness acceptability curve
CEP	cost-effectiveness plane
CIC	chronic intrahepatic cholestasis
C_{max}	maximum plasma concentration
CMH	Cochran Mantel Haenzel
DSMB	Data and Safety Monitoring Board
EASL	European Association for the Study of the Liver
EC	European Commission
ECG	Electrocardiogram
ED_{50}	dose required to produce 50% of the response
EMA	European Medicines Agency
ERG	Evidence review group
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19
FIC-(1)	familial intrahepatic cholestasis-(1)
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	Gastrointestinal
GIC	Global impression of change
GIS	Global impression of symptoms

GP	general practitioner
HCC	hepatic cell carcinoma
HDN	haemorrhagic disease of the newborn
HR	hazard ratio
HRQL	Health-related quality of life
HST	highly specialised technology
IBAT	ileal bile acid transporter
IC_{50}	half maximal inhibitory concentration
ICER	Incremental cost-effectiveness ratio
IE	ileal exclusion
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INN	International Nonproprietary Name
LTx	liver transplantation
MAA	marketing authorisation application
MDR3	multidrug resistant 3 protein
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MOA	mechanism of action
n	number of subjects with an observation
NAPPED	*Na*tural course and *P*rognosis of *P*FIC and *E*ffect of biliary *D*iversion
NDA	new drug application
NLS	native liver survival
ObsRO	observer reported outcome
ODD	orphan drug designation
ONS	Office for National Statistics
PAS	Patient access scheme
PBC	primary biliary cirrhosis
PD	pharmacodynamic(s)
PEBD	partial external biliary diversion
PEDFIC1	Clinical Study A4250-005
PEDFIC2	Clinical Study A4250-008
PedsQL	Pediatric Quality of Life Inventory
PFIC	progressive familial intrahepatic cholestasis
PIBD	partial internal biliary diversion
PK	pharmacokinetic(s)
PRO	patient reported outcome
PSA	Probabilistic sensitivity analysis
PSC	primary sclerosing cholangitis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit

QALY	quality adjusted life year
Q2	second quarter of the year
QoL	quality of life
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SAS	safety analysis set
sBA	serum bile acid
SBD	surgical biliary diversion
SD	standard deviation
SF-6D	Short Form 6-Dimension
SOC	standard of care
TEAE(s)	treatment-emergent adverse event(s)
Tmax	maximum concentration
TP	transition probability
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
UK	United Kingdom
US	United States
VAS	visual analogue scale
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

Executive summary

Nature of the condition

Progressive familial intrahepatic cholestasis (PFIC) is a rare, heterogeneous group of liver disorders of autosomal recessive inheritance that affect the flow of bile from the liver. PFIC is characterised by an early onset of cholestasis (usually during infancy) with pruritus and malabsorption, which rapidly progresses and leads to liver failure[1]. Without biliary diversion surgery or liver transplantation (LTx), people with PFIC do not generally survive beyond the age of 20 years.[2]

PFIC is generally categorised into three main subtypes, PFIC1, PFIC2, and PFIC3, caused by mutations on different genes. At least three other subtypes have been described in the literature (PFIC4, PFIC5 and PFIC6) however identified cases are extremely rare. Elevated serum bile acid (sBA) is evident across all subtypes, as is debilitating pruritus and the potential for progressive liver disease.[3] PFIC1 and PFIC2 have an intermittent form known as known as benign recurrent intrahepatic cholestasis 1/2 (BRIC1/2) characterised by acute episodes of cholestasis and severe pruritus that often transitions to a persistent progressive form of the disease. [10,12]

PFIC is associated with a range of potentially fatal complications of the liver, including portal hypertension, liver failure, cirrhosis and hepatocellular carcinoma (PFIC2), as well as extrahepatic manifestations (PFIC1).[4] Fat malabsorption results in low weight, growth retardation and vitamin deficiencies that can result in life-threatening complications.[5] Diarrhoea, pancreatitis, failure to thrive, and hearing deficits are extrahepatic manifestations of the genetic defect in PFIC1.[6] Those with PFIC3 may also develop intrahepatic gallstone disease.[2,6]

PFIC has a devastating impact on children's lives, as well as on their parents and families. In particular, pruritus is an extremely distressing manifestation of the disease and its relief is often the initial goal of therapy. Significant pruritus can lead to severe cutaneous mutilation (often drawing blood), loss of sleep, irritability, poor attention, and impaired school performance. The severity and impact of pruritus cannot be underestimated; it is described in some cases as head to toe itching that is constant and often unbearable, where children scratch themselves until they bleed. One child describes it as feeling like "*a million ants under my skin, 24/7."* The constant pruritus means that children are often unable to sleep, waking up multiple times in the night. Pruritus severity is the leading factor in the decision to seek a liver transplant.

The burden for caregivers is substantial, with many reporting feeling lonely, overwhelmed, anxious, scared, frustrated and confused. Seeing their children upset due to the unbearable itching is extremely distressing for parents, especially when there is little they can do to help their child. Since children with PFIC often cannot sleep due to their pruritus, their parents must stay up to comfort them, and describe having years of sleepless nights.[7] Attending frequent hospital appointments, making decisions on treatment and surgery, experiencing emergency hospitalisations and seeing their child undergo life-threatening surgery all add to the burden.

PFIC carries a significant burden on the entire family. In some cases, more than one child in a family may be affected, and those siblings without PFIC have their lives and schooling disrupted. The burden on parents means that they often have to give up work to care for their child, or children, with PFIC.

Current treatment options

The initial treatment option for PFIC is nutritional management and off-label oral therapies. There is no pharmaceutical treatment approved for use in this condition. In the UK, ursodeoxycholic acid (UDCA) is the first line oral treatment, and rifampicin may also be tried to reduce pruritus.[8] A minority of patients respond to these medications, and do so only transiently.[9]

Once pharmaceutical options have been exhausted due to escalating symptoms of intractable pruritus, growth failure and nutritional deficiencies, surgical biliary diversion (SBD) is an option. SBD aims to decrease the size of the bile acid pool by interrupting the enterohepatic circulation.[10]

SBD is an invasive procedure that carries the risk of peri-operative and post-operative complications, such as stoma relapses, infections, bowel obstruction and dehydration.[11] In addition, with the most common type of SBD, partial external biliary diversion (PEBD), the young person is required to accept and manage life with a stoma. Data on outcomes following SBD are available from the NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion (NAPPED) consortium, the largest genetically-defined cohort of PFIC patients to date.[10,12] The study has shown that surgery is associated with a decrease in sBAs and prolongs native liver survival in patients with PFIC1 and PFIC2.[10,12]

Despite the use of biliary diversion surgery, in the majority of cases LTx is required because of severe cholestasis and unremitting pruritus, hepatic failure, or hepatocellular carcinoma.[13,14]

LTx is a complicated surgery associated with significant risks including infection and rejection.[2] For people with PFIC, LTx is not considered a cure due to the requirement for ongoing monitoring, lifelong immunosuppression, the potential for occurrence of extrahepatic complications in some subtypes, and the possibility of disease recurrence post-LTx, particularly in those with PFIC1. Many individuals with PFIC and their caregivers tend to be anxious about LTx due to the extreme nature of the procedure and associated risks. Patients and their families describe ongoing anxiety around maintaining the health of the transplant, as well as fear of everyday infections such as a cold leading to severe illness and hospitalisation.[7]

A new medical therapy is desperately needed in this patient population with a serious unmet need.

The technology

Odevixibat (Bylvay®) is a reversible potent selective inhibitor of the ileal bile acid transporter (IBAT). It acts locally in the distal ileum to decrease the reuptake of bile acids and increase the clearance of bile acids through the colon. A Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) was submitted on the 9th of November 2020. A positive CHMP opinion is anticipated on the 20th of May 2021. The proposed indication is for treatment of PFIC in patients aged 6 months or older.[15]

Odevixibat is an oral therapy (provided as capsules containing 200 µg, 400 µg, 600 µg or 1,200 µg odevixibat which have a proposed list price of [redacted] per pack of 30 capsules). The recommended dose is 40 µg/kg administered orally once daily in the morning, with or without food.[15]

Improvement in pruritus and reduction of serum bile acid levels can occur gradually in some patients after initiating odevixibat therapy. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 µg/kg/day.[15] Odevixibat is a long-term therapy anticipated to continue throughout life, or until LTx is required. Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment.[15]

Impact of the new technology

The primary evidence of the efficacy and safety of treatment with odevixibat in the proposed indication is based on two Phase 3 studies conducted in patients with PFIC. PEDFIC1 (Study A4250-005) was a multicentre, multinational, randomised, double-blind, placebo-controlled study which enrolled 62 paediatric patients with a clinical diagnosis of PFIC1 or PFIC2.[16,17] The study evaluated two doses of odevixibat (40 and 120 µg/kg/day) and placebo administered for 24 weeks. Long-term efficacy and safety data in patients with PFIC are available from a 24-week interim analysis of the ongoing Phase 3, open-label extension study, PEDFIC2 (Study A4250-008), which is evaluating treatment with odevixibat 120 µg/kg/day.[18,19] As well as providing long-term data in patients that participated in PEDFIC1, PEDFIC2 is investigating efficacy, safety and tolerability in an additional cohort that includes patients of any age with any type of PFIC. Given the rare nature of PFIC, the odevixibat clinical studies were conducted globally across 15 countries (including the UK). As of 15 July 2020, a total of 77 patients had received treatment with odevixibat across both Phase 3 studies, including 42 patients in Europe and 15 patients in the UK.

The demographic characteristics of the paediatric patients with PFIC studied in the odevixibat Phase 2 and 3 clinical development programme are consistent with the known characteristics of the PFIC patient population.[4] The majority of patients in PEDFIC1 were receiving UDCA and/or rifampicin at study entry and continued to receive these treatments during the study.[16,17] The existence of this patient population with high levels of sBA and uncontrolled pruritus despite the use of UDCA and rifampicin further highlights the lack of efficacy of these off-label therapies and the high unmet need.

A key objective in patients with PFIC is to reduce the intense and intractable pruritus that can necessitate LTx. Treatment with odevixibat led to statistically significant and clinically meaningful reductions in pruritus severity over the 24-week treatment course of PEDFIC1 and continued during treatment in PEDFIC2 with patients treated for 48 weeks or longer.[17,19]

Elevated bile acid levels in the liver evoke progressive liver damage, therefore reducing these levels slows progression of liver damage. Treatment with odevixibat at doses of 40 and 120 µg/kg/day was shown to be effective in reducing sBA in patients with PFIC. Both doses of odevixibat led to a statistically significantly higher proportion of patients experiencing at least a 70% reduction in sBA concentration from baseline or reaching a level of ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment in PEDFIC1 compared to placebo (primary endpoint analysis).[17] The reductions in sBA produced by odevixibat generally occurred rapidly, within 4 weeks following initiation of treatment, and were maintained during continued treatment with odevixibat in PEDFIC2; some patients have continued to receive odevixibat [redacted].

The clinical relevance of this decrease in sBAs with respect to long-term benefit has recently been established in the largest natural history study of its kind in PFIC (NAPPED), where reduction in bile acids levels was associated with prolonged native liver survival in PFIC1 and PFIC2 patients following SBD.[10,12]

Odevixibat directly addresses the elevated sBAs and pruritus by inhibiting IBAT in the terminal ileum, transporters common to patients with all PFIC subtypes. The site of action of odevixibat is distal to the underlying biochemical abnormalities and is independent of the genetic abnormalities responsible for the different PFIC subtypes. Therefore, all subtypes of PFIC are expected to benefit from odevixibat treatment.

Subgroup analyses of PEDFIC1 indicate that the positive treatment effects for both reduction in sBA and improvement in pruritus severity were similar across patient subgroups based on demographic and baseline disease characteristics. Importantly, both patients with PFIC1 and those with PFIC2 obtained substantial benefit from treatment with odevixibat, including reductions in sBA levels and improvement in pruritus symptoms. Although limited, accumulating data provide a strong initial signal for efficacy in patients with PFIC3 and demonstrate success in the single patient with PFIC6. [18,19]

The very small numbers of patients with PFIC3, PFIC4, PFIC5 and PFIC6 make conducting a randomised, controlled clinical trial in these populations extremely challenging. However, as with PFIC1 and PFIC2, there is a critical unmet medical need in these populations as acknowledged by CHMP in indicating odevixibat for all subtypes of PFIC in the SmPC.

Improvements relative to placebo were also observed for other clinically meaningful secondary endpoints, including sleep parameters and growth. Odevixibat treatment

resulted in reductions in the percentage of days requiring help falling asleep, days requiring soothing, and days sleeping with the caregiver; in contrast, minimal changes were observed for these sleep parameters in placebo-treated patients.[16] Continued improvement in growth was observed in patients continuing odevixibat treatment in the open label extension study. [18,19]

In parallel with improvements in clinical signs and symptoms of the underlying disease, odevixibat improved patient and family quality of life. Results of the PedsQL total score and family impact scores showed improvements at Week 24 for patients who received odevixibat and minimal change for patients who received placebo.[16] Among PedsQL domains, improvements were observed with odevixibat in physical, emotional, social and school functioning, whereas with placebo, three of four domains showed worsening. Caregivers of patients who received odevixibat reported greater improvements in both itch and sleep of patients at Week 24 compared with caregivers of patients who received placebo. Consistent with these assessments of the impact of odevixibat on the overall well-being of patients and families, [redacted]

Odevixibat is considered to be an alternative to PEBD and therefore is expected to reduce the requirement for this type of surgery. There are currently no head-to-head studies comparing odevixibat and PEBD. Long-term comparative data are expected to be available [redacted]

As pruritus is one of the two indications for LTx in children with PFIC, by effectively reducing pruritus odevixibat has the potential to delay, or perhaps prevent, LTx in this patient population. To the extent that bile acids contribute to the ongoing liver damage, reduction of bile acid levels by odevixibat could also result in improved hepatic health and delay of LTx; this potential is supported by the improvement in hepatic biochemical parameters observed in patients receiving odevixibat.

Odevixibat has been generally well tolerated in all completed studies. Adverse events (AEs) reported have primarily been of mild to moderate intensity.

Treatment continuation will be based on the summary of product characteristics which states that alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat.[15] In clinical practice, assessment of an adequate response is expected to be based on sBA levels and pruritus, which are currently regularly assessed, however the

exact criteria that will be used are unclear. Work is underway with clinical experts to assess how these assessments would be conducted in clinical practice.

Value for money

As part of the submission, a patient access scheme (PAS) has been proposed, with a simple discount. Results for both list and PAS price have been modelled in the cost-effectiveness analysis.

An eight-state Markov model was developed, capturing the differences in costs and health outcomes associated with the reduced need for LTx between the odevixibat and standard of care arms. The choice of the model structure was based on previous NICE submissions with similar health-states (TA443 and HST9). A life-time horizon (100 years) was adopted to fully capture the impact of the progression of PFIC and mortality, and a cycle of one year (365.25 days) was modelled.

The cost-effectiveness model has been built on the sBA primary endpoint reported in PEDFIC1, a ≥70% reduction in sBA concentration from baseline to end of treatment or reaching a level ≥70µmol/L after 24 weeks of treatment. Transition probabilities between health states were derived from available data sources in PFIC for the odevixibat and standard of care arms. Published survival curves from NAPPED were used to estimate the transition to PEBD and LTx.

Health state costs, patient utilities and caregiver disutilities for PFIC patients were based on NHS reference costs, expert clinical opinion and relevant published literature.

To address the limitations in the lack of published evidence and better model the pathway of a child and adult with odevixibat, Albireo is collecting the following additional data to support the evidence package for odevixibat, alongside the PEDFIC1, PEDFIC2 and NAPPED data:

- Burden of illness study (PICTURE study) to estimate resource use and the financial burden of caregivers (interim results incorporated)
- Caregiver targeted literature review to understand the burden of rare diseases on caregivers
- A utility elicitation study, to estimate the utility of children with PFIC
- The Odevixibat vs External Control [redacted] to compare clinical outcomes in odevixibat to comparable external controls [redacted]

- Prospective, registry-based studies to investigate the long-term safety and efficacy of odevixibat in patients with PFIC.

Odevixibat dosing is based on weight at either 40 µg/kg or 120 µg/kg, resulting in nine potential weight bands that patients are categorised into for dosing purposes. Patients are assumed to be in the 25th percentile of weight in the year they start the treatment, moving to the 33rd percentile in year 2 and then 50th percentile each year after that. Weights for children have been derived from growth charts and weights for adults have been taken from the HSCIC Health Survey data.

After applying a discount rate of 1.5%, patients receiving odevixibat accrued [redacted] QALYs compared to SoC, at an additional cost of [redacted] per patient. This corresponds to an incremental cost-effectiveness ration (ICER) of [redacted]. When the PAS discount is applied the incremental cost is [redacted] which results in an ICER of [redacted]. Deterministic, probabilistic and scenario analyses were performed. The most significant drivers of cost-effectiveness are the cost of odevixibat, utilities for model health states and time spent on treatment.

According to consultant hepatologists from the three treatment centres in England, there are approximately [redacted] paediatric patients in England currently diagnosed with PFIC, excluding patients with episodic PFIC forms (BRIC).[20] Of these, there is an estimated xx prevalent patients eligible for odevixibat in the first year following introduction. This assumes that patients with the BSEP3 mutation and those that have had LTx or SBD will not be treated with odevixibat. There are estimated to be [redacted] new cases of PFIC diagnosed across England each year, [redacted] of which (i.e., excluding those with BSEP3 mutations) would be eligible for treatment with odevixibat in Year 1. Therefore, in Year 1 there are an estimated [redacted] patients eligible for treatment.

Estimates of the budget impact associated with the introduction of odevixibat, factoring in cost savings, are [redacted] in Year 1 rising to [redacted] in Year 5, at the proposed list price, and [redacted] in Year 1 rising to [redacted] in Year 5, with the proposed PAS.

Impact of the technology beyond direct health benefits

The intractable pruritus and lack of sleep experienced by children with PFIC mean that they may struggle at school.[7] Some parents are therefore unable to work or have to reduce working hours and lose income in order to care for their child.[7] Children treated with odevixibat are expected to be less impacted by their symptoms, sleep better and

therefore be more able to engage fully at school. Siblings will also benefit from fewer disruptions to their schooling. As a result of their children attending school more and fewer sleep disturbances, caregivers will need less time off work and will be able to fulfil their career potential.

Having surgery requires time off school for the patient as well as time off work for the caregiver. Recovering from a liver transplant can be a long process, and it can take 3 months or longer to return to school or work, and up to a year to fully recover.[21] Furthermore, complications such as rejection or infections may require further hospitalisation. Although it is not possible to quantify at this stage, it is likely that there will be significant savings to patients and their families through reduction or elimination of symptoms, avoidance of SBD and delay or avoidance of LTx.

In England there are three highly specialised centres that manage patients with PFIC, and these are study sites for the odevixibat clinical trials. King's College and Birmingham Women's and Children's Hospital are recognised internationally as two of the leading centres in expanding the scientific knowledge on PFIC natural history, genetics, types of PFIC, diagnosis and management. The leading UK experts are highly respected and sought after by their peers and colleagues for their opinion and expertise in the management of PFIC. Odevixibat will be the first approved treatment for PFIC, and its availability in England will allow the key centres in the UK to be at the forefront of research into outcomes following its use in clinical practice.

The overall pathway of care is not expected to change following the introduction of odevixibat. In England, odevixibat treatment will be initiated and monitored in the three highly specialised centres. Other than monitoring for an adequate response, there are no additional monitoring requirements with odevixibat. No changes to the way services are delivered are expected as a result of odevixibat introduction, and there are no additional, staffing, training or infrastructure requirements.

Odevixibat is expected to remove the need for biliary diversion surgery. Odevixibat may have the potential to delay or avoid LTx in the patients who would otherwise have been transplanted due to uncontrolled severe pruritus or progression to cirrhosis and end stage liver disease due to the persistently elevated sBA.

By offering an effective non-surgical treatment option odevixibat has the potential to transform the lives of individuals with PFIC and their families.

Section A — Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with progressive familial intrahepatic cholestasis (PFIC)	None, although it should be noted that the expected indication is for patients with PFIC who are aged 6 months or older	
Intervention	Odevixibat (A 4250)	None	
Comparator(s)	Established clinical management without odevixibat (A 4250) which may include: • off-label drug treatments such as ursodeoxycholic acid (UDCA) • surgical interventions such as partial external biliary diversion or internal ileal exclusion	Although off-label drug treatments are included in the economic model they are not considered to be a direct comparator.	Off-label oral drug treatments, such as UDCA and rifampicin, have very limited symptomatic efficacy and do not alter the underlying disease or change the course of disease. No RCTs investigating off-label therapies have been identified. In clinical practice, odevixibat may be used in addition to off-label oral therapies (as was the case in the Phase 3 clinical trial). In the economic model off-label oral therapies are assumed to have no treatment effect and costs for off-label therapies are included both for patients receiving odevixibat and the comparator arm.
Outcomes	The outcome measures to be considered include: • change in serum bile acid level • change in symptoms of PFIC including reduction of pruritus • measures of faltering growth • overall survival	No variation, however as part of the assessment of health-related quality of life, sleep parameters as measured by the observer-reported outcomes (ObsRO) instrument, a validated tool for assessment of pruritus and sleep disturbance in PFIC, have been included.	Reporting of sleep parameters is of particular importance in PFIC as patients will often experience intense pruritus at night, disturbing their sleep and that of the caregiver. Poor sleep leaves patients and parents exhausted, leading to poor performance at school and work with significant impact on quality of life.

	• measures of disease progression • number of patients requiring surgical interventions • adverse effects of treatment • health-related quality of life (for patients and carers)		
Subgroups to be considered	None	None	
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options	None	
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	None	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation	None	

	• The impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.		
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangement for the intervention under evaluation	None	

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Bylvay®; approved name: odevixibat.
Therapeutic class: Odevixibat has been assigned the temporary Anatomical Therapeutic Chemical (ATC) code A05AX05 – Alimentary tract and metabolism; bile therapy; other drugs for bile therapy.

2.2 What is the principal mechanism of action of the technology?

Odevixibat (A4250) is a small molecule that acts as a potent, highly selective inhibitor of ileal bile acid transporter/apical sodium-dependent bile acid transporter (IBAT/ASBT). Odevixibat acts locally in the gut where it binds reversibly to IBAT to decrease the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acids.[15] By inhibiting the IBAT with high selectivity and potency, odevixibat has the potential to reduce the systemic accumulation of bile acids that result from cholestasis, relieve pruritus, improve liver function, and modify the progression of liver damage in patients with PFIC without surgical intervention.

2.3 Please complete the table below.

Table 2. Dosing Information of technology being evaluated

<table>
<tr><td>Pharmaceutical formulation</td><td>Hard capsules produced in 4 strengths: 200 µg, 400 µg, 600 µg, and 1200 µg.</td></tr>
<tr><td>Method of administration</td><td>Odevixibat (Bylvay) is for oral use. To be taken with or without food in the morning.[15]

While all capsules can be either swallowed whole or opened and sprinkled on food, the larger 200 µg and 600 µg capsules are designed to be opened to have the contents sprinkled on food.</td></tr>
<tr><td>Doses</td><td>The recommended dose of odevixibat is 40 µg/kg administered orally once daily in the morning. Odevixibat can be taken with or without food.
The table below shows the strength and number of capsules that should be administered daily based on body weight to approximate a 40 µg/kg/day dose.[15]
Number of Bylvay capsules needed to achieve the nominal dose of 40 µg/kg/day
<table>
<tr><th>Body weight (kg)</th><th>Number of 200 µg capsules</th><th></th><th>Number of 400 µg capsules</th></tr>
<tr><td>4 to < 7.5</td><td>1</td><td>or</td><td>N/A</td></tr>
<tr><td>7.5 to < 12.5</td><td>2</td><td>or</td><td>1</td></tr>
<tr><td>12.5 to < 17.5</td><td>3</td><td>or</td><td>N/A</td></tr>
<tr><td>17.5 to < 25.5</td><td>4</td><td>or</td><td>2</td></tr>
<tr><td>25.5 to < 35.5</td><td>6</td><td>or</td><td>3</td></tr>
<tr><td>35.5 to < 45.5</td><td>8</td><td>or</td><td>4</td></tr>
</table></td></tr>
</table>

45.5 to < 55.5	10	or	**5**
≥ 55.5	12	or	**6**

Capsule strength/number in bold is recommended based on predicted ease of administration.

Dose escalation

Improvement in pruritus and reduction of serum bile acid levels may occur gradually in some patients after initiating odevixibat therapy. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 µg/kg/day.

The table below shows the strength and number of capsules that should be administered daily based on body weight to approximate a 120 µg/kg/day dose, with a maximum daily dose of 7200 µg per day.[15]

Number of Bylvay capsules needed to achieve the nominal dose of 120 µg/kg/day

Body weight (kg)	Number of 600 µg capsules		Number of 1200 µg capsules
4 to < 7.5	**1**	or	N/A
7.5 to < 12.5	**2**	or	1
12.5 to < 17.5	**3**	or	N/A
17.5 to < 25.5	**4**	or	2
25.5 to < 35.5	6	or	**3**
35.5 to < 45.5	8	or	**4**
45.5 to < 55.5	10	or	**5**
≥ 55.5	12	or	**6**

Capsule strength/number in bold is recommended based on predicted ease of administration.

Dosing frequency	Administered orally once daily in the morning. Odevixibat can be taken with or without food.[15]
Average length of a course of treatment	Odevixibat is a long-term therapy anticipated to continue throughout life, or until the patient is no longer benefitting from treatment. Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment. Prior to changing to alternative treatment, concomitant UDCA and/or rifampicin can be considered.
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	The recommended dose of odevixibat is 40 µg/kg administered orally once daily in the morning. Odevixibat can be taken with or without food. Improvement in pruritus and reduction of serum bile acid levels can occur gradually in some patients after initiating odevixibat therapy. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 µg/kg/day.[15]

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

A marketing authorisation application (MAA) to the European Medicines Agency (EMA) was submitted on the 9th November 2020.

In Europe, odevixibat is the only IBAT inhibitor granted accelerated assessment by the EMA and has been granted Orphan Designation as well as access to the PRIority MEdicines (PRIME) scheme for the treatment of PFIC. The EMA's Paediatric Committee has agreed to Albireo's odevixibat paediatric investigation plan (PIP).

The Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in Q2 2021 (20th May).

Based on the detailed guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) on the reliance procedure, Albireo will submit the MAA to the MHRA within 5 days of receipt of the CHMP opinion in order to receive a UK marketing authorization very shortly after the European Commission (EC) decision (which will also be sent to the MHRA).

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Odevixibat will be available in the UK at the point of the first reimbursement approval.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Odevixibat is not yet approved in any country globally. In addition to the EMA MAA, a new drug application (NDA) for odevixibat was submitted on 20th November 2020 to the US Food and Drug Administration (FDA) for approval of odevixibat for the treatment of pruritus in patients with PFIC. The FDA granted Priority Review and set a Prescription Drug User

Fee Act (PDUFA) goal date of July 20, 2021. Odevixibat previously received Fast Track, Rare Pediatric Disease and Orphan Drug Designations in the U.S.

3.4 If the technology has been launched in the UK provide information on the use in England.

Not applicable.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

4.1.1 Clinical studies

NOTE: The double-blind, randomised, placebo-controlled PEDFIC1 (A4250-005) study is completed, and all results are available, however the study is not yet fully published (manuscript ready for submission). The study results are published on the EU Clinical Trials Register (as required per regulation).

4.1.1.1 PEDFIC2

PEDFIC2 is an ongoing Phase 3, multi-centre, open-label extension study to investigate the long-term efficacy and safety of a 120 µg/kg/day daily dose of odevixibat in patients with PFIC.

- Cohort 1 consists of children with PFIC Types 1 and 2 who have participated in study PEDFIC1.
- Cohort 2 consists of patients with PFIC who have elevated serum bile acids (SBAs) and cholestatic pruritus and who either did not meet eligibility criteria for PEDFIC1 or who were eligible for enrolment in PEDFIC2 after recruitment to PEDFIC1 has been completed.

The ongoing PEDFIC2 study aims to generate long-term efficacy and safety data; Cohort 2 in the study is still recruiting patients and therefore the data will become available after the submission to NICE, [redacted]. The study is collecting data on sBA levels, pruritus,

growth, liver disease parameters, HRQOL, mortality, and the rate of surgical interventions and LT. An interim data cut was conducted for this study based on a cut-off date of 15 July 2020 and is presented in section C9.

Additional interim data [redacted] has recently been carried out to address a [redacted] however due to the timescales it was not possible to include the data in this submission (a brief summary is provided in Section 9).

4.1.1.2 Odevixibat vs External Control [redacted] study

Albireo is also planning to perform the Odevixibat vs External Control [redacted] study aiming to compare clinical outcomes in odevixibat to comparable external controls [redacted] The study will compare firstly odevixibat versus external controls without prior PEBD (Part A), and then odevixibat without prior PEBD versus external controls receiving PEBD (Part B). The study results are expected in [redacted]

- The primary endpoint (Part A only) is planned as [redacted]
- The secondary endpoints will include:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Exploratory
  - [redacted]
  - [redacted]
  - [redacted]

The [redacted] is planned to be locked after all patients in [redacted]. To maintain data integrity and minimise potential bias, the Albireo team does not have access to the [redacted]. At this stage Albireo is therefore unable to carry out interim analyses of the [redacted]. See section 9.8 for further detail.

The NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion (NAPPED) study has the largest genetically defined cohort of PFIC patients to date, providing retrospective analysis of 130 PFIC1 and 264 PFIC2 patients (at latest data cut-off) in >50 centres globally.

NAPPED aims to:

- Characterise the natural course of disease in PFIC1 and PFIC2
- Determine associations between genotype and phenotype
- Assess effects of surgical biliary diversion on native liver survival
- Identify an early surrogate marker for long-term native liver survival

The NAPPED study is a key source of data for this submission. Data from NAPPED is presented in two recent publications:

PFIC1: van Wessel et al. Impact of Genotype, Serum Bile Acids, and Surgical Biliary Diversion on Native Liver Survival in FIC1 Deficiency, Hepatology 2021[12]

PFIC2: van Wessel et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. Journal of Hepatology 2020[10]

4.1.1.3 Expanded access programme for odevixibat

The aim of this expanded access programme (EAP; study A4250-014) is to provide treatment access to patients with PFIC in the US and RoW (Rest of World) who have elevated sBAs and who are not able to enrol in PEDFIC2 for the following reasons:

1. They do not meet eligibility criteria for PEDFIC2
2. They are not able to get to a PEDFIC2 site for geographical reasons
3. They do meet the eligibility criteria for PEDFIC2, however, recruitment had been completed

To date, some of the patients included in the EAP that did not meet the eligibility criteria for the odevixibat PEDFIC2 study include patients who are unable to reach a study site for geographical reasons, patients who have confirmed clinical diagnosis of PFIC with uncertain genetic results, patients who had a liver transplant and recurrent PFIC symptoms following the transplant (pruritus or elevated sBA), as well as patients with BRIC (benign recurrent intrahepatic cholestasis), who have a cholestatic episode with elevated sBA and/or uncontrolled pruritus and are in need of treatment.

Data collection in the EAP is optional and ongoing.

4.1.2 Burden of illness studies

4.1.2.1 PICTURE study

Albireo is sponsoring the Burden of Illness of PFIC in the US, UK, France and Germany: the PICTURE (**P**rogressive Familial **I**ntrahepatic **C**holes**t**asis Disease B**ur**d**e**n of Illness) study. The PICTURE study aims to examine the substantial burden and unmet medical need of PFIC and support the evidence base for this community. The study is overseen by an independent Expert Review Group which includes PFIC medical experts, academics and patient advocates.

- Data will be collected at the patient, caregiver and physician-level (retrospective and cross-sectional).
- A dataset of unit costs will be created for the resource use items, and costing profiles will be developed. Mean per-patient costs, including direct medical, direct non-medical and indirect resources, will be calculated by multiplying the individual resource utilisation with country-specific unit costs.
- The impact of PFIC on caregiver HRQoL through the CarerQoL-7D and their work productivity through the Work Productivity and Activity Impairment (WPAI) questionnaire, as well as impact on patient HRQoL (5-D Itch Scale) will be assessed.

As a result of COVID-19, the PICTURE study recruitment is delayed, and it was not possible to have complete data in time for our NICE submission. However, interim data from the study have been used to inform the economic modelling as well as section E of this submission. In addition, a targeted literature review on caregiver disutilities in rare diseases among children has been conducted to support the submission and model.

4.1.2.2 Utilities elicitation survey

To elicit utilities for health states in the economic model, Albireo is carrying out a valuation survey to explore public preferences (utilities) for treatment in PFIC.

The survey is underway with result expected in May 2020. The study protocol is provided as a reference.[22]

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

[redacted]

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

The use of odevixibat is not expected to raise any equality issues.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B — Nature of the condition

6 Disease morbidity

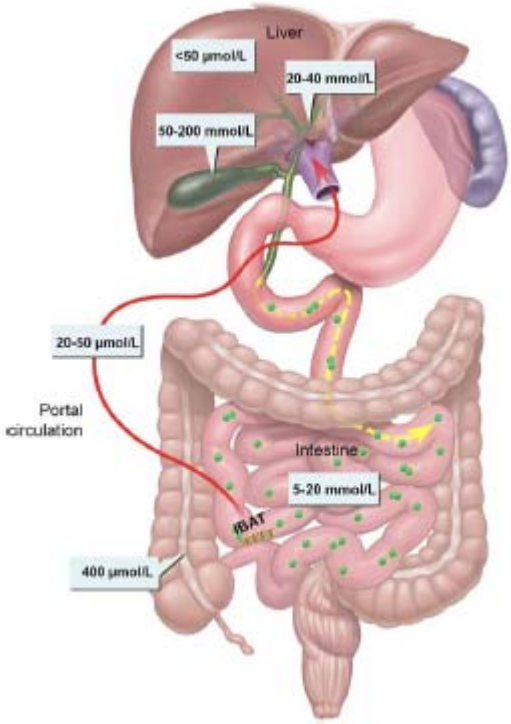
6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

6.1.1 Definition and pathophysiology

Progressive familial intrahepatic cholestasis (PFIC) is a rare, heterogeneous group of liver disorders of autosomal recessive inheritance that affect the flow of bile from the liver. PFIC is characterised by an early onset of cholestasis (usually during infancy) with pruritus and malabsorption, which rapidly progresses and ends up as liver failure.[1] PFIC has a devastating impact on children's lives, as well as on their parents and families. Unfortunately, without surgical biliary diversion (SBD) or liver transplantation (LTx), PFIC is usually fatal by age 20.

The bile acid cycle (known as enterohepatic circulation) is shown in Figure 1. Bile is produced in the liver and contains several different substances including bile acids, bilirubin, cholesterol, fats, water and other waste products.[23] After bile has been produced by the liver, it is transported to and stored in the gall bladder. When food is consumed, the gall bladder releases bile through bile ducts into the duodenum, to help with digestion and remove waste products. Further down the intestine, in the terminal ileum, most of the bile acids are reabsorbed back into the bloodstream so they can return to the liver to be reused.

Figure 1. Bile acid cycle



Bile acids (green dots in picture), synthesized in and secreted from the liver, travel to the small intestine where they aid in digestion and absorption of nutrients. Bile acids are reabsorbed from the terminal ileum by IBAT (95%) and return to the liver through the portal veins (indicated by the red line). This cycle is known as enterohepatic circulation. Bile acids not recovered in this process are replaced by nascent synthesis (5%). Typical bile acid concentrations in liver cells, the biliary and intestinal tracts and the portal circulation are given in milli- or micromolar quantities, as applicable.
Source: Kamath BM, et al. Liver Int. 2020;40:1812–1822

In healthy children serum bile acids are reported to be <10 µmol/L in children age up to 11 years and <4 µmol/L in adolescents aged above 11 years. Source: Jahnel, J et al. CCLM 2015; 53

The function of bile is to aid digestion by breaking down fats for absorption, enabling the body to absorb fat-soluble vitamins and assist the body in removal of waste products such as bilirubin and excess cholesterol.[23]

If the production and excretion of bile are impaired (cholestasis), cholestatic liver disease develops, where biliary substances cannot be eliminated from the liver and thus re-enter the circulation.[24] Bile trapped in the liver may cause progressive damage including fibrosis and cirrhosis. If untreated, the effects of cirrhosis can include portal hypertension, increased risk of liver cancer, swollen blood vessels in the lining of the oesophagus, ascites and liver failure.[24]

Deposition of bilirubin pigments in the tissues as skin, sclerae, and mucous membranes will cause jaundice. However, the most unbearable symptom of cholestasis for the patient is pruritus.[23] It is considered to be induced by the stimulation of nonmyelinated subepidermal free nerve ends due to increased serum bile acids.[25]

6.1.2 Classification

PFIC is sub-grouped according to the genetic defect, clinical presentation, laboratory findings, and liver histology.[1] PFIC is generally categorised into three main subtypes, PFIC1, PFIC2, and PFIC3 (Table 3), although at least three other subtypes have been described in the literature.[1,3,14,26] PFIC1 and PFIC2 together represent approximately two-

thirds of cases of PFIC, and PFIC3 approximately one-third.[27] PFIC is caused by defects in bile secretion from hepatocyte to canaliculi, however, in simple terms, bile acid secretion is depleted in PFIC1 and PFIC2, whereas bile phospholipid secretion is impaired in PFIC3.

For both PFIC types 1 and 2, there are multiple different mutations in the *ATP8B1* or the *ABCB11* genes respectively that result in symptomatic disease. PFIC types 1 and 2 have an episodic form, referred to as benign recurrent intrahepatic cholestasis (BRIC) types 1 and 2. It is now generally recognized that, within each subtype, PFIC and BRIC represent two extremes of a continuous spectrum of phenotypes of the one disease.[28]

6.1.3 Clinical features

In PFIC toxic accumulation of serum bile acids leads to pruritus so severe it can lead to self-mutilation and drive the decision to seek liver transplant. Patients with PFIC1 and PFIC2 generally present with jaundice and severe pruritus in the first few months of life, with 78% developing jaundice before the age of 12 months.[2] PFIC3 can occur during infancy, childhood and even into young adulthood. Pruritus can be slightly less severe in PFIC3 in comparison to PFIC1 and 2 but the severity of the condition differs between individuals.

As shown in Table 3, distinct clinical and laboratory features may be observed for each subtype. However, elevated sBA is evident across all subtypes, as is debilitating pruritus and the potential for progressive liver disease.[3]

Table 3. Genetic and clinical features of PFIC subtypes

Disease	**PFIC1** **(Byler disease)**	**PFIC2** **(SPGP/BSEP deficiency)**	**PFIC3** **(MDR3 deficiency)**
Chromosome	18q21-q22	2q24	7q21
Gene	FIC1 (*AT8B1*)	BSEP (*ABCB11I*)	PGY3 (*ABCB4,* MDR3)
Gene function	FIC1 translocates phospholipids from outer to inner canalicular membrane	Bile salt export pump	Phosphatidylcholine transport into bile
Age at presentation	Infancy	Neonatal period – early infancy	Late infancy (30%) to early adulthood
End-stage liver disease	First decade	Rapid, first few years	First to second decade of life
Course of disease	Moderately severe Liver cirrhosis and rapid progression to ESLD. Patients do not have increased risk for development of liver tumours.	Very severe Progression even more rapidly to ESLD, requiring LTx during the first decade of life.	Insidious Risk of liver tumours developing mildly increased.

Disease	PFIC1 (Byler disease)	PFIC2 (SPGP/BSEP deficiency)	PFIC3 (MDR3 deficiency)
Pruritus	Severe	Very severe	Moderate
Extrahepatic features	Watery diarrhoea Pancreatitis Sensorineural hearing loss	Absent	Absent
Cholesterol stone formation	Absent	Increased	Increased
Risk of development of liver tumours	Not reported	High	Not reported
Serum ALT	Mild elevation	Moderate elevation	Mild elevation
Serum GGT	Normal	Normal	Elevated
Serum bile acids	Raised ++	Raised +++	Raised +
Serum direct bilirubin	Elevated	Elevated	Elevated
Serum ALP	Elevated	Elevated	Elevated
Biliary phospholipids	Normal	Normal	Low
Serum5'-nucleotidase	Elevated	Elevated	Elevated
Serum AFP	Normal	Elevated	Normal

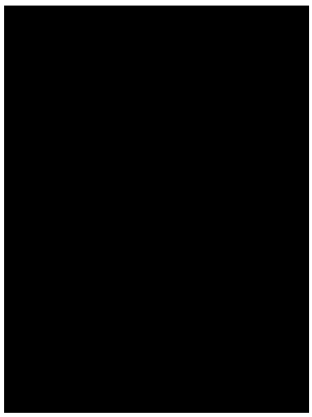
Source: Adapted from Srivastava et al. 2014[3] and Gunyadin et al. 2018[1]
Abbreviations: AFP, alphafetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ESLD, end-stage liver disease; GGT, gamma-glutamyl transferase; PFIC, progressive familial intrahepatic cholestasis

Pruritus is the most common and debilitating symptom of PFIC. Indeed, itching (and subsequent scratching) is a significant morbidity for these patients and their families. For children and their parents, pruritus is an extremely distressing manifestation of disease and its relief is often the goal of early therapy. Significant pruritus can lead to severe cutaneous mutilation (often drawing blood;

Figure 2), loss of sleep, irritability, poor attention, and impaired school performance.[26]

Pruritus is one of the two indications for liver transplantation in children with PFIC. Indeed, confidential data from the NAPPED study show that [redacted] for liver transplantation in PFIC patients, with approximately [redacted] of the PFIC1 and PFIC2 patients being [redacted].[29]

Figure 2. Severity of pruritus in PFIC



Patients may also present with short height, growth retardation, deafness, diarrhoea, pancreatitis, increased sweat electrolyte concentration, hepatic steatosis and epistaxis despite bleeding diathesis.[1]

Liver biochemistry shows cholestasis with hyperbilirubinemia and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The concentrations of bile acids in serum are typically very high, while serum gamma-glutamyl transferase (GGT) is normal or low (except for PFIC3); cholesterol concentrations are typically normal.[9]

PFIC is associated with a range of potentially fatal complications of the liver, including portal hypertension, liver failure, cirrhosis and hepatocellular carcinoma (PFIC2), as well as extrahepatic manifestations (PFIC1).[4] Portal hypertension and decompensation may be evident in the first year of life in PFIC2 and in early childhood in PFIC1.[3,27]

PFIC results in progressive liver disease, usually progressing to cirrhosis within the first decade of life, that typically leads to liver failure.[26] The rate of progression varies by subtype and reflects the general rate of progression of clinical symptomatology. In general, PFIC patients with an *ATP8B1* mutation (PFIC1) typically progress to cirrhosis in the first decade of life. Those with an *ABCB11* mutation (PFIC2) present earlier and more severely: cirrhosis has been identified as early as 6 months of age and most patients tend to progress rapidly to cirrhosis.[30] Those with an *ABCB4* mutation (PFIC3) have a more heterogeneous presentation and may be diagnosed later in childhood.[3] Progression to cirrhosis is typically slower in patients with PFIC3, and is usually first identified in late childhood and young adulthood.[1,30]

PFIC2 may present with a malignancy such as hepatic cell carcinoma (HCC). In PFIC3 damage to the bile ducts can occur, gallstones are common and there is a high risk of portal hypertension.

Other features include fat malabsorption resulting in weight and height below normal centiles, and fat-soluble vitamin (A, D, E, and K) deficiency. Secondary vitamin K deficiency related to fat malabsorption and inadequate dietary intake may predispose to haemorrhagic disease of the newborn (HDN); late HDN (seen in infants aged 1 week to 6 months) may be associated with serious and life threatening intracranial haemorrhage.[5]

Individuals with PFIC may also display signs of rickets and osteopenia and have an increased risk of fractures associated with vitamin D deficiency.[31,32]

BRIC is a type of PFIC characterised by episodes of cholestasis lasting from weeks to months, with irresistible pruritus. In a proportion of those with BRIC, the disease progresses to complete cholestasis over time. In recently published data relating to PFIC1 patients in the NAPPED study, 15 patients who initially presented with the BRIC phenotype later evolved into a severe PFIC1 phenotype.[12] Similarly, 11 patients who previously presented with a BRIC2 phenotype later presented with severe BSEP deficiency (PFIC2) phenotypes (i.e. continuous cholestasis and/or pruritus and continuous hepatocellular damage) and had pathological mutations.[10]

Individuals with PFIC often require biliary diversion surgery or a liver transplant at an early age

Pruritus that is intractable despite medical treatment, growth failure and nutritional deficiencies necessitates surgical biliary diversion (SBD). Unfortunately, not all patients benefit from SBD and, at some point, many require LTx for refractory pruritus or end-stage liver disease.

In the NAPPED study, during the follow-up periods, 48% of PFIC1 and 23% of PFIC2 patients had undergone SBD.[10,12] PFIC1 and PFIC2 patients underwent SBD at a median age of 5.9 years and 2.3 years, respectively.[10,12]

Only 44% of PFIC1 patients and 32% of PFIC2 patients were alive with their native liver at 18 years of age. [10,12] For the BSEP deficiency (PFIC2) population, genotype severity was strongly associated with NLS, falling from a median of 20.4 years for BSEP1 to 3.5 years for BSEP3 ($p<0.001$).[10]

In a UK study, Ruth et al. 2018 reported SBD rates of 37.5% and 30%, and LTx rates of 75% and 35% in patients with PFIC1 and PFIC2, respectively.[33]

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

PFIC is a rare disease estimated to affect between one in every 50,000 to 100,000 children born worldwide [27]. While global and/or country specific prevalence estimates are not available for PFIC, it is believed to be responsible for about 10% to 15% of children with cholestatic liver diseases and 10% to 15% of liver transplantation indications in children.[27]

Although published data are very limited,[4] given the number of births in England (610,505; mid-2019 population estimates), and an estimated survival of 30 years, an incidence of 1 in 75,000 births corresponds to 238 patients living with PFIC in England. The number of diagnosed paediatric PFIC patients (excluding episodic cases; BRIC) in England was estimated by clinical experts as approximately [redacted] patients.[20]

A consultant paediatric hapatologist from [redacted] advised that there are 10–12 new PFIC patients diagnosed per year at his centre. As this is based on data from the genetic lab that covers two-thirds of the patients in England, this means there are estimated to be 15–18 new cases of PFIC diagnosed across England each year.

PFIC1 and PFIC2 account for the majority of the diagnosed cases, with PFIC2, which generally presents earlier and more severely, the most common subtype diagnosed. In terms of gender, recent reviews suggest PFIC affects males and females equally.[3]

In a retrospective review of patients presenting between 1984 and 2017 at a UK centre (Ruth et al, 2018)[33] that included 80 patients with a genetic or phenotypic diagnosis of PFIC or BRIC, 10% had PFIC1, 25% had PFIC2 and 3% had PFIC3 (16% had BRIC and 46% were of unknown subtype). Clinical experts consulted at a UK advisory board estimated that, of their PFIC patients, 16% have PFIC1, 38% have PFIC2, 20% have PFIC3, and 26% have other types or are not genetically confirmed (responses from eight consultants from three centres in England were averaged).[8]

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

PFIC can be a rapidly progressing condition. It is associated with a range of complications of the liver, including portal hypertension, liver failure, cirrhosis and HCC (ABCB11).[4] Therefore, without LTx, PFIC may lead to fatal liver conditions, including end-stage liver disease and liver cancer, as early as in childhood (Table 3). Survival in patients with PFIC

not undergoing surgical bile diversion or liver transplant is 50% at age 10 and almost none at age 20, highlighting the rapid rate of progression and life-threatening nature of the disease.[2] The NAPPED study (see box above) reports pre-transplant mortality to be 9% for PFIC1 and 5% for PFIC2.[10,34,35]

Mortality is generally reported in studies following LTx (Table 4). Varamparampil et al. 2019 observed increased mortality in PFIC1 following LTx compared to PFIC2/3/4 (27% compared to 15%).[36] Ruth et al. 2018 noted earlier presentation of disease was found to be significantly associated with mortality ($p< 0.01$) for PFIC1.[33] In contrast, one study observed that for PFIC3, living-donor LTx for PFIC3 has favourable outcome with 0% mortality at 3 years follow-up.[37]

In the study by Davit-Spraul et al, 54 of the 62 patients (87%) were alive at the last follow-up, at a median age of 10.5 years (range: 1-36). Six PFIC1 patients had received a transplant, two of whom died (median age 15 years), and four survived at last follow-up (aged 4–20 years). Fifteen PFIC2 patients had received a transplant, one of whom died (age not reported), and fourteen survived at last follow-up (aged 3–36 years).[38]

Table 4. Mortality rates in European and global studies

Study	Country	Methods	Population	Age at transplant	Mortality
Acar (2019)[37]	Turkey	Retrospective data analysis	22 patients with PFIC3	Median 2.4 years (n=13)	PFIC3: 0% (3 years post-LT)
Davit-Spraul (2010)[38]	France	Retrospective chart review: 1978-2007	62 children with cholestasis	PFIC1 median 4 years (n=6) PFIC2 median 7 years (n=15)	PFIC1: 15% (median 15 years of age) PFIC2: ~8% (median 1 year of age)
Ruth (2018)[33]	UK	Retrospective descriptive study	80 patients with a genetic or phenotypic diagnosis of PFIC	PFIC1 median 6.2 years (n=6, 75%); PFIC2 n=7, 35%	PFIC1: 25% (median 12.1 years follow-up) PFIC2: 10% (median 9.9 years follow-up)
Schatz (2018)[39]	Germany	Retrospective collection of clinical and laboratory data	38 patients with PFIC3 (n=31), ICP or LPAC syndrome	Median 6.9 years (n=13 with PFIC3)	PFIC3: 6.4% following LTx (LTx-related complications)
Valamparampil (2018)[40]	NR	Prospective	25 patients with PFIC and LTx (PFIC1 (n=7, PFIC2 n=7, PFIC n=10 and PFIC4 n=1)	Median 3.8 years (n=25)	All PFIC 1-year graft and patient survival was 84% (no mortality reported during 3.5 year follow-up)
Van Wessel (2020)[10]	Global	Retrospective cohort study	Patients with FIC1 deficiency	120/264 (45%) had undergone LTx (median follow-up 4.1 (1.5–12.3) years)	Pre-LTx mortality BSEP1: 4% BSEP2: 6% BSEP3: 9% Deaths were all liver-disease

					related and occurred at median age 1.6 [1.1–3.5] years
Van Wessel (2021)[12]	Global	Retrospective cohort study	130 patients with PFIC1	38/130 (29%) had undergone LTx (median follow-up of 4.2 (2.2- 9.8) years)	Pre-LTx mortality PFIC1: 6% (n=8) 7 deaths were disease related at median 5.0 years
Wanty (2004)[41]	Germany	Retrospective chart review: 15-year follow-up	49 children with PFIC	38/49 (76%) underwent LT. PFICI and 2 median 4.2 years (n=22). PFIC3 median 5.3 years (n=13)	Overall: PFIC1/2:10% PFIC3: 5% Post-LTx: 8% (2 of 3 patients died from LTx-related complications)

Abbreviations: ALGS, Alagille syndrome; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis 1; GGTP, gamma-glutamyl transpeptidase; ICD, International Classification of Diseases; ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholestasis; LTx, liver transplant; NR, not reported; PFIC, progressive intrahepatic cholestasis

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

7.1.1 Impact of symptoms on patients with PFIC

PFIC may manifest with many symptoms, and there are several aspects of the condition that have a negative impact on health-related quality of life (HRQL).

For children and their parents, pruritus is an extremely distressing manifestation of the disease and its relief is often the initial goal of therapy. Significant pruritus can lead to severe cutaneous mutilation (often drawing blood), loss of sleep, irritability, poor attention, and impaired school performance (

Figure 2).

As shown in Figure 3, pruritus is the most common and debilitating symptom, with pruritus-related sleep disturbance reported by 67% of PFIC patients.[42] Pruritus was reported to occur all over the body. All respondents reported that pruritus occurred most frequently at night and was also reported to occur frequently upon waking and when tired or unwell. Pruritus-related sleep disturbance, including difficulty falling and staying asleep, and requiring soothing from caregivers to sleep, was the most salient impact (77% reported).[42]

Video testimony shared with the PFIC Network at a meeting with the FDA to discuss PFIC burden and the unmet need highlights the unbearable nature of pruritus that some children experience (video can be accessed here; https://www.youtube.com/watch?v=rfESst9x19I&t=988s; time reference 6 minutes, 45 seconds).

Further patient testimonials illustrate the intensity of pruritus and the impact on everyday life:[7]

Girl with PFIC (and parent): "I was itchy at school, but tried to contain it. I would sometimes scratch when I was distracted by something. If it was really bad, I would go to the nurse and itch there. But when I went home the scratching was constant and would never stop." "Our quality of life was horrible," [mother] remembers [after the girl had received biliary diversion surgery], "I kept thinking to myself, 'Oh my god, she is going to itch herself to death."

Boy with PFIC2: *"There is a desperation from the liver itch that is devastating. People tell me they understand because their child has eczema and itches all the time, but it's totally different. It's horrifying and nothing makes it better." "[His] skin was so bad that he really couldn't be left alone because of the damage he was doing to himself. He was covered in scars and scratch marks." Due to his severe pruritis and declining quality of life, the boy underwent a liver transplant when he was two and a half years old."*

Boy with PFIC3*: "[He] would scratch the inside of his ears so much that he would bleed." His mother noticed that the itching seemed to be spreading to his toes and arms.*

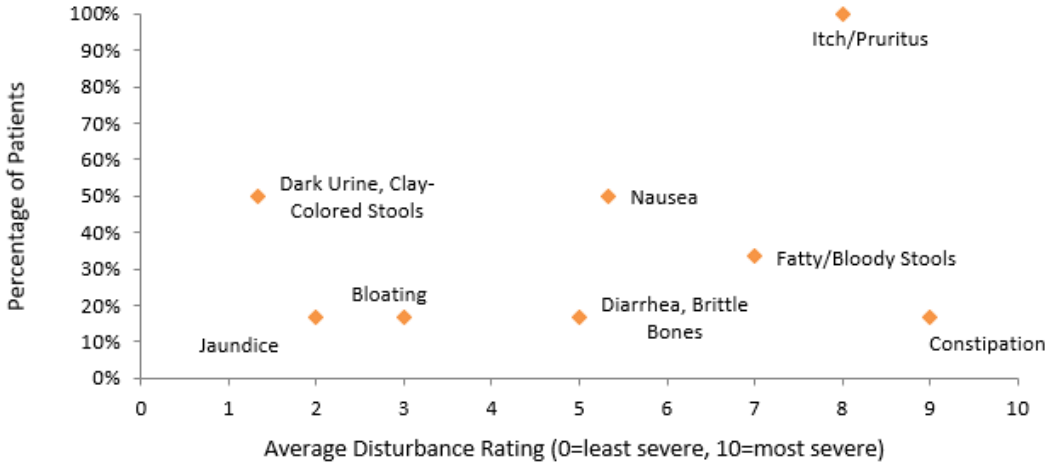
Girl with PFI2: *"Feels like a million ants under my skin, 24/7."* The patient takes shoes, socks off periodically to apply lotion; puts hands in water for relief. The patient pulls out their own hair, and bites her arms to distract herself from scratching.

Girl with BRIC: *"The scratching was near constant"* "[She] *was also beginning to violently tear at her scalp and ears, almost to the point of mutilation." [The mother] and her husband*

tried everything to soothe the constant itch that accompanies PFIC, including giving [her] cold baths and applying various creams. Their efforts were futile, and the severe pruritis diminished the entire family's quality of life.

Again, highlighting the gravity of this symptom, approximately [redacted] of the PFIC1 and PFIC2 patients being [redacted].[29]

Figure 3. Disturbance rating for PFIC symptoms



Source: Adapted from Torfgard et al. 2018[42]

Growth retardation and failure to thrive is another worrying symptom for carers and clinicians, particularly affecting PFIC1 patients (Table 5).

Quotes from parents of children with PFIC highlight the impact and severity:

> Girl with PFIC2 (UK): *"She also experienced severe deficiencies in vitamins A, E, D and K. Eventually, she had to be fed through a nasal gastric tube to supplement her nutrition. [Her teachers] learned how to tube-feed her so that she could attend school with her peers for the entire day."*
>
> Girl with PFIC1: *"Her failure to thrive persisted, and she depended on a 24-hour gastronomy-tube (or g-tube) to support growth. She also received occupational therapy to learn how to chew food through her mouth."*

Table 5. Growth retardation in PFIC patients

	ATP8B1 Patients	ABCB11 Patients
Failure to thrive	46/51 (90%)	46/78 (59%)
Height (<3rd percentile)	33/39 (85%)	32/65 (49%)
Weight (<3rd percentile)	23/41 (56%)	20/68 (29%)

Source: Pawlikowska et al. 2010[2]

General quality of life data in PFIC patients are limited; however, unsurprisingly, existing evidence in patients with intrahepatic cholestasis patients indicates lower HRQL compared to healthy children.[43] PedsQL and Patient Satisfaction Questionnaire (PSQ) have been

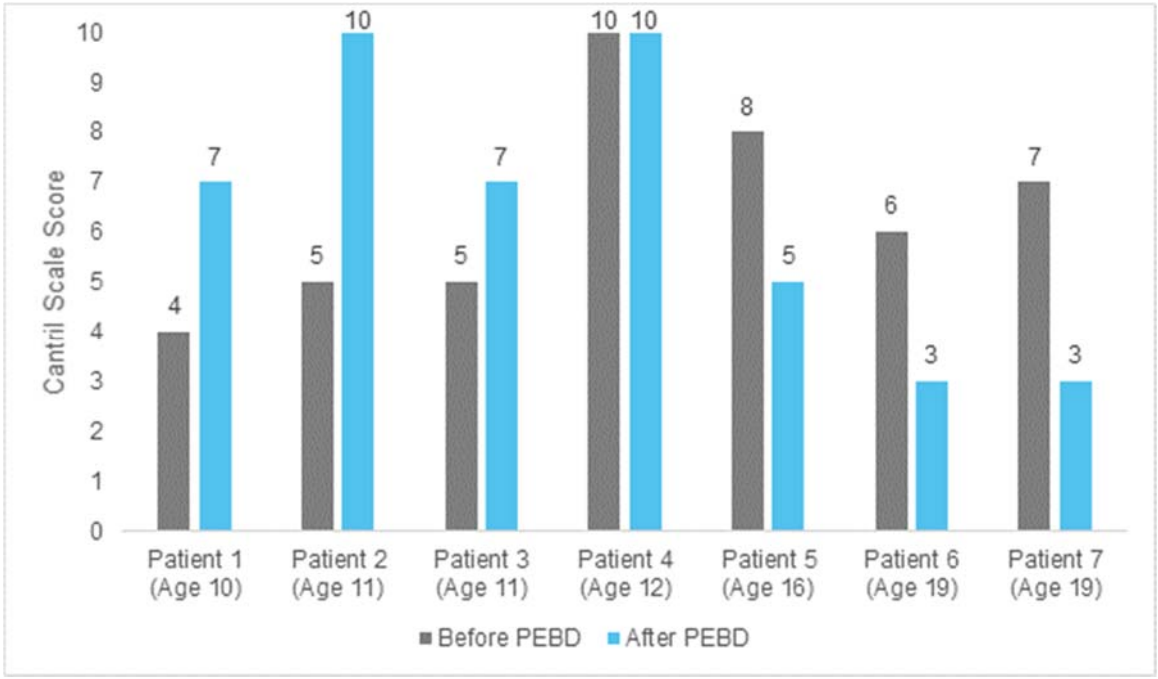
used most frequently to measure HRQL in PFIC; however these instruments may not adequately assess the specific symptoms of PFIC.[4]

Three studies have reported HRQL outcomes in patients with PFIC after LTx and PEBD[44,45].

In one study (Yee, 2018[45]) patients who underwent SBD all experienced improvements in HRQL, mainly due to improved sleep (73.4%), improved mood (67.4%) and less itching (63.3%). Wassman et al. (2018) reported that post-PEBD HRQL is similar to healthy children. Several important medical aspects, such as stomata or stigmatising scars, and everyday aspects such as the possibility of pursuing certain hobbies like swimming, were not included in the survey[44].

Overall HRQL before and after PEBD surgery was reported in only one study of 7 PFIC patients age 10-19 years.[46] Quality-of-life was measured using the Cantril scale, which measures general well-being, mental health, and happiness using a scale from 0-10, with higher values indicating greater HRQL. Among younger patients (age 10-11), HRQL improved following PEBD surgery. Alternatively, worsening HRQL or no change in HRQL was noted in older patients (age 12-19; Figure 4).[46]

Figure 4. Health-Related Quality-of-Life Before and After PEBD Surgery



Source: Kwak et al, 2005[46]

Wassman et al. (2018) also reported HRQL in patients with PFIC after LTx. A significantly lower mean score in school functioning was observed in the LTx group when compared

with healthy children.[44] The authors suggested that the impact of calcineurin inhibitors may be responsible, since they are known to affect the cognitive functioning of children after LTx. This was supported by the observation that PFIC patients living with their native liver did not have poorer HRQL scores than the healthy controls. The study by Yee et al (2018) observed that LTx was associated with more frequent post-surgery complications than BD.[45] A major problem with LTx is exacerbation of diarrhoea, which may impair quality of life and may prevent catch-up growth after transplantation especially in patients with PFIC1.[47]

Many individuals with PFIC and their caregivers tend to be anxious about LTx because of the extreme nature of the procedure and associated risks. Patient testimonials illustrate the anxiety experienced:

> Girl with PFIC2 (UK): *"We still live with worries that come along with a liver transplant. Threats of rejection, post-transplant cancers and risks associated with [her] now-suppressed immune system loom over us every day. We know that a simple cold or flu might lead to severe illness and hospitalisation."*
>
> Girl with PFIC2: *"While she was comforted by sharing the experience with her brother, seven-year-old [girl] still lives with anxiety and fear surrounding maintaining her health post-transplant. [She] has had a difficult time coping since her transplant. She is afraid to be alone in case she has a health emergency. [Her brother] sleeps on her bedroom floor to comfort her.*"

The further complications and impact of LTx on patients and caregivers is discussed in section 8.2.6.

7.1.2 Caregiver burden

The burden for caregivers is substantial, where many report feeling lonely, overwhelmed, anxious, scared, frustrated and confused. When listening to parents describe their child's condition, it is obviously hugely distressing for them to see their children, from a very young age, suffer the unbearable 'head to toe' itching that cannot be controlled. Since children with PFIC often cannot sleep due to their pruritus, their parents must stay up to comfort them and describe sleeping on their child's floor so they can be nearby. Caregivers also describe having years of sleepless nights and night-time routines that involve various methods of attempting to sooth itching every few hours, such as applying lotion, showering, foot soaks and distraction techniques such as tickling.[7]

PFIC is a life-threating disease, and children experience multiple hospitalisations from a young age. Children have to attend frequent hospital appointments and often families travel long distances to seek specialist care. The very limited treatment options and the need for invasive surgery create significant anxiety and it is difficult for parents to make decisions about treatment options and when to list their child for LTx. When the decision is made to go ahead with LTx, parents then have to watch their child (or children) go through major surgery and are left with other concerns including the worry of transplant rejection, post-transplant complications and the burden of life-long immunosuppressive therapy.

There is a significant burden on the entire family. In some cases, more than one child in a family may be affected. The burden on parents means that they often have to give up work to care for their child or children with PFIC.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Current off-label phamarcological treatment is ineffective, leading to the need for surgical procedures (biliary diversion/transplant) to gain control of disease. These procedures carry risks for the patient and are undesirable to the family. Therefore, a pharmacological treatment that offers a degree of stability through better control of pruritus and, ideally, disease progression for a significant period of time to prevent more invasive procedures, would be hugely beneficial.

Treatment with odevixibat improves pruritus, reduces serum bile acid, is well tolerated and has the potential to delay liver transplant in the patients who would otherwise have been transplanted due to uncontrolled severe pruritus.

- In a Phase 2 study in cholestatic pruritus patients, including PFIC patients, the majority of patients experienced reductions in sBA that correlated with improvements in pruritus and improvements in sleep.
- In a Phase 3 randomized double-blind study in children with PFIC, treatment with odevixibat at doses of 40 and 120 µg/kg/day led to statistically significant reductions in sBA levels and pruritus symptoms over 24 weeks compared with placebo. These improvements occurred rapidly and were sustained during continued treatment.

- Treatment with odevixibat overall and at doses of 40 µg/kg/day and 120 µg/kg/day led to statistically significant improvements in pruritus and sBA levels compared with placebo over the 24-week treatment period based on the Albireo ObsRO instrument, a validated tool for assessment of pruritus and sleep disturbance in PFIC.

In conclusion, odevixibat is expected to significantly improve the QoL of children affected by PFIC by reducing the amount of unbearable pruritus that is often experienced, and improving their sleep. This will also have a significant impact on other family members who often have their sleep disturbed and need to soothe their child in the night. Since reduction in sBA can be correlated with increase in native liver survival, treatment with odevixibat alters the course of PFIC disease progression, with the potential to delay or avoid liver transplants in patients who would have been transplanted due to uncontrolled severe pruritus.

Odevixibat is expected to have a significant impact beyond direct health benefits.
The impact of itching/pruritus on patients can completely disrupt every aspect of life and can have serious long-term effects such as post-traumatic stress disorder, impulse control and other social-emotional disabilities. Adolescents with PFIC have described bullying and social isolation from classmates and teachers, and they feel ashamed about their uncontrolled itching. Of consequence also is the sleep disruption experienced by all members of the family. This impacts the growth and development of a child affected by PFIC, and their ability — as well as that of any siblings — to participate fully in school and other activities. Caregivers have described strained relationships, divorce, and having to make difficult trade-offs around their careers and managing a child with a serious, progressive chronic liver condition.

Odevixibat is the medical equivalent of partial external biliary diversion (PEBD) and therefore it is considered as the relevant comparator for this submission. Whilst this type of surgery may postpone or eliminate the need for liver transplantation and improve pruritus associated with PFIC in some patients, it is an invasive procedure with unwanted consequences, including complications and anxiety related to the external stoma.

By improving symptoms such as pruritus, sleep and growth (height and weight z-scores), delaying disease progression and avoiding or delaying surgical procedures and/or liver transplantation, odevixibat treatment is expected to have a positive impact on schooling and employment opportunities for people with PFIC.

Odevixibat may also reduce the caregiver burden and improve productivity that is lost as a result of disturbed sleep, as well as reduce the cost of special education services and the cost of hiring additional caregivers.

Two caregivers have described their child's life before and after odevixibat treatment:[7]

Boy with PFIC2:

"He spent his childhood tortured by the symptoms of PFIC. His nightly routine involved waking up at least four or five times due to severe pruritis. Lack of sleep made him irritable, and he frequently fell asleep at school. He had a difficult time coping with the seemingly endless needle sticks performed during his frequent appointments at doctors' offices and hospitals and developed severe anxiety."

After odevixibat*: "He gradually began sleeping through the night and his skin began to heal because he was not constantly scratching himself. He was finally able to have sleepovers at his friends' houses because he could make it through the night without scratching himself to the point of bleeding through his bed sheets. Parents also noticed that his skin was less yellow and his irritability was beginning to decrease.*

"One morning, we got up and realized that [he] hadn't woken us up all night," remembers [parent]. "He is able to manage his itching and put himself back to sleep better now."

His parents have also benefitted from their son's improvement. They are now able to sleep in the same room for the entire night for the first time since he was born. [Mother] had to leave her job so that she could manage [boy's] daily care when he was a baby but she now feels comfortable returning to work.

Girl with PFIC2:

"Night and day did not exist for her—her day was divided into periods of scratching followed by crashing from exhaustion. She had to wear gloves nearly 24 hours a day to keep her from ripping her skin open. She spent the first two years of her life unable to eat solid food because she could not sit still long enough to learn how to chew and eat. Her growth and development suffered as a result."

"There is a period of about five months that I do not remember much of because I was not sleeping," recalls [parent]. "I was the only one who could comfort her and I felt like the only person who could handle her needs. There were many days where I would lie on the floor with her because I was afraid to drop her. I was too exhausted to safely hold my child."

After odevixibat*: Her parents noticed improvements within days. She began playing with her toys without her "itchy gloves" on—something that was never possible before. She started to pick flowers and play peek-a-boo with a washcloth. These activities may seem unremarkable to most parents, but to [her] they were reasons for celebration. [Her] mood improved dramatically because she was less itchy and started to sleep better during the night. She was even able to sit down with her parents and eat solid food for the first time at about 18 months old.*

While there are still unknowns surrounding [her] future, the hope of a pharmaceutical treatment approval allows [parent] to remain optimistic. She [patient] has grown and developed rapidly over the last few months, quickly catching up to healthy children her age. When planning for what's next, [parent] looks forward to seeing her daughter go to school and hopes that her symptoms will remain as manageable as they are today.

"Experiencing having a treatment is like having a miracle. I felt we were living in a haze of horrible itching and lack of sleep before, but the fog was lifted once she had access to this drug. We have had many tears of joy."

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are no NICE, NHS England or UK-specific guidelines relating to the treatment of PFIC.

The European Association for the Study of the Liver (EASL) report that no medical therapy of proven benefit for the long-term prognosis of PFIC exists. However, they have provided some recommendations.[48]

Recommendations for PFIC:

1. Supplementation with medium chain triglycerides and fat-soluble vitamins is generally recommended in children.

2. While UDCA has been reported to improve biochemical tests in almost 50% of patients with PFIC3, it generally does not affect PFIC1 and PFIC2.

3. Rifampicin may alleviate pruritus.

4. Partial biliary diversion has shown beneficial clinical and biochemical effects in PFIC1 and PFIC2.

5. Liver transplantation is recommended for end stage disease.

Recommendations for BRIC:

1. BRIC is characterised by acute episodes of cholestasis, jaundice and severe pruritus which after weeks to months completely resolve.

2. No evidence-based treatment of BRIC is known. Treatment attempts with UDCA, rifampicin or nasobiliary drainage are still experimental.

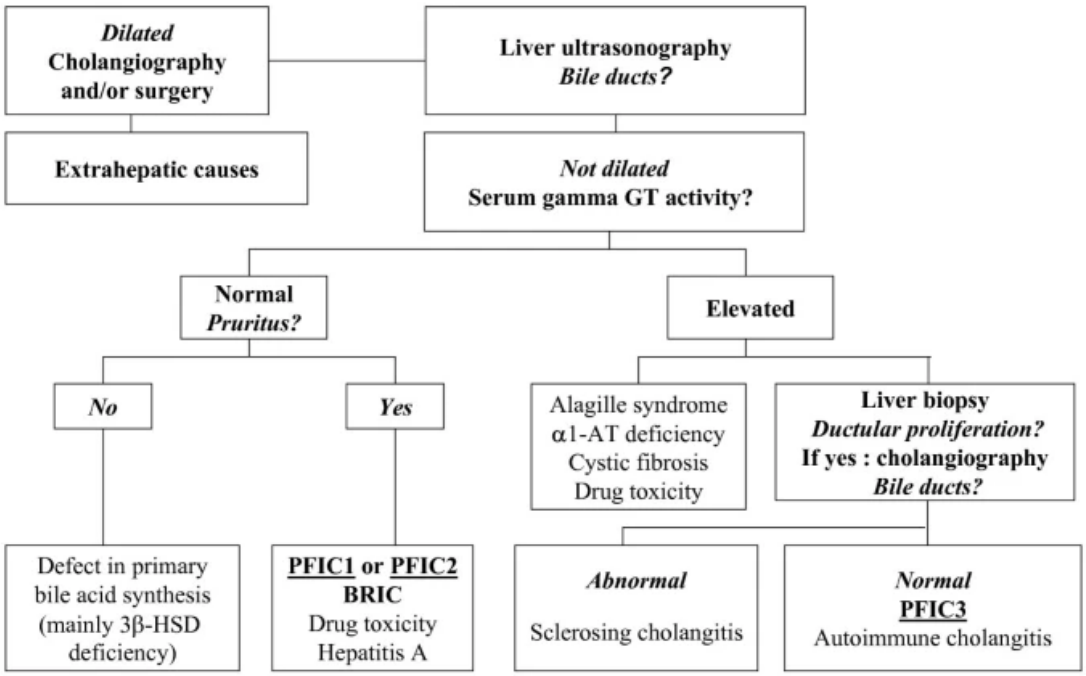
8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

8.2.1 Diagnosis

PFIC is generally suspected in children with a clinical history of cholestasis of unknown origin after exclusion of other main causes of cholestasis, (e.g. biliary atresia, Alagille syndrome, alpha 1 antitrypsin deficiency, cystic fibrosis, sclerosing cholangitis and extrahepatic bile duct obstruction).[1,27] Liver function tests, serum bile acids and imaging studies help to rule out the cause of liver disease.[1]

Figure 5 presents a suggested approach to the diagnosis of PFIC.[49] This is a combined clinical, biochemical, radiological and histological approach associated with liver immunostaining and biliary lipid analysis, to identify PFIC candidates in whom a molecular diagnosis can be proposed. Genetic testing can confirm a PFIC diagnosis, however it should be noted that a significant proportion of patients have uncertain genetic diagnosis but severe phenotype, and the diagnosis is primarily clinical.

Figure 5. An approach to the diagnosis of PFIC excluding the neonatal period



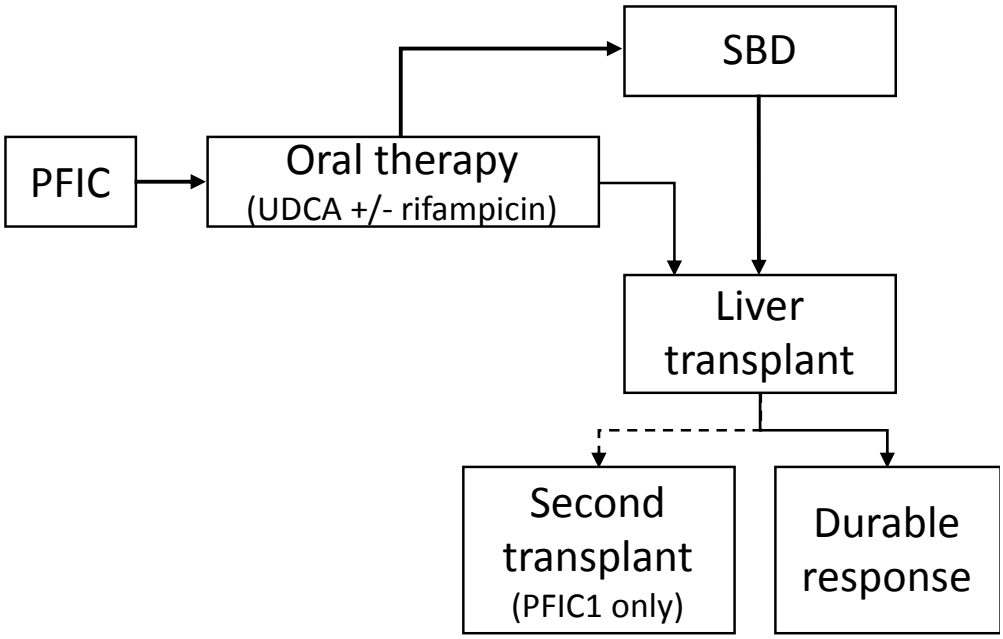
Source: Davit-Spraul et al. 2009[27]

8.2.2 Treatment of PFIC - overview

There is currently no pharmaceutical treatment approved for use in PFIC. The therapeutic choices are restricted to nonspecific therapy to address the symptoms and signs of the disease, such as UDCA, rifampicin, nutritional support, preventing vitamin deficiencies, and treatment of extrahepatic features. Beyond the limited off-label pharmacologic choices which offer only symptomatic treatment[9], the only options for patients are partial external biliary diversion (PEBD) surgery or liver transplant.

The treatment pathway for PFIC is shown in Figure 6.

Figure 6. Treatment pathway for PFIC



SBD, surgical bile diversion; UDCA, ursodeoxycholic acid
SBD is most commonly a partial external biliary diversion (PEBD)

8.2.3 Nutritional management

Nutritional management is the first step in the physician's treatment plan where the patient's formula is changed to a specialised one to maintain growth and manage malabsorption.[1] Dietary fat is mainly provided as medium chain triglycerides. The fat-soluble vitamin supplements (A, D, E and K) are administered to ensure proper absorption.[50] Calcium intake and adequate exposure to sunlight are also essential. Deoxycholic acid may also be included to assist in fat absorption.

8.2.4 Pharmacological treatment

Pharmacological treatment is prioritised over surgical intervention for the treatment of PFIC; this often leads to prescribing multiple drugs simultaneously. That said, there is no pharmaceutical treatment approved for use in this condition.

The focus of pharmacological treatment is to relieve pruritus, which is the most distressing symptom in PFIC.[1] However, other aims are to slow the disease progression by enhancing the bile flow and inhibiting the accumulation of metabolites in the liver (choleresis), improve the nutritional status, correct vitamin deficiencies, ensure continuity of growth and treat the complications of advanced liver disease such as ascites and variceal bleeding. Since the need for symptom relief is critical, supportive medication is often started in conjunction with, or very soon after nutritional therapy.

Medical treatment options include off-label use of UDCA, rifampicin, antihistamines, cholestyramine and naltrexone. A minority of patients respond to these medications and, if so, only transiently.[9] In the UK, UDCA is the first line oral treatment, and rifampicin may also be tried to reduce pruritus symptoms.[8]

UDCA is commonly prescribed because of its ability to promote bile flow which can subsequently assist with pruritus; however not all patients respond.[1,9] It is a hydrophilic bile acid and is thought to reverse the potential hepatotoxicity of the accumulating endogenous bile acids. UDCA regulates bile acid distribution, reduces the amount of cholesterol in the bile, and provides mitochondrial integrity. However, it is not licensed for PFIC; it is not effective in two-thirds of PFIC1 and PFIC2 and half of PFIC3 patients, although UDCA does appear to be more effective in patients with missense mutations with less severe disease.[4,6,38] Whilst a proportion of PFIC1 and PFIC2 patients may have some response to UDCA, by age 11 years 50% of those treated have received LTx.[38]

In the literature review carried out for this assessment, 20 studies were identified that investigated UDCA for treatment of PFIC (Appendix 17.6). There have been no randomised studies: all studies were uncontrolled, and the majority were retrospective. It is difficult to draw firm conclusions from these studies because of to the lack of controls, retrospective design and the use of various and often subjective definitions of response used, for example “improved pruritus” or “complete response: jaundice resolved and normalisation of biochemistry”.

Rifampicin, which inhibits the uptake of bile acids by hepatocytes, may alleviate pruritus in people with PFIC.[6] Rifampicin indirectly induces hydroxylation of bile salts which are further glucuronidated and excreted in urine. It also induces conjugation and excretion of bilirubin through uridine diphosphate-glucuronosyl transferase.[51] In one small study, only a partial response (decrease in intensity of pruritus but persistence of the pruritus) was seen in 3 of the 8 patients with PFIC.[52]

In the odevixibat PEDFIC1 study, the majority of patients were receiving UDCA and/or rifampicin at study entry. The existence of this patient population with high levels of sBA and uncontrolled pruritus despite the use of UDCA and rifampicin further highlights the lack of efficacy of these off-label therapies and the high unmet need.

Other off-label therapies that are used less frequently than UDCA and rifampicin include antihistamines such as chlorpheniramine to alleviate pruritis. Although antihistamines do not affect serum bile acids, they may reduce the sensation of pruritus.[53] Cholestyramine is

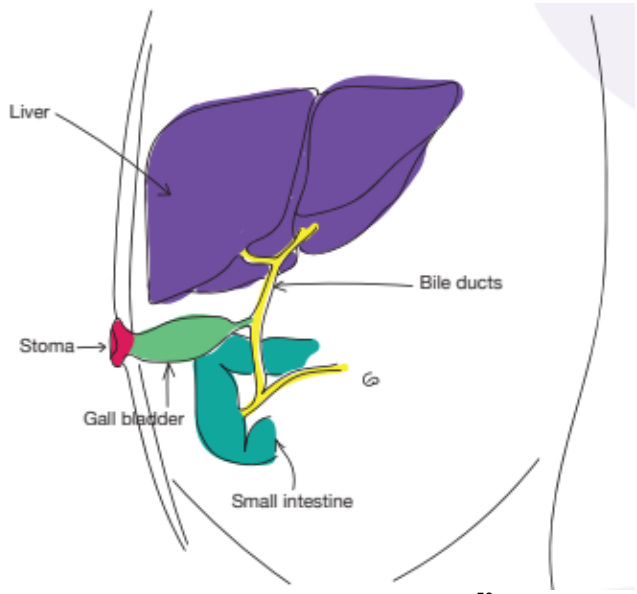
an oral bile acid binding resin. It forms nonabsorbable micelles with the bile acids in the intestines and prevents bile acids from entering the enterohepatic cycle.[1]

8.2.5 Surgical treatment

Pruritus that is intractable despite medical treatment, growth failure and nutritional deficiencies necessitates surgery. Biliary diversion is used to interrupt the enterohepatic circulation of bile acids by diverting bile from the gallbladder, thereby decreasing the influx of bile acids to the gut and reuptake of bile acids in the small intestine and thereby lowering the bile acid pool. Diversions help to improve liver function, growth, liver histology, reduce progression of fibrosis and extend the time interval before liver transplantation in the majority of patients with PFIC1 and 2.[1]

PEBD involves use of a 10–15 cm jejunal conduit between the fundus of the gallbladder and abdominal skin where a permanent stoma is created (Figure 7).[1] Diversion of bile interrupts the enterohepatic circulation of bile salts, diminishes subsequent reuptake and decreases the pool of bile salts.

Figure 7. Partial external biliary diversion



Source: Children's Liver Disease Foundation, (2019)[50]

PEBD is often used as the first line surgery in PFIC1 and 2 patients and can successfully delay or avert the need for LTx. This form of biliary diversion results in rapid, dramatic reductions in serum bile acids (Table 6) leading to improvement in pruritus and sleep disturbance with longer-term reduction in fibrosis and a catch-up in linear growth over 1 to 2 years.[54-56]

Table 6. Serum Bile Acid Levels Before and After PEBD In Studies with Aggregate Data

		Pre-PEBD		Post-PEBD	
Study	**N**	**Mean (SD)**	**Median (Range)**	**Mean (SD)**	**Median (Range)**
Ismail 1999	16	249.4		65.7	
Melter 2000	6	307 (72)		7 (2)	
Kaliciński 2003	21	293.3	299	-79.9[a]	86.5
Yang 2009[55]	11		346 (23-527)		189 (12-939)
Schukfeh 2012	21		337 (27-909)		11 (1-552)
Jankowska 2016	26	286.7 (130.8)		96.3 (94.3)	
Wassman 2018	10	266 (143)		56 (72)	
Bjornland 2020	24		339 (65-687)		60 (3-577)

Note: all values reported as µmol/L
[a] value was reported as a negative number in the publication
Abbreviations: PEBD, partial external biliary diversion; SD, standard deviation
Source: Albireo SLR and Meta-analysis on PEBD, 2021[57]

Results from the NAPPED study show that SBD is associated with a significant decrease in the levels of sBAs in PFIC1 and PFIC2 patients.[10,12] In addition, for patients with PFIC1, the post-SBD sBA levels were associated with presence of pruritus: patients with a post-SBD sBA <65 µmol/L were less likely to experience pruritus.

Data presented by the NAPPED Consortium support the impact of serum bile acid reduction and native liver survival rates across PFIC types.[10,12] Patients with PFIC2 have significantly higher native liver survival after biliary diversion surgery (Figure 32). Similarly, in PFIC1 SBD tended to be associated with NLS (Figure 34).

The beneficial impact of surgical biliary diversion on long-term native liver survival has also been shown to correlate with the reduction in serum bile acids observed following the surgery.[10,12,35] In those with PFIC2, reduction of bile acid levels below 102 µmol/L, or a 75% reduction from pre-diversion values, significantly increased native liver survival (Figure 33).[10] Recent analysis of patients with PFIC1 in NAPPED showed that post-SBD sBA level <65 µmol/L tended to be associated with prolonged NLS after SBD (P = 0.05; Figure 35).[12]

For further results from the NAPPED study see section 9.8.

A systematic literature review and meta-analysis by Verkade et al (2020)[58] evaluated relationships between liver biochemistry parameters and early response (pruritus improvement) or long-term outcomes (need for liver transplant) in patients with PFIC who underwent PEBD. In ROC analyses of individual patient data, post-PEBD concentration of

sBA, in particular, could discriminate responders from non-responders for pruritus improvement (area under the curve, 0.99; P<0.0001, n=42); to a lesser extent, this was also true for bilirubin. Reductions from pre-PEBD values in sBA concentration (0.89; p=0.0003; n=32) and bilirubin (0.98; p=0.002; n=18) significantly discriminated responders in terms of the need for liver transplant.

Albireo has recently updated this review with similar findings.[57] In this analysis, in ten studies that evaluated pruritus improvement post-PEBD, [redacted] had an early response of pruritus improvement following PEBD [redacted] showed a partial response, and [redacted] patients were non-responders. Bile acid levels decreased in patients classified as responders [redacted], partial responders [redacted] and non-responders [redacted] In the ROC analysis, absolute post-PEBD bile acid levels could differentiate PFIC patients with an [redacted] Table 7).

Overall, among [redacted] in three studies reporting long-term outcomes, [redacted] did not receive a liver transplant (responders), and [redacted] needed a liver transplant and/or died during follow-up (non-responders). In the ROC analysis, absolute post-PEBD bile acid levels could differentiate patients who demonstrated [redacted] from those who required [redacted]; Table 7).

Table 7. Ability of Liver Biochemistry Parameters to Discriminate Responders from Non-Responders: Early and Long-Term Responses

ROC analysis	Bile acids AUC, *P* value	Bilirubin AUC, *P* value	ALT AUC, *P* value
Early response (pruritus improvement)			
Patients, n	[redacted]	[redacted]	[redacted]
Post PEBD level	[redacted]	[redacted]	[redacted]
Absolute reduction*	[redacted]	[redacted]	[redacted]
Percent reduction*	[redacted]	[redacted]	[redacted]
Long-term response (decreased need for liver transplantation)			
Patients, n	[redacted]	[redacted]	[redacted]
Post PEBD level	[redacted]	[redacted]	[redacted]
Absolute reduction*	[redacted]	[redacted]	[redacted]
Percent reduction*	[redacted]	[redacted]	[redacted]

* Reductions from pre-PEBD levels
Abbreviations: ALT, alanine transaminase; AUC, area under the ROC curve; PEBD, partial external biliary diversion; ROC, receiver operating characteristic
Source: Albireo SLR and Meta-analysis on PEBD, 2021[57]

However, for many patients, biliary diversion is not a permanent solution because of refractory pruritus or end-stage liver disease.[4,59] While successful surgery is associated with reduction in SBA, improved pruritus, better sleep and improved liver function, pruritus may return after a few years.[54] In a study of 24 patients (age 26 months [4 months–17y]) who received PEBD, 54% had a successful outcome with normalisation of serum bile acids. None of these cases showed any progression of cholestasis over a median follow-up of 9.8 years. In comparison, 46% cases failed to show normalisation of bile acids, with 9/11 of them requiring liver transplantation over a short mean follow-up period of 1.9 years.[54]

Biliary diversion surgery is an invasive procedure with unwanted consequences. Patients experience complications related to the external stoma requiring surgical revision, and biliary diversion can lead to post-operative cholangitis.[1] High rates of clinically significant dehydration and hyponatremia have also been reported after biliary diversion surgery.[26]

As with any surgery, there are associated risks. Post-surgery complications may occur following PEBD. Amongst 40 PEBD surgeries in one study, complications included one patient with intestinal ischemia, three with stoma prolapses, one with bowel obstruction, and four episodes of dehydration/electrolyte derangements.[11]

There is also the risk of negative feelings due to the creation of a stoma, such as anxiety, depression and anguish, often concomitant with concerns about social life and insecurity by reintegration of previous social roles and functions[60]. Indeed, some caregivers decline surgery due to the stoma, drainage bag, nasogastric tubing, complications of PEBD, its unpleasantness or feeling it is an extreme measure for a young child. There is also the infection risk, stoma complications, psycho-social stigma and electrolyte imbalance.[61]

Partial internal biliary diversions (PIBDs), a relatively recent technique, represent an alternative to PEBD. Initial results from these techniques have been promising, but longer follow-up data are needed.[26] As with any surgery there is a risk of complications with PIBD. In a patient testimonial (provided during the PFIC Network at a meeting with the FDA; https://www.youtube.com/watch?v=rfESst9x19I&t=988s; time reference 14 minutes, 40 seconds), one parent describes the severe complications experienced following PIBD. Although initially successful, the child went on to suffer severe life-threatening vitamin K deficiency.

Ileal exclusion/bypass (IE) is a technique where an ileocolonic anastomosis is made, bypassing the distal 15% of small intestine and interrupting the enterohepatic circulation of bile salts by decreasing the reuptake of bile components.[1] This type of surgery is not commonly carried out (approximately 15% of SBD[10,12]) but can be used in patients with previous cholecystectomy, and aims to avoid an external stoma and related complications. The disadvantage is that ileal adaptation occurs in time and symptoms recur in the majority of patients by the end of first year.

8.2.6 Liver transplant

Most PFIC patients ultimately require liver transplantation. Even though current oral therapy and/or surgical therapy, such as biliary diversion, might provide some symptomatic relief, in the majority of cases LTx is required because of severe cholestasis and unremitting pruritus, hepatic failure, or hepatocellular carcinoma.[13,14] Studies have shown that survival in patients with PFIC not undergoing surgical diversion or LTx is 50% at the age of 10 and almost none at the age of 20 years, highlighting the rate of progression and the life-threatening nature of the disease.[2]

The age at which a transplant occurs is variable based on disease severity. PFIC2 patients tend to require a transplant earlier in their lives (2–3 years), compared with PFIC1 patients who can survive up to 10 years old before transplant is required.[1,3] While some PFIC3 patients respond to UDCA treatment, those who do not receive or respond to UDCA undergo LTx at a mean age of 6.9 years.[39]

However, LTx is not considered a cure by physicians for the following reasons:

- Patients still require monitoring for intestinal and pancreatic complications
- All patients require immunosuppression
- Occurrence of extrahepatic complications in some subtypes
- Disease recurrence post-LTx has been found

It should be recognised that LTx is a complicated surgery associated with significant risks including infection and rejection.[2] For liver transplant of patients <18 years old, the 1-year rejection rate is 24.7% and for patients 18 years or older, 1-year rejection rate is 11.7%.[62] Also, one study showed that in two *ATP8B1* children, despite successful liver transplantation, evolution (follow-up: 9.5–11 years) was characterised by exacerbation of diarrhoea and no catch-up of stature growth, and appearance of liver steatosis. In addition

to diarrhoea, pancreatitis and sensorineural deafness have been described in patients with normal GGT PFIC.[63]

The need for suitable organ donors also needs to be considered. In the UK, the number of patients on the active liver transplant list as of February 2020 was 466, an increase of 8% from 2019.[64]

Nearly a quarter of all liver transplants in children fail within the first six months, almost a third within 5 years and almost half within 20 years[65] (Table 8).

Table 8. Overall and graft survival in paediatric patients receiving a liver transplant

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%

806 children received 1,016 isolated paediatric liver transplantation between February 1984 and June 2017 at a sinle-centre in the US. Median follow-up was 12 years. Leading indications for liver transplantation were cholestatic liver disease (40%), retransplantation (21%), and fulminant hepatic failure (14%).
Source: Venick et al, 2018[65]

As described above, many individuals with PFIC and their caregivers tend to be anxious about LTx, feeling that it is extreme and will lead to complications in daily life. Patient testimonials illustrate the impact further:

Girl with PFIC2: *"[The child] must now be closely monitored because of the high risk of complications associated with transplant surgery, and because of unique complications associated with PFIC. Because [the child] has a compromised immune system, she is home schooled to reduce her risk of infection. She is held back from activities that may cause her to get sick, like play dates.*

"We knew that a liver transplant was the right decision. But it was extremely hard to accept that this is what needed to happen. We kept thinking that maybe if she was born ten years from now there would be medications or other treatment options that could help or cure her."

Boy with PFIC2: *"After experiencing a bout of rejection almost immediately following the transplant, he also had to be treated for post-transplant lymphoma for about a year, which can be a complication of transplant. Now at age five, his liver is functioning well. However, the immunosuppressants he will need to take for the rest of his life"*

Girl with PFIC3 (UK): *"It was so hard for us to watch our child suffer through surgery and being on a ventilator. Allowing your child to undergo a transplant is not an easy decision. If patients had an option to take a pill every day that could help them avoid that pain and enjoy their lives, that would be a wonderful option."*

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

8.3.1 Diagnosis

Physicians acknowledge that diagnosis of PFIC without expertise is extremely difficult. Therefore, several delays can occur in the patient flow:

- If a paediatrician/GP does not send the patient to a specialist who is familiar with PFIC, the diagnosis can be delayed, as a general hepatologist or gastroenterologist will need to refer again.
- Delay can be caused by attributing itch to non-liver issue e.g. sending patient to a dermatologist.
- Physician may also ignore prolonged jaundice, attributing it to random jaundice or breast milk jaundice.

Most PFIC patients will reach the paediatric hepatologist/gastroenterologist on referral from the paediatrician and often the referral is in acknowledgement of a liver problem due to symptoms.

Since variation in symptom presentation highlights the challenge in diagnosing PFIC, patients often go through a rigorous process of ruling out other conditions before eventually arriving at a diagnosis. As genetic analysis is uncertain in a significant proportion of patients, the diagnosis is primarily clinical.

8.3.2 Unmet need

PFIC is fatal if untreated and is associated with significant morbidity where the treatment options of off-label medicines, SBD or LTx are insufficient. There are no pharmacologic treatment options approved for patients with PFIC that relieve symptoms or prevent disease progression.

Off-label treatments include UDCA, bile acid sequestrants and agents for the symptomatic relief of pruritus, such as antihistamines and rifampicin.[4] However, as described above, less than half of patients have improvements in pruritus of liver function tests in response to UDCA. Cholestyramine and rifampicin do not appear to be effective in patients with *ATP8B1* or *ABCB11* mutations and, furthermore, rifampicin has a potential hepatoxic effect.[66]

The limited benefit of off-label therapies and the lack of evidence regarding their use in PFIC lead to a great deal of uncertainty regarding pharmacological treatment, leaving surgery as the only remaining treatment option.

In terms of surgical options, PEBD and LTx are complex, risky procedures with significant impact on the patient/carer and associated costs to the healthcare system. Even though PEBD can be a successful treatment, whereby 50%-100% of the re-absorption via IBAT is interrupted, there is the risk of peri-operative complications; a second problem is that many of these young patients have difficulties in accepting a stoma. In addition, many patients will not respond to PEBD and it is not possible to predict which patients will respond. Even when listed for LTx, availability of a donor liver is uncertain. LTx is not curative, patients may experience rejection of the liver and transplant-related complications, and recurrence of disease may necessitate a second transplant.[59]

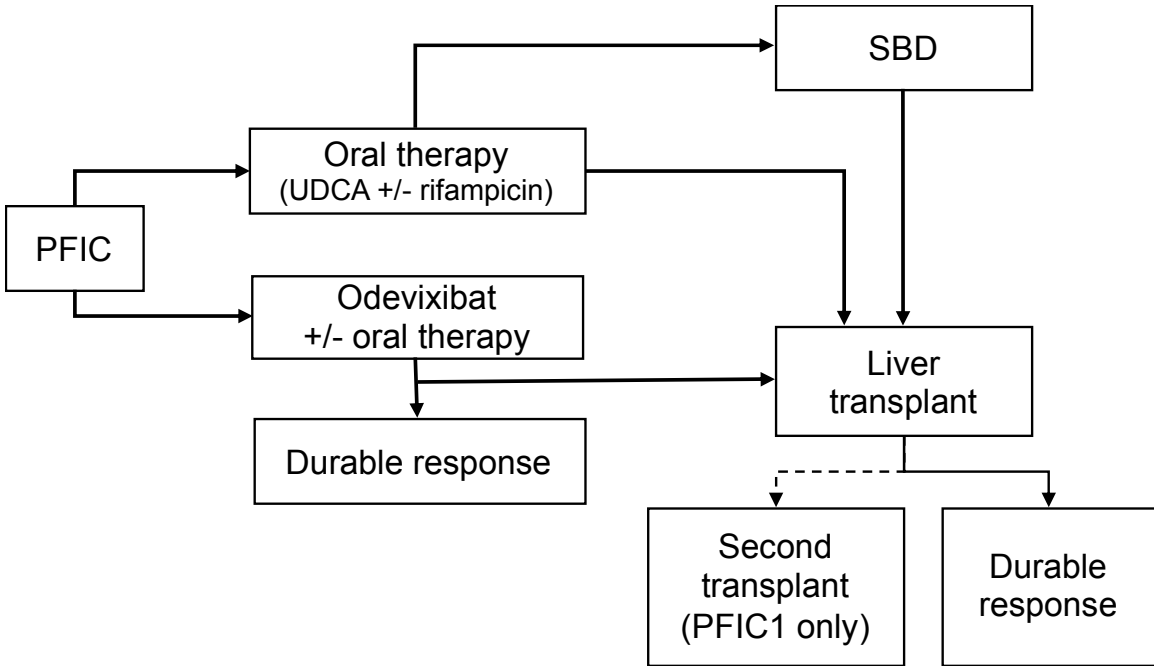
8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

According to experts, odevixibat is best positioned first-line, either with or without off-label oral therapies (Figure 8) for the following reasons:

- All PFIC subtypes, regardless of the underlying genetic mutation, result in cholestasis characterised by elevated bile acid concentrations and intense pruritus. These features of PFIC are clinically relevant; elevated bile acid concentrations because they lead to ongoing hepatocyte damage and progressive live disease, and pruritus because it is often the most troubling symptom, frequently leading to liver transplantation in patients with PFIC.

- Odevixibat directly addresses the elevated serum bile acids and pruritus by inhibiting IBAT in the terminal ileum, transporters common to patients with all PFIC subtypes. The site of action of odevixibat is distal to the underlying biochemical abnormalities and is independent of the genetic abnormalities responsible for the different PFIC subtypes.
- Reducing serum bile acids is associated with improvement in short-term (pruritus) and in long-term clinical outcomes in patients with PFIC.[58]
    - Data from the NAPPED study show that biliary diversion surgery is associated with significantly higher native liver survival. Furthermore, serum bile acid levels after diversion are associated with native liver survival.
- Data from the odevixibat Phase 2 study, A4250-003, provide further support for the finding that reducing serum bile acids is correlated with improvement in pruritus.

Figure 8. Position of odevixibat in the treatment pathway for PFIC



8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Odevixibat is a novel bile acid modulator which is expected to be the first licensed pharmacological treatment for PFIC using pivotal phase III data to show reduction in serum bile acids, the underlying cause of the disease. It is likely to be the first ileal bile acid transporter (IBAT) inhibitor approved globally. Odevixibat is a once-daily oral medication, delivered in a capsule which can be opened and emptied into food for younger children.

Odevixibat is a potent and selective inhibitor of the IBAT, sometimes referred to as the apical sodium dependent bile acid transporter (ASBT), that has minimal systemic exposure at therapeutic doses and acts locally in the gut.

There are currently no effective or approved pharmacological treatments for PFIC (standard medical treatments are supportive only). Therefore, new, non-invasive options like odevixibat represent a step-change in management of the condition because existing treatments have significant risk of treatment failure and disease recurrence and can be extremely invasive.

Partial external biliary diversion is one approach to reducing pathologic bile acid accumulation in the body by diverting bile acids to an external stoma.[50] It involves the use of stoma, drainage bags, and nasogastric tubing, which presents a difficult choice for the parents of the children. Internal biliary diversions have also been performed and while initial results from these techniques have been promising, longer follow-up data are needed.[67]

Liver transplantation is typically viewed as an option when patients have failed medical treatment and/or biliary diversion and have a poor quality of life (QoL) due to refractory pruritus, impaired growth, and/or irreversible fibrosis, cirrhosis and end-stage liver disease. However, liver transplantation is a complicated surgery with a 10-20% mortality rate; it is associated with significant risks, including infection and rejection and the need for lifelong anti-rejection medication, and is not always curative.[2,26] In addition, there is a shortage of suitable organ donors.

Survival in patients with PFIC not undergoing surgical diversion or liver transplant is 50% at the age of 10 and almost none at the age of 20 years, highlighting the rate of progression and the life-threatening nature of the disease.[2]

Treatment with odevixibat improves pruritus, reduces serum bile acid, is well tolerated and has the potential to delay liver transplant in patients who would otherwise have been transplanted due to uncontrolled severe pruritus or progression to cirrhosis and end stage liver disease, as well as avoiding the need for biliary diversion surgery.

PFIC has profound impacts beyond physical and mental health alone (as captured through EQ-5D) including but not limited to educational attainment, ability to work, ability to contribute to society, ability to make and keep friends, and so on. These broader impacts of the disease could be reduced with better control.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

No changes to the way services are delivered are expected as a result of odevixibat introduction.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

There are no additional monitoring requirements and no special warnings associated with the use of odevixibat.[15]

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure are required.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Odevixibat is expected to remove the need for biliary diversion surgery. Odevixibat has the potential to delay or avoid liver transplant in patients who would otherwise have been transplanted due to uncontrolled severe pruritus or progression to cirrhosis and end-stage liver disease due to persistently elevated sBA.

Section C — Impact of the new technology

9 Published and unpublished clinical evidence

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A systematic literature review (SLR) was carried out to identify clinical evidence for treatments for PFIC. The review was broad, including all PFIC subtypes, and both randomised controlled trials (RCTs) and non-randomised controlled studies and uncontrolled studies. The interventions included odevixibat, surgery (including partial external biliary diversion and internal ileal exclusion), liver transplant, and off-label pharmacological treatments (UDCA and rifampicin).

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

The EU Clinical Trials Register (Clinicaltrialsregister.eu), the U.S. National Institutes of Health clinical trials registry and results database (clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/) were searched to identify ongoing studies or results that may not have been published.

Since the clinical trial data for odevixibat are yet to be fully published, Albireo has provided all relevant unpublished data that supports the regulatory application in the indication related to this submission.

9.2 Study selection

Published studies

9.2.1 Complete Table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

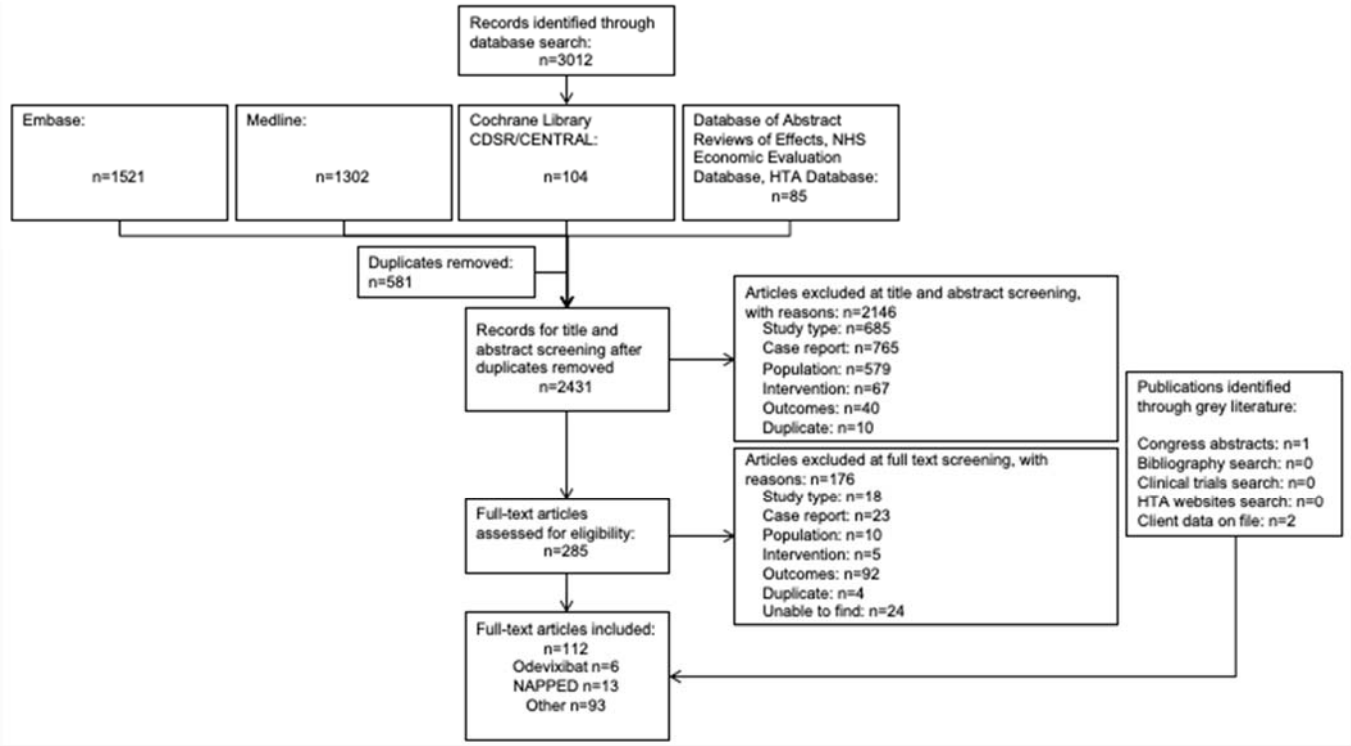
Table 9. Selection criteria used for published and studies

Inclusion criteria	
Population	People with progressive familial intrahepatic cholestasis (PFIC) Note: All PFIC subtypes will be eligible for inclusion, extracted as defined in the study, including, but not limited to: • PFIC1 (Byler disease, FIC1 deficiency) • PFIC2 (bile salt export pump [BSEP] deficiency, Byler Syndrome) • PFI3 (multidrug-resistant 3 protein [MDR3] deficiency) • PFIC 4 (Tight junction protein two [TJP 2] gene (chromosome 9) subtype) • PFIC5 (farnesoid X receptor [FXR] mutations) • PFIC6 • Benign recurrent intrahepatic cholestasis (BRIC) 1 • BRIC2 • Unspecified types of PFIC or BRIC
Interventions	• Odevixibat (A 4250, A4250) • Surgery (including partial external biliary diversion and internal ileal exclusion) • Liver transplant • Ursodeoxycholic acid • Rifampicin/rifampin
Outcomes	**Clinical efficacy or effectiveness:** • Change in serum bile acid level • Change in symptoms of PFIC including, but not limited to, a reduction in pruritus • Measures of faltering growth • Overall survival • Measures of disease progression • Number of patients requiring surgical interventions • Quality of life • Improvement in sleep parameters • Improvement in hepatic biochemistry parameters (AST, ALT, bilirubin) **Safety** • Adverse effects of treatment • Mortality
Study design	• Randomised controlled trials • Non-randomised controlled studies • Non-controlled studies
Language restrictions	No restriction
Search dates	No restriction; any study date
Exclusion criteria	

Population	Any other population
Interventions	Any other treatment
Outcomes	Any other outcomes
Study design	• Animal studies • In-vitro studies • Editorials • Reviews • Letters • Comments • Notes • Erratum • Case studies or case series of population size n<5 SLRs will be included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.
Language restrictions	No restriction
Search dates	No restriction; any study date

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 9. Clinical SLR PRISMA



Unpublished studies

9.2.3 Complete Table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Inclusion and exclusion criteria were as per Table 10.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

See Figure 9.

9.3 Complete list of relevant studies

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

9.3.1.1 Odevixibat

The odevixibat studies are listed in Table 10.

The primary data in support of the efficacy of odevixibat are derived from PEDFIC1 (study A4250-005), a completed Phase 3, randomised, double-blind, placebo-controlled, 24-week study of 2 dose levels of odevixibat, 40 and 120 µg/kg/day, conducted in paediatric patients with PFIC1 or PFIC2. PEDFIC1 is the largest phase 3 PFIC randomised study conducted to date.

Long-term efficacy data are available from PEDFIC2 (Study A4250-008), an ongoing, open label, 72-week extension study of odevixibat 120 µg/kg/day, including patients with any type of PFIC.

Supportive efficacy data for the proposed indication are provided by the results of the 4-week, Phase 2 study, A4250-003, which evaluated multiple dose levels of odevixibat up to 200 µg/kg/day in patients with cholestatic pruritus.

The odevixibat clinical trials are not yet fully published, therefore the information presented in the submission is taken from the clinical study reports (CSRs).

Manuscripts relating to the phase 2 study and PEDFIC1 have been submitted for publication.[68,69] A manuscript relating to the interim PEDFIC2 data is in development.

Conference abstracts relating to the odevixibat studies identified in the SLR are listed in Table 11.

Table 10. List of relevant unpublished studies

Primary data source	Study name (acronym)	Description	Population	Intervention	Comparator	Status
Clinical study report: protocol A4250-003	**A4250- 003** **Phase 2**	An exploratory study to demonstrate the safety and efficacy of odevixibat in children with cholestatic pruritus	Paediatric chole-stasis N=20	Odevixibat, from 0.01 to 0.2 mg/kg/day	None	Completed
Clinical study report: protocol A4250-005	**A4250- 005** **PEDFIC 1** **Phase 3**	A double-blind, randomised, placebo-controlled study to demonstrate efficacy & safety of odevixibat.	Children with PFIC1 & 2 N=62	Odevixibat, once daily oral administration of 40 or 120 µg/kg/day, 6 months	Placebo	Completed
Clinical study report: protocol A4250-008	**A4250- 008** **PEDFIC 2** **Phase 3**	An open-label extension study to evaluate long-term efficacy & safety of odevixibat	Cohort 1: Children with PFIC 1 & 2 (who participated in PEDFIC1 Cohort 2: People with PFIC (including those with other PFIC types such as PFIC3 and PFIC 6 already enrolled) N=120	Odevixibat, once daily oral administration of 120 µg/kg/day, 18 months (24 months for patients on active drug in A4250-005)	None	Enrolling

Table 11. List of available conference abstracts or posters for the odevixibat studies

Study name (acronym)	Citation
A4250- 003 Phase 2	Baumann U, Lacaille F, Sturm E, Gonzales E, Arnell H, Jørgensen MH, Thompson RJ, Ekelund M, Mattsson JP, Lindström E, Gillberg PG. The Ileal Bile Acid Transport inhibitor A4250 decreases pruritus and serum bile acids in cholestatic liver diseases–an ongoing multiple dose, open-label, multicentre study. Journal of Hepatology. 2017 Jan 1;66(1):S91
	Sturm E, Baumann U, Lacaille F, Gonzales E, Arnell H, Fischler B, Jorgensen MH, Thompson RJ, Mattsson J, Ekelund M, Lindstrom E et al. The ileal bile acid transport inhibitor a4250 reduced pruritus and serum bile acid levels in children with cholestatic liver disease and pruritus: Final results from a multiple-dose, open-label, multinational study. Journal of Pediatric Gastroenterology and Nutrition. 2017; 65(S2): S168-S169
	Sturm E, Baumann U, Lacaille F, Gonzales E, Arnell H, Fischler B, Jorgensen MH, Thompson RJ, Mattsson J, Ekelund M, Lindstrom E et al. The ileal bile acid transport inhibitor A4250 reduced pruritus and serum bile acid levels in children with cholestatic liver disease and pruritus: final results from a multiple-dose, open-label, multinational study. Hepatology 2017 Oct 1;66(S1):646A-647A
PEDFIC 1	Thompson RJ, Kjems L, Hardikar W, Lainka E, Calvo PL, Horn P. Improved Quality of Life in Children With Progressive Familial Intrahepatic Cholestasis Following 24 Weeks of Treatment With Odevixibat, an Ileal Bile Acid Transporter Inhibitor- Results From the Phase 3 PEDFIC 1 Study. Value in Health. 2021;24(5):S1
	Thompson RJ, Baumann U, Czubkowski P, Dalgic B, Durmaz Ö, Grammatikopoulos T, Gupte G, Kjems L, Lachaux A, Mattsson JP, McKiernan P, Rajwal SR, Shagrani MA, Sturm E, Verkade HJ, Horn P. Efficacy and Safety of Odevixibat, an Ileal Bile Acid Transporter Inhibitor, in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2: Results From PEDFIC 1, a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial. AASLD The Liver Meeting. November 2020.
PEDFIC2	Thompson RJ, Artan R, D'Antiga L, Houwen RHJ, Kamath BM, Kjems L, Lacaille F, Mattsson JP, Özen H, Roquelaure B, Shteyer E, Tessier ME, Wallefors T, Warholic N, Horn P. Long-term Efficacy and Safety of Odevixibat, an Ileal Bile Acid Transporter Inhibitor in Children With Progressive Familial Intrahepatic Cholestasis: Interim Results From PEDFIC 2, an Open-Label Phase 3 Trial. Presented at the Annual Meeting of the American Association for the Study of Liver Diseases, November 13–16, 2020

9.3.1.2 Comparator studies

The PEDFIC1 study was a placebo-controlled study. In clinical practice, odevixibat may be used in addition to off-label oral therapies (as was the case in the Phase 3 clinical trial).

As described in section 8, there is currently no pharmaceutical treatment alternative approved for use in PFIC and very limited evidence to support the use of off-label treatments such as UDCA. The SLR identified 21 studies that reported on the use of UDCA or rifampicin in patients with PFIC. These are listed in Section 17.6 and described in Section 8.2.4.

In clinical practice the use of pharmaceutical therapies may be reduced or obviated by the use of odevixibat but they may still be used to provide short-term supportive care alone or in addition to odevixibat. This is reflected in the design of the placebo-controlled Phase 3 trial in which patients could continue to receive treatments such as UDCA and rifampicin.

Since PEDFIC1 provides comparative data in patients receiving odevixibat in addition to off-label oral therapies compared to off-label therapies alone, no further analysis of the 21 UDCA or rifampicin studies was carried out.

As symptomatic treatment is rarely effective, surgical options are considered, including PEBD and liver transplantation. Odevixibat is the medical equivalent of PEBD and therefore it is considered as the relevant comparator. No head-to head studies of odevixibat and PEBD were identified in the SLR.

As described in section the NAPPED consortium has the largest genetically defined cohort of PFIC patients to date, providing retrospective analysis of 130 PFIC1 and 264 PFIC2 patients (at latest data cut-off) in >50 centres globally.[10,12] The NAPPED study compares outcomes in PFIC1 and PFIC2 with or without biliary diversion surgery.

The NAPPED studies are described in detail in section 9.8. A complete list of citations for NAPPED analyses and a critical appraisal is shown in Appendix 17.6.

An additional 43 studies examining SBD in patients with PFIC were identified. These studies were all non-controlled studies of smaller size and are not included in the clinical evidence section.

36 additional studies investigating outcomes in patients receiving LTx were identified (7 also investigated SBD and are included in the 44 studies above). Since LTx is not a

comparator in this submission, these studies are not included in this clinical evidence section.

9.3.2 State the rationale behind excluding any of the published studies listed in Tables C3 and C4.

No studies were excluded.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using Tables C5 and C6 as appropriate. A separate table should be completed for each study.

9.4.1.1 Phase 2 study (A4250-003)

This was an exploratory Phase 2 single and multiple dosing open-label dose-escalating study (EudraCT 2015-001157-32) of odevixibat to evaluate its safety and efficacy when administered for 4 weeks in 20 paediatric patients diagnosed with cholestatic pruritus (PFIC, ALGS, BA, SC or other types of cholestasis).[70]

The study was conducted at six active sites and included five dose cohorts (0.01 mg/kg/day, 0.03 mg/kg/day, 0.06 mg/kg/day, 0.1 mg/kg/day and 0.2 mg/kg/day), with four or six patients in each cohort. Four of the 20 enrolled patients were re-enrolled into a later cohort after completion and a washout period, with at least two dose cohorts between the enrolments.

Ten patients with PFIC were included (including patients who re-enrolled, a total of 13 patients with PFIC were treated across the dose groups). The study included two patients with PFIC3.[70]

The primary aims were to:

- Assess the safety and tolerability of odevixibat, orally administered first as a single dose and then during a 4-week treatment period, as determined by the occurrence of treatment-emergent SAEs
- Explore changes in serum bile acid levels after a 4-week treatment period

As this was an exploratory study that does not include treatment at the expected licensed dose, the efficacy results are not presented in detail in the submission. However, since

PFIC specific data including data from two patients with PFIC3 are available, these results have been included. In addition, safety results have been presented.

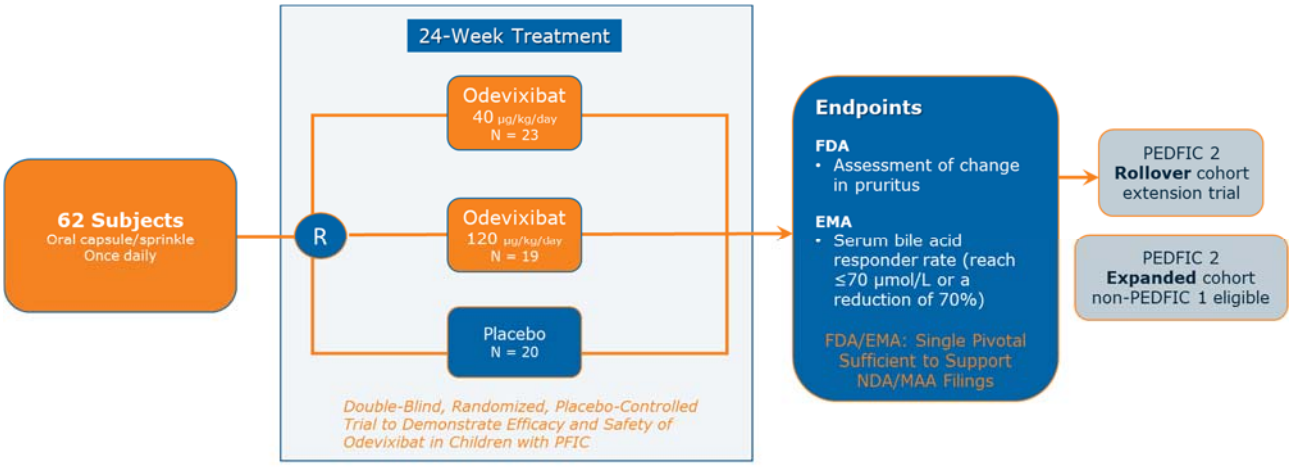
Detailed methodology and a critical appraisal can be found in Appendix 5.

9.4.1.2 PEDFIC 1

PEDFIC1 (A4250-005) was a multicentre, double-blind, randomized, placebo-controlled, Phase 3 study to demonstrate efficacy and safety of odevixibat in children with PFIC1 and PFIC2.[16,17] Patients who completed the PEDFIC1 treatment period could continue into an optional 72-week open-label extension study (PEDFIC 2; A4250-008) in which all patients received odevixibat.

PEDFIC1 was a six-month study with two dose levels of odevixibat (40 and 120 µg/kg/day) in 62 patients (Figure 10). The study was conducted at sites in the US, Canada, the EU, the Middle East, and Australia.

Figure 10. PEDFIC 1 Phase 3 study design



Source: PEDFIC1 CSR[16]; Thompson et al, 2020[17]

Table 12. Summary of methodology for randomised controlled trials (PEDFIC1)

Study name	A4250-005; PEDFIC1
Objectives	The primary objectives were to demonstrate the efficacy of repeated daily doses of 40 µg/kg/day and 120 µg/kg/day odevixibat in children with progressive familial intrahepatic cholestasis (PFIC) Types 1 and 2, as determined by the following: • Proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to end of treatment or reaching a level ≤70 µmol/L compared to placebo after 24 weeks of treatment • Proportion of positive pruritus assessments at the subject level over the 24-week Treatment Period
Location	US, Canada, the EU, the Middle East, and Australia
Design	Double-blind, randomized, placebo-controlled, Phase 3 study
Duration of study	24 weeks

Sample size	N=62
Key inclusion criteria	• A male or female patient, with clinical diagnosis of PFIC Type 1 or 2, between the ages of ≥6 months and ≤18 years at Visit 1 with a body weight above 5 kg • A clinical genetic confirmation of PFIC1 or PFIC2 through identification of biallelic pathogenic variants in either the ATP8B1 or ABCB11 genes • Patient must have elevated sBA concentration, specifically measured to be ≥100 µmol/L, taken as the average of two samples at least 7 days apart (Visits 1 and 2) prior to randomization • Patient must have history of significant pruritus and a caregiver-reported observed scratching in the electronic diary (eDiary) average of ≥2 (on 0 to 4 scale) in the 2 weeks prior to randomization • Patient and/or legal guardian must sign informed consent (and assent) as appropriate. Patients who turn 18 years of age (or legal age per country) during the study will be required to re-consent in order to remain in the study • Patients are expected to have a consistent caregiver for the duration of the study
Key exclusion criteria	• Patient with pathologic variations of the *ABCB11* gene that predict complete absence of the BSEP protein • Patient with past medical history or ongoing presence of other types of liver disease including, but not limited to, the following: o Biliary atresia of any kind o Benign recurrent intrahepatic cholestasis, indicated by any history of normal sBAs o Suspected or proven liver cancer or metastasis to the liver on imaging studies o Histopathology on liver biopsy is suggestive of alternate non-PFIC related aetiology of cholestasis • Patient with a past medical history or ongoing presence of any other disease or condition known to interfere with the absorption, distribution, metabolism (specifically bile acid metabolism), or excretion of drugs in the intestine, including but not limited to, inflammatory bowel disease. • Patient with past medical history or ongoing chronic (i.e., >3 months) diarrhoea requiring intravenous fluid or nutritional intervention for treatment of the diarrhoea and/or its sequelae • Patient has a confirmed past diagnosis of infection with human immunodeficiency virus or other present and active, clinically significant, acute, or chronic infection, or past medical history of any major episode of infection requiring hospitalization or treatment with parenteral anti-infective treatment within 4 weeks of treatment start (study Day 1) or completion of oral anti-infective treatment within 2 weeks prior to start of Screening Period • Any patient with suspected or confirmed cancers except for basal cell carcinoma, and non-liver cancers treated at least 5 years prior to screening with no evidence of recurrence • Patient with a past medical history of chronic kidney disease with an impaired renal function and a glomerular filtration rate <70 mL/min/1.73 m^2 • Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period

	• Patient has had an LTx or an LTx was planned within 6 months of randomisation • Decompensated liver disease, coagulopathy, history or presence of clinically significant ascites, variceal haemorrhage, and/or encephalopathy • INR >1.4 (the patient may be treated with Vitamin K intravenously, and if INR is ≤1.4 at resampling the patient may be randomized) • Serum ALT >10 × upper limit of normal (ULN) at Screening • Serum ALT >15 × ULN at any time point during the last 6 months unless an alternate aetiology was confirmed for the elevation • Total bilirubin >10 × ULN at Screening • Patient suffers from uncontrolled, recalcitrant pruritic condition other than PFIC. Examples include, but not limited to, refractory atopic dermatitis or other primary pruritic skin diseases • Patient who has been previously treated with an IBAT inhibitor whose pruritus has not responded to treatment
Method of randomisation	After completion of the Screening Period, eligible patients (20 per treatment group) were randomised on Day 0 (Visit 3) in a 1:1:1 fashion to receive 40 µg/kg/day or 120 µg/kg/day of odevixibat, or a matching placebo. After written informed consent was obtained, an 8-digit patient identification number was assigned by the Interactive Web Response System (IWRS). Patients determined to be eligible for randomisation were assigned a unique 4-digit randomisation number by the IWRS that identified which treatment was allocated to the patient. Randomisation was done in block size of 6 and stratified according to PFIC type (Type 1 or 2) and age group (6 months to 5 years, 6 to 12 years, and 13 to ≤18 years) to ensure approximate balance between dose schemes (1:1:1).
Method of blinding	This was a double-blind study. To ensure blinding of treatment assignment, the study drug and the matching placebo had the same shape and size. Labels on the study drug containers did not identify the randomised treatment assignment. Traceability of the treatment was ensured by the study drug number that corresponded to the randomisation arm and was assigned by the IWRS. Additionally, in order to maintain the blind, all serum bile acids results during the treatment period and at follow-up were blinded; samples were processed at a central laboratory.
Intervention(s) (n =) and comparator(s) (n =)	Odevixibat 40 µg/kg/day (n=23) Odevixibat 120 µg/kg/day (n=19) Placebo (n=20)
Baseline differences	With regard to age, PFIC type, concentration of bile acids and level of pruritus, the groups are well balanced.
Duration of follow-up, lost to follow-up information	Overall, 49 (79%) patients completed the planned 24-week treatment period, 11 patients rolled over to the long-term extension trial prior to completion of 24 weeks of treatment per protocol due to intolerable symptoms after completing between 12 and 18 weeks, 1 patient discontinued treatment due to an AE of diarrhoea, and 1 patient discontinued for other reasons (non-compliance/inability to travel to the site).
Statistical tests	**Sample size and power** Approximately 60 patients diagnosed with PFIC1 or PFIC2 would be randomised, with a target of 15% to be PFIC1 patients. If enrolment of all PFIC2 patients was complete and the 15% enrolment of PFIC1 patients had not yet

	been achieved, then enrolment of PFIC2 patients would continue to reach the total study target enrolment. **Primary endpoint analysis** The primary objective of this study was to demonstrate the efficacy of repeated daily doses of 40 µg/kg/day and 120 µg/kg/day odevixibat in children with PFIC1 and PFIC2. The Cochran Mantel Haenzel (CMH) test stratified by PFIC class and age class was performed to compare the proportion in fasting bile acid responders at the end of treatment (Week 22 and 24) in the two odevixibat dose groups to the placebo group. To ascertain that all data are used in the CMH analysis, neighbouring strata were pooled when all subjects in a stratum had the same response. The proportion together with the corresponding 95% CI, odds ratio and corresponding 95% Clopper-Pearson exact CI and p-value for the CMH test was presented. For the primary efficacy variable of the proportion of positive pruritus assessments at subject level over the 24-week treatment period, an ANCOVA model was used to analyse the comparisons between the treatment groups. The model included treatment arm, AM baseline pruritus score, PM baseline pruritus score, and randomisation stratification factors, i.e. PFIC class and age class. LS mean (SE) by treatment arm and LS mean difference (SE), 95% confidence intervals, and p-values (where applicable) between treatments (120 µg/kg/day and 40 µg/kg/day, respectively) vs. placebo were provided. LS mean/SE on the outcome by treatment arm and LS mean difference/SE between active dose and placebo were determined. For each primary endpoint by region (EU & RoW and US), a pooled analysis for the closed testing procedure was applied to control the 1-sided overall type I error rate for two treatment comparisons vs. the placebo at the 0.025 level, as specified below: • In the closed testing procedure, the low and high dose groups were pooled to compare with the placebo group first. If the 1-sided p-value was ≤0.025, the 1-sided p-values for low dose vs. placebo and high dose vs. placebo would be calculated respectively. • If both individual p-values were ≤0.025, a significant treatment effect would be declared on both dose groups. • If only one of them was ≤0.025, a significant treatment effect would be declared on the corresponding dose group. For the pruritus primary endpoint, all intermittently missing assessments were classified as non-positive pruritus assessments and all missing planned assessments after premature treatment discontinuation were counted as non-positive pruritus assessments. All planned assessments after death or initiation of rescue treatments such as biliary diversion surgery or liver transplantation were counted as negative pruritus assessments. For the SBA primary endpoint, the end value was calculated as the average of the values at Weeks 22 and 24 after the start of treatment. If one value was missing, then the non-missing value was used as the end value. If both values were missing, then the end value was considered missing. Patients with missing data at the end of treatment were classified as non-responders.

	Key secondary endpoint analysis No adjustments for other secondary and exploratory outcome variables were for performed for multiple comparisons.
Primary outcomes (including scoring methods and timings of assessments)	**EU and RoW** • Proportion of patients experiencing at least a 70% reduction in fasting SBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L compared to placebo after 24 weeks of treatment. **US** • Proportion of positive pruritus assessments at the subject level over the 24-week Treatment Period. Positive pruritus assessment defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the Albireo ObsRO instrument (see o Figure 13 and section 9.4.1.4 below). o Completed twice daily by the caregiver
Secondary outcomes (including scoring methods and timings of assessments)	**EU and RoW** • Proportion of positive pruritus assessments at the subject level over the 24-week Treatment Period. **US** • Proportion of patients experiencing at least a 70% reduction in fasting SBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L compared to placebo after 24 weeks of treatment. **All regions:** • Change from baseline to Week 12 and to Week 24 in fasting SBA, ALT and growth • Proportion of responders for pruritus scores at Weeks 12 and 24 based on the Albireo PRO and ObsRO instruments • Change in sleep parameters measured with the Albireo PRO and ObsRO instruments from baseline over the 24-week Treatment Period • Proportion of individual assessments meeting the definition of a positive pruritus assessment at the subject level over the 24-week Treatment Period. A positive pruritus assessment includes an itch score ≤1, or at least a one-point drop from baseline based on the Albireo PRO instrument; only patients ≥8 years of age will complete the Albireo PRO instrument • Proportion of individual assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0 – 20, Weeks 0-24, respectively, and the proportion of positive pruritus assessments at each 4-week interval. • Proportion of individual AM and PM assessments meeting the definition of a positive pruritus assessment at the patient level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, and the proportion of positive pruritus assessments at each 4-week interval. • Proportion of individual PM assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, or the proportion of positive pruritus assessments at each 4-week interval.

	• Number of patients undergoing biliary diversion surgery or liver transplantation • Number and percent of patients achieving positive pruritus assessment for more than 50% of the time during the 24-week treatment period.

9.4.1.3 PEDFIC2

PEDFIC2 is an ongoing Phase 3, multi-centre, open-label extension study to investigate the long-term efficacy and safety of a 120 µg/kg/day daily dose of odevixibat in patients with PFIC (Figure 11).[18,19] Cohort 1 consists of children with PFIC Types 1 and 2 who have participated in study PEDFIC1. Cohort 2 consists of patients with PFIC who have elevated sBAs and cholestatic pruritus and who either:

1. did not meet eligibility criteria for PEDFIC1, or
2. were eligible for enrolment in PEDFIC2 after recruitment to PEDFIC1 has been completed.

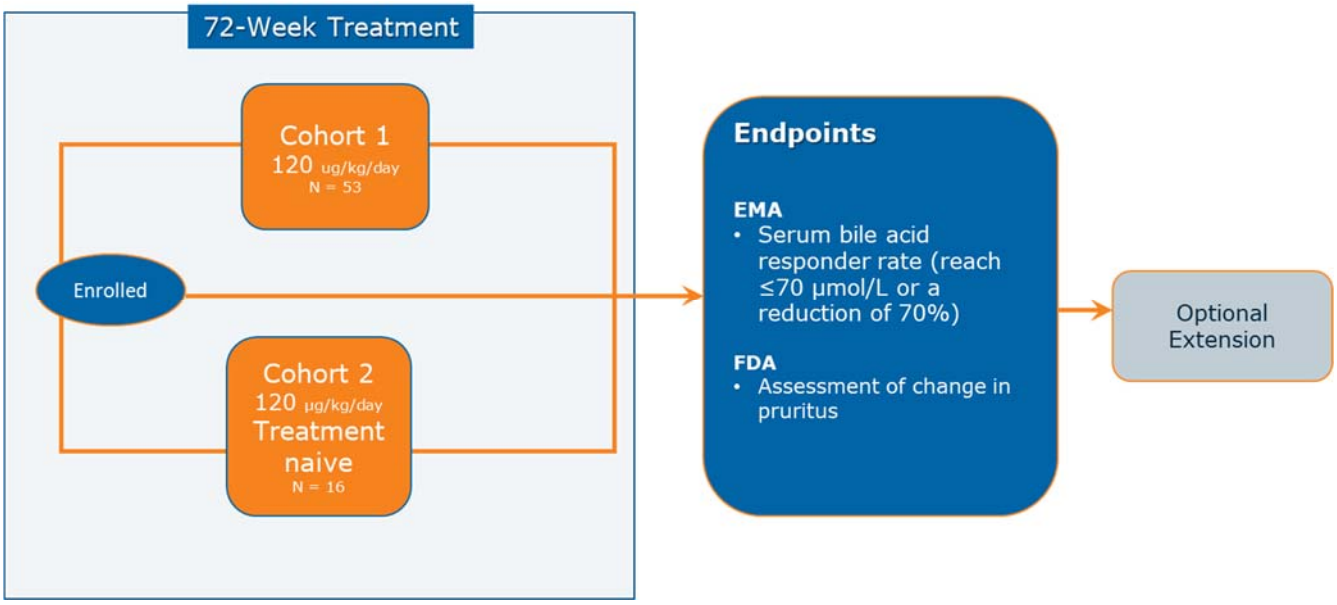
Eligible patients were enrolled into this open-label extension study and treated with a daily dose of 120 µg/kg/day of odevixibat for 72 weeks.

Patients not tolerating the 120 µg/kg/day dose after a minimum of one week have the option to down-titrate to a lower dose (40 µg/kg/day). The patient should return to the higher dose as soon as deemed appropriate by the investigator. However, more than one upward dose titration (from 40 µg/kg/day directly to 120 µg/kg/day) for the same event is not recommended.

Patients who wish to continue receiving odevixibat after 72 weeks will have the option to remain on treatment until the drug is commercially available, provided continued use is supported by the risk-benefit profile and the subject has not been previously withdrawn or discontinued from the study.

The primary analysis will be performed after the last patient (from Cohort 1 or 2) completes the 72-week treatment period. Analyses during the extension period will consist of safety summaries and other evaluations on an ongoing basis per the schedule of assessment for the extension period.

Figure 11. PEDFIC2 Open-label extension study



Note: patient numbers are as per the data cut-off of 15 July 2020
Source: PEDFIC2 CSR[18]; Thompson et al, 2020[19]

Table 13. Summary of methodology for randomised controlled trials (PEDFIC2 - extension)

Study name	A4250-008; PEDFIC2
Objectives	To investigate the long-term efficacy and safety of a 120 µg/kg/day daily dose of odevixibat in patients with PFIC
Location	US, Canada, the EU, the Middle East, and Australia
Design	Phase 3, multi-centre, open-label extension study
Duration of study	72 weeks
Sample size	N=120 (N=69 as of the data cut-off of 15 July 2020)
Inclusion criteria	**Cohort 1:** 1. Completion of the 24-week Treatment Period of Study PEDFIC1 or withdrawn from PEDFIC1 due to patient/caregiver judgment of intolerable symptoms after completing at least 12 weeks of treatment. 2. Patients expected to have a consistent caregiver for the duration of the study. Caregivers (and age-appropriate patients) must be willing and able to use an electronic diary (eDiary) device as required by the study **Cohort 2:** 1. A male or female patient of any age, with a clinical diagnosis of PFIC and with a body weight ≥5kg at Visit S-1 2. Patient must have clinical genetic confirmation of PFIC 3. Patient must have elevated SBA concentration, specifically measured to be ≥100 µmol/L, taken as the average of 2 samples at least 7 days apart (Visits S-1 and S-2) prior to the Screening/Inclusion Visit (Visit 1) 4. Patient must have history of significant pruritus and a caregiver-reported observed scratching or patient-reported itching (for patients >18 with no caregiver-reported observed scratching) in the eDiary

	average of ≥2 (on 0 to 4 scale) in the 2 weeks prior to the Screening/Inclusion Visit (Visit 1) 5. Age-appropriate patients are expected to have a consistent caregiver for the duration of the study 6. Caregivers and age-appropriate patients (≥8 years of age, if able) must be willing and able to use an eDiary device as required by the study
Key exclusion criteria	**Cohort 1:** • Decompensated liver disease: coagulopathy, history, or presence of clinically significant ascites, variceal haemorrhage, and/or encephalopathy. • Noncompliant with treatment in Study A4250-005. • Any other conditions or abnormalities which, in the opinion of the investigator or medical monitor, may compromise the safety of the patient, or interfere with the patient's participation in or completion of the study. **Cohort 2:** In Cohort 2 exclusion criteria were the same as for PEDFIC1, but did NOT exclude the following groups: 1. Patient with a past medical history of chronic kidney disease with an impaired renal function and a glomerular filtration rate <70 mL/min/1.73 m^2 2. Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period 3. Patient who has been previously treated with an IBAT inhibitor whose pruritus has not responded to treatment
Intervention(s) (n =) and comparator(s) (n =)	Odevixibat (n=69, as of July 2020)
Baseline differences	Differences between Cohort 1 and Cohort 2 are presented in section 9.4.3.
Duration of follow-up, lost to follow-up information	The primary analysis will be performed after the last patient (from Cohort 1 or 2) completes the 72-week treatment period. Analyses during the extension period will consist of safety summaries and other evaluations on an ongoing basis per the schedule of assessment for the extension period.
Statistical tests	Descriptive statistics will mainly be used in this open-label extension study. The proportion of positive pruritus assessments at the patient level over the 72-week treatment period will be summarized. All secondary and exploratory variables will be analysed descriptively for categorical and continuous data, as applicable. For continuous data, the change from baseline will be analysed in addition to the actual visit values. For categorical data, shift tables or frequency and percentages of patients will be presented as appropriate. Safety data will be analysed using descriptive statistics and summaries overall of SAEs, AEs, vital signs, clinical laboratory tests (haematology, clinical chemistry and urinalysis) and concomitant medication. Analyses will be performed using the full analysis set.

Primary outcomes (including scoring methods and timings of assessments)	**EU and ROW:** • Change from baseline in SBA after 72 weeks of treatment (reach ≤70 µmol/L or a reduction of 70%) **US:** • Proportion of positive pruritus assessments over the 72-week treatment period using the Albireo ObsRO instrument
Secondary outcomes (including scoring methods and timings of assessments)	**EU and ROW:** • Proportion of positive pruritus assessments using ObsRO instrument **US:** • Change from baseline in sBA **All regions:** • All-cause mortality • Number of patients undergoing BD • Number of patients listed for LT • Change in growth from baseline to weeks 24, 48 and 72 after initiation of A4250 treatment. Defined as linear growth deficit (height/length for age, weight for age and body mass index [BMI]) compared to a standard growth curve. • Change in AST to platelet ratio index (APRI) score and Fib-4 score • Change to paediatric end-stage liver disease (PELD)/model for end-stage liver disease(MELD) • Change in antipruritic medication • eDiary - Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument

9.4.1.4 Patient- and Observer-Reported Outcome Pruritus Measures: Summary of Measurement Characteristics

Patients with PFIC experience significant pruritus and reducing the severity of pruritus is a key objective of PFIC treatment.

Albireo conducted a literature review with the objective to identify the instruments that are currently used to measure pruritus in adolescents and adults. However, no publicly available instruments were found to adequately assess symptoms and impact from the paediatric PFIC patient and/or caregiver perspective. The Itch Reported Outcome instrument appeared to address pruritus in paediatric patients with cholestatic liver disease from both patient and caregiver perspectives, but it is not publicly available and therefore could not be used or adapted for the odevixibat programme.

Based on this review, Albireo developed novel patient-reported outcome (PRO) and observer-reported outcome (ObsRO; PRUCISION©; [redacted]

[redacted] Figure 12) instruments for the paediatric cholestatic liver disease population to assess itching, scratching, and sleep disturbance.[71,72] The quantitative measurement characteristics of these instruments, including assessment of the item performance and psychometric properties (reliability, validity, and sensitivity to change), were established through the analysis of the final data from PEDFIC1 conducted by a group independent of the sponsor that confirmed that the instruments were appropriate for their intended use.

The development of the PRO and ObsRO pruritus measures followed industry and regulatory best practice guidelines.[73-76] Several lines of evidence support the conclusion that the ObsRO measure is fit for purpose in evaluating changes in pruritus in PEDFIC1. Analyses were conducted on the PRO data despite the [redacted] However, the results may be [redacted] Figure 12. Validated PRUCISION (ObsRO) Instrument - Summary

[redacted]

The final ObsRO and PRO instruments focused on the key symptoms of pruritus, sleep disturbance and associated tiredness and used 0 to 4 pictorial response scales, where each response was distinguished by a unique facial expression, verbal anchor, number, and colour code.

- The ObsRO (PRUCISION©) instrument (completed by every patient's caregiver regardless of patient age), asks caregivers about the patient's scratching and other related behaviours observed during the daytime and night-time hours (

- Figure 13). [redacted] rating scales (e.g. 0 = no scratching 1 = a little scratching, 2 = medium scratching, 3 = a lot of scratching, 4 = worst possible scratching), [redacted]. Higher scores indicated a greater amount of scratching, sleep disturbance, and tiredness.
- The PRO instrument (for patients ≥ 8 years old) asked patients about their itching during the day and night-time hours (Figure 14). [redacted] (e.g. 0 = no itching, 1 = a little itching, 2 = medium itching, 3 = a lot of itching, 4 = the worst itching). Higher scores indicated a greater amount of itching, sleep disturbance, and tiredness.

The measurement characteristics of the ObsRO pruritus measure have been established. The measure is reliable, valid, and sensitive to change. Thresholds for meaningful change from Baseline to Week 24 have been established:

- The results of the blinded analysis established a threshold of a 1.0-point change as a clinically meaningful reduction in pruritus scores based on the ObsRO. It is anticipated that the 1-point reduction would be meaningful [redacted]

Therefore, the developed ObsRO instrument is fit for purpose in evaluating pruritus among paediatric patients with PFIC in the PEDFIC1 study [redacted] The measures may also be used in other cholestatic liver disease areas [redacted]

Figure 13. Albireo ObsRo instrument (PRUCISION©)

[redacted]

Figure 14. PRO Pruritus Items (Study A4250-005)

Morning Diary (to be completed shortly after waking each morning; measuring night-time pruritus)	
Please answer the questions on the following screens. There are no right or wrong answers. Please think about the time since you went to bed last night (beginning when you started trying to fall asleep)	
How bad was your worst itching since you went to bed last night?	
Bedtime Diary (to be completed when child is going to bed each night; measuring daytime pruritus)	
Please answer the questions on the following screens. There are no right or wrong answers. Please think about the time since you woke up this morning	
How bad was your worst itching since you woke up this morning?	

9.4.1.5 NAPPED

Owing to the rarity of the disease, the associations between PFIC genotype and natural history, or outcomes following PEBD, remain elusive. The NAPPED study aims to determine these associations by assembling the largest genetically defined cohort of patients with BSEP (PFIC2) and FIC1 (PFIC1) deficiency to date.

Albireo provides support for the NAPPED natural history study, where the data will support the Phase 3 programme by further demonstrating the importance of bile acid reduction for symptoms and disease modification as well as serving as a “control” arm for the open-label extension study (PEDFIC2).

The NAPPED natural history study provides a key source of comparative data for this submission. Data from this study are available in PFIC1 and PFIC2 patients, details of which are provided in section 9.8.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Study reference sources are provided in Table 10 and Table 11. PEDFIC2 is an open-label extension study of PEDFIC1.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

The key evidence for odevixibat is from the Phase 3 study PEDFIC1 and its extension PEDFIC2.

In PEDFIC1 the groups are well balanced with regard to age, PFIC type, concentration of bile acids and level of pruritus. Median age of the patients was 3.2 years and ranged from 6 months to 15.9 years. Patients treated with odevixibat 120 µg/kg/day were older (median age 4.9 years) compared with patients in the placebo group (2.8 years) and in the 40 µg/kg/day group (3.2 years). See section 9.6.1.3.

In PEDFIC2 Cohort 1 consists of children with PFIC Types 1 and 2 who have participated in study PEDFIC1 and rolled over to PEDFIC2. Cohort 2 consists of patients with PFIC who have elevated SBAs and cholestatic pruritus and who either:

1. did not meet eligibility criteria for PEDFIC 1, or

2. were eligible for enrolment in PEDFIC2 after recruitment to PEDFIC1 has been completed.

Cohort 2 therefore includes patients with other subtypes of PFIC in addition to PFIC 1 and 2, including PFIC3 and PFIC 6 currently (recruitment is ongoing).

Patients enrolled to date in Cohort 2 were slightly older (median age 6.3 years) as compared with patients in Cohort 1 (median age ≤ 3.6 years), as might be expected since PFIC3 patients were allowed to be enrolled in this cohort.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Subgroup efficacy analyses on the primary endpoint and selected secondary endpoints (changes from baseline to each visit in serum bile acid, ALT, and growth) were performed by:

- Age group (PEDFIC1: 6 months to 5 years, 6 to 12 years, and 13 to 18 years; PEDFIC2: < 6 months, 6 months to 5-years-old, 6 to 12-years-old, 13 to 18-years-old, and > 18 years)
- PFIC type (1 and 2), region (US, Europe and RoW)
- Sex (male and female), race (White and non-White)
- Ethnicity (Hispanic, non-Hispanic, and unknown)
- Baseline serum bile acids level (≥250 and <250 µmol/L)
- Child-Pugh classification (A, B, C)
- BSEP type of PFIC2 patients
- Use of UDCA and rifampicin (alone or either)

Subgroup analyses have been conducted for hepatic impairment classification per National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG).

PEDFIC1: Statistical analysis was performed only when the sample size was ≥10 in each treatment group. If the sample size was <10 in any treatment group, only summary statistics are provided; the p-value is not reported. Forest plots were also produced. Due to

the anticipated small sample size in these subgroups, analyses by subgroups did not include the stratification factors.

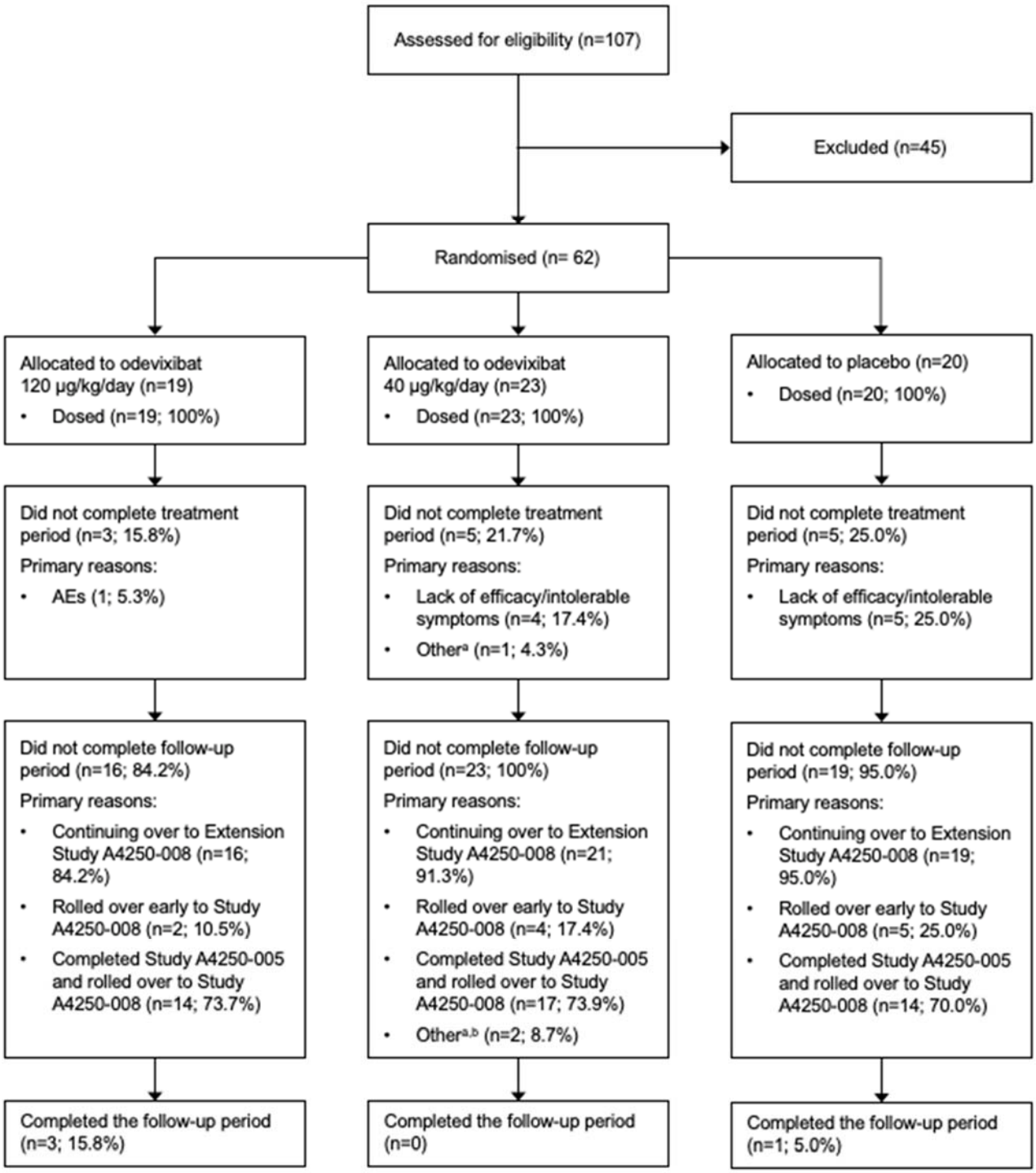
9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

9.4.5.1 PEDFIC1

A total of 107 paediatric patients were screened with 62 were enrolled into the study, including 23 patients who received odevixibat 40 µg/kg/day, 19 patients who received odevixibat 120 µg/kg/day, and 20 patients who received placebo.

Overall, 49 (79%) patients completed the planned 24-week treatment period, 11 patients rolled over to the long-term extension trial prior to completion of 24 weeks of treatment per protocol due to intolerable symptoms after completing between 12 and 18 weeks, one patient discontinued treatment due to an AE of diarrhoea, and one patient discontinued for other reasons (non-compliance/inability to travel to the site).[16,17]

Figure 15. Patient disposition for PEDFIC1 (all screened patients)



[a] Non-compliance/inability to travel to the site
[b] Non-compliance with visits, eDiary, and dosing
Note: Percentages were calculated based on all randomised patients.
Source: PEDFIC1 CSR[16]

9.4.5.2 PEDFIC2

A total of 71 patients were enrolled in PEDFIC2 as of the data cut-off of 15 July 2020; of these, 69 had received treatment as of the data cut-off:[18,19]

- 53 patients in Cohort 1 rolled over from PEDFIC1
- 16 patients in Cohort 2

As of the data cut-off, two patients (one from each Cohort) had not started treatment.

Of the 53 patients in Cohort 1 who had rolled over from PEDFIC1, 34 had previously been treated with odevixibat and 19 had received placebo. Thus, 34 of the 69 patients had previously been treated with odevixibat and 35 were treatment-naïve:

- Cohort 1: 19 placebo patients in Study PEDFIC1
- Cohort 2: 16 patients

Most patients were ongoing on treatment as of the data cut-off (65/69, 92%).[18,19]

Table 14. Patient disposition

Disposition category	Odevixibat 120 µg/kg, once daily dosing						
	Cohort 1[a]				Cohort 2 n (%)	Cohort 2 + placebo[b] n (%)	Overall n (%)
	Odevixibat 40 µg/kg n (%)	Odevixibat 120 µg/kg n (%)	Odevixibat All Doses n (%)	Placebo n (%)			
Screened	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Screening failures					[redacted]		
Enrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dosed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not dosed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed treatment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing on treatment[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed the study[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing on the study[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment early	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for treatment discontinuation							
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent/assent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a For patients in Cohort 1, dose indicated is dose administered during participation in Study A4250-005.
b Cohort 2 + Placebo = Patients enrolled in Cohort 2 and patients who were assigned to placebo during participation in Study A4250-005.
c Completed 72 week treatment period.
d Ongoing on treatment/the study as of the data cutoff date of 15JUL2020.
e Completed the follow-up period.
f Patient 24103-502 in Cohort 2 discontinued treatment following withdrawal of consent, but the EOT form was not completed at the interim cut and there is a query for the site to complete the EOT form (see Section 12.3.3.3.3).
g Patient 24103-503 discontinued treatment due to liver transplant and Patient 25101-201 due to withdrawal of consent.
Note: Cohort 1 patients entered from Study A4250-005 and therefore did not undergo screening.
Source: PEDFIC2 CSR[18]

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Details are provided above.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in Tables C7 and C8.

Table 15. Critical appraisal of randomised control trials

Study name	**PEDFIC1**		**PEDFIC2 (open-label extension)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	The randomisation codes were computer generated by a biostatistician at ICON and kept by an unblinded statistician at Firma, independent from the project team.	NA – not randomised	Following the first study, patients were invited to participate in a 72-week open-label extension study (A4250-008) in which all patients received odevixibat 120 µg/kg/day
Was the concealment of treatment allocation adequate?	Yes	An 8-digit patient identification number was assigned by the Interactive Web Response System (IWRS). The randomisation codes were computer generated and kept independent from the project team.	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline demographic characteristics were largely similar between the treatment groups. In terms of disease characteristics, higher proportions of patients in the placebo group were concurrently using UDCA and rifampicin. These differences would not, however, be expected to favour outcomes for odevixibat	NA – as no treatment comparison, but groups compared by Cohort 1 (patients from Study A4250-005 who were eligible and elected to continue treatment, and Cohort 2 (patients who did not meet eligibility criteria for Study A4250-005 or who did meet the eligibility criteria after recruitment of Study A4250-005	Demographic characteristics were generally similar across the study groups in Cohort 1 and Cohort 2

			had been completed)	
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The patient, investigator, study centre personnel, and the sponsor were blinded to study treatment until all patients completed the study. The authors stated that as changes in the measured serum bile acids had the potential to unblind a patient's assignment to either placebo or odevixibat, this outcome was evaluated by a central laboratory	NA – as open label	A central laboratory (ARUP Laboratories) performed the quantitative assessment of the serum bile acids levels
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	5 (25.0%) in the placebo group, 5 (21.7%) in the odevixibat 40 µg/kg group, and 3 (15.8% on the odevixibat 120 µg/kg group did not complete the treatment period. Reasons for withdrawal were reported; higher percentages of patients withdrew from the placebo and the odevixibat 40 µg/kg groups, than in patients who received 120 µg/kg. The highest drop-out in the placebo group may not be unexpected	No	There were very few discontinuations in the open-label study, with little difference between the two cohort groups (5.6% and 2.8%, respectively). Reasons for withdrawal were reported
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes defined in the methods section of the clinical study report were reported	No	All outcomes defined in the methods section of the clinical study report were reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety analyses were primarily based on the Full Analysis Set (FAS) defined as all randomised patients who received at least 1 dose of study treatment. All patients were included in the analyses	Yes	The efficacy and safety analyses were based on the Full Analysis Set (FAS) defined as all patients who received at least 1 dose of study treatment. In this extension study, 2 patients enrolled (1 from each cohort)

				were not included in the efficacy analyses
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.				

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

9.6.1.1 PEDFIC1 and PEDFIC2 - Summary of primary endpoint analysis

Table 16. PEDFIC1 Primary endpoint analysis

Proportion of patients with an sBA response (at least a 70% reduction from baseline or reaching a level ≤70 µmol/L)				
Statistic	**Placebo N=20**	**Odevixibat 40 µg/kg/day N=23**	**Odevixibat 120 µg/kg/day N=19**	**Odevixibat all doses N=42**
Responders, n (%)	0	10 (43.5)	4 (21.1)	14 (33.3)
95% CI[a]	(0.00, 16.84)	[redacted]	[redacted]	(19.57, 49.55)
Proportion difference without adjusting for stratification factors (odevixibat — placebo)		[redacted]	[redacted]	[redacted]
95% CI[a]		[redacted]	[redacted]	[redacted]
Proportion difference adjusting for stratification factors (odevixibat —placebo)		[redacted]	[redacted]	[redacted]
95% CI[b]		[redacted]	[redacted]	[redacted]
1-sided unadjusted p-value[d]		[redacted]	[redacted]	0.0015
1-sided adjusted p-value[e]		[redacted]	[redacted]	-
Proportion of positive pruritus assessments				
mean (SE)	28.74 (5.209)	[redacted]	[redacted]	53.51 (5.006)
median	[redacted]	[redacted]	[redacted]	[redacted]
min, max	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)[f]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (SE) (odevixibat — placebo)[f]		[redacted]	[redacted]	[redacted]
95% CI[f]		[redacted]	[redacted]	[redacted]

One-sided p-value (unadjusted)[f]		[redacted]	[redacted]	[redacted]

Notes:

a. Clopper-Pearson exact CI is reported for the percentage of responders, and the exact unconditional CI is reported for the proportion difference without adjusting for stratification factors.
b. Miettinen-Nurminen (score) CI is reported adjusting for stratification factors.
c. The exact CI is reported based on Vollset, Hirji, and Elashoff adjusting for stratification factors.
d. Based on the Cochran-Mantel-Haenszel test adjusting for stratification factor (PFIC type).
e. For an individual dose, the adjusted p-value was calculated as the maximum value of the unadjusted p-value for odevixibat all doses and the unadjusted p-value for the individual dose
f. non-parametric ANCOVA

Source: PEDFIC1 CSR[16]

Table 17. PEDFIC2 Primary endpoint analysis

Summary of change in serum bile acids (µmol/L) after 24 Weeks of treatment						
	Odevixibat 120 µg/kg, Once Daily Dosing					
	Cohort 1[a]				**Cohort 2 N=16**	**Cohort 2 + Placebo[b] N=35**
	40 µg/kg N=19	**120 µg/kg N=15**	**All Doses N=34**	**Placebo N=19**		
Change from baseline, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change from baseline, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of Positive pruritus assessments over the 24-Week treatment period						
Statistic	Odevixibat 120 µg/kg, once daily dosing					
	Cohort 1[a]				**Cohort 2 N=16**	**Cohort 2 + placebo[b] N=35**
	40 µg/kg N=19	**120 µg/kg N=15**	**All doses N=34**	**Placebo N=19**		
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Max: maximum; min: minimum; ObsRO: observer-reported outcome; SE: standard error
Notes:
a, For patients in Cohort 1, dose indicated is dose administered during participation in PEDFIC1
b, Cohort 2 + Placebo = Patients enrolled in Cohort 2 and patients assigned to placebo during participation in PEDFIC1

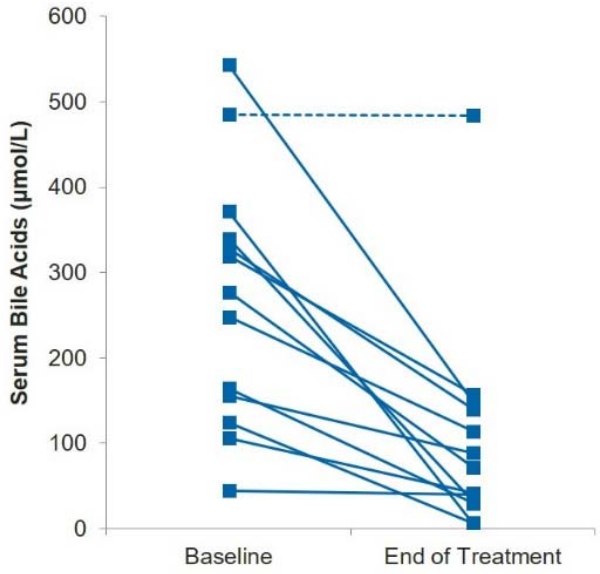
Source: PEDFIC2 CSR[18]

9.6.1.2 Phase 2 study (key results of relevance to this submission)

A reduction in sBA levels was observed after four weeks of daily treatment with odevixibat in all dose groups. The lowest dose of 0.01 mg/kg showed a mean decrease of 30.9% and the 0.06 mg/kg group showed the largest decrease in sBA with a mean reduction of 62.8%. Further dose escalation did not show any additional decrease in serum bile acids. Analyses in PFIC patients only (10 patients + 3 patients re-exposed, i.e., 13 treated patients, different doses) showed a reduction in serum bile acids of [redacted].

Reductions in serum bile acid levels were also observed in the PFIC subgroup, which included patients with PFIC1, PFIC2 or PFIC type 3) (Figure 16). Overall, mean change in serum bile acid levels was −165.1 µmol/L (range, −394 to −1.2) in patients with PFIC.[70] In the PFIC subgroup, all patients experienced reductions in serum bile acids except one patient whose serum bile acids changed little over the course of treatment; this patient had an intronic splice site mutation indicating a complete absence of BSEP.

Figure 16. Change from baseline in serum bile acids at the end of the 4-week treatment period (subgroup of patients with PFIC)



Improvements in mean pruritus scores across three separate scales and in mean sleep scores were observed with all doses of odevixibat at the end of the 4-week treatment period versus baseline, except for the lowest dose investigated. Similar improvements in pruritus and sleep scores were observed in the subgroup of patients with PFIC. In this

subgroup, mean change in VAS-itch scores was −2.7 (range, −5.9 to 0.4); mean change in PO-SCORAD itch score was −2.5 (range, −6 to 0.3); mean change in Whitington itch score was −1.1 (range, −3 to 0.1); and mean change in PO-SCORAD sleep disturbance score was −2.4 (range, −5.8 to 0.4).[70]

Mean decreases were observed in autotaxin levels in all dose groups after treatment with odevixibat.

9.6.1.3 PEDFIC1

Baseline demographics and characteristics

Baseline demographics and characteristics are described in Table 18. With regard to age, PFIC type, concentration of bile acids and level of pruritus, the groups are well balanced.

Median age of the patients was 3.2 years and ranged from 6 months to 15.9 years. Patients treated with odevixibat 120 µg/kg/day were older (median age 4.9 years) compared with patients in the placebo group (2.8 years) and in the 40 µg/kg/day group (3.2 years). Most patients were enrolled at sites in Europe [redacted] were enrolled at sites in the US [redacted] in the rest of world.

Table 18. Summary of patient characteristics for PEDFIC1

	Placebo (n=20)	Odevixibat (n=42)
Age (years)	3.75 (0.5 – 15.0)	4.48 (0.6 – 15.9)
Sex (% female)	40.0	54.8
PFIC type, n (%)	Type 1: 5 (25) Type 2: 15 (75.0)	Type 1: 12 (28.6) Type 2: 30 (71.4)
Bile acids and range (µmol/L)	247.53 (56.5 – 435)	252.1 (36 – 605)
Pruritus (0-4 scale)	3.02 (1.5 – 4.0)	3.00 (2.0 – 4.0)
UDCA, n (%)	18 (90.0)	32 (76.2)
Rifampicin, n (%)	17 (85.0)	24 (57.1)
ALT and range (U/L)	76.9 (19.0 – 236)	110.2 (16.0 – 798)
Total bilirubin and range (mg/dl)	3.12 (0.3 – 11.4)	3.18 (0.2 – 18.6)

Abbreviations: ALT, UDCA, ursodeoxycholic acid
Figures presented are means (range) or n (%)
Source: A4250-005 CSR; Thompson 2020[17]

Most patients (45 patients, 73%) had PFIC2 and 17 (27%) had PFIC1. The majority of patients were receiving UDCA and/or rifampicin at study entry with 50 patients (81%) on UDCA and 41 (66%) on rifampicin.

Median levels of serum bile acids were extremely elevated at baseline at 228.0 µmol/L (93.1 µg/mL), 188.5 µmol/L (77.0 µg/mL), and 254.5 µmol/L (104.0 µg/mL) in the odevixibat 40 µg/kg/day, odevixibat 120 µg/kg/day, and placebo groups, respectively. Median levels of hepatic biochemical parameters were also elevated at baseline, including ALT (65 U/L, approximately 2× upper limit of normal [ULN]), AST (83.5 U/L, less than 2× ULN), and total bilirubin (36.8 µmol/L; 2.2 mg/dL, 1.8× ULN); median GGT was 17.0 U/L (within normal range).

The existence of this patient population with high levels of sBA and uncontrolled pruritus despite the use of UDCA and rifampicin further highlights the lack of efficacy of these off-label therapies and the high unmet need.

Primary endpoint results

PEDFIC1 met both primary efficacy endpoints (reduction in serum bile acids for EU and ROW, and improvement in pruritus for the US). Treatment with odevixibat at doses of 40 and 120 µg/kg/day led to a statistically significant higher proportion of patients experiencing at least a 70% reduction in serum bile acids concentration from baseline or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment, as well as a statistically significant higher proportion of positive pruritus assessments at the patient level over the 24-week treatment period compared with placebo.

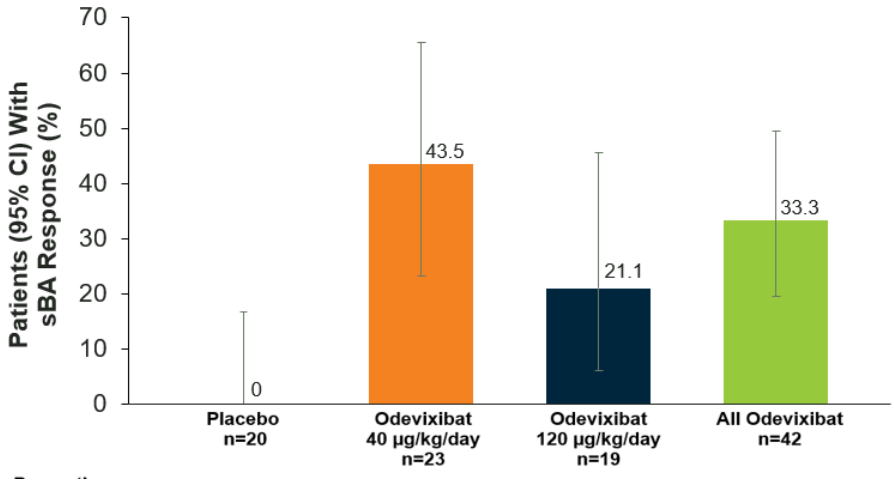
Serum bile acids

Treatment with odevixibat overall and at doses of 40 and 120 µg/kg/day led to statistically significant improvements in serum bile acids concentrations compared with placebo (Table 16*;* Figure 17). After 24 weeks of treatment, the proportion of patients with at least a 70% reduction in serum bile acid concentration from baseline or reaching a level ≤70 µmol/L (28.6 µg/mL) was 33.3% across all patients who received odevixibat, including 43.5% and 21.1% of patients in the odevixibat 40 and 120 µg/kg/day dose groups, respectively; none of the patients in the placebo group met the sBA endpoint. The reduction in sBA with odevixibat occurred early and remained consistent across the study period (Figure 18).

Patients with both PFIC types responded to odevixibat and sBA concentration was reduced to a similar level in both PFIC1 and PFIC2 patients (Figure 19). All statistical comparisons to placebo were significant at the one-sided level: odevixibat overall (p =

0.0015), odevixibat 40 µg/kg/day (adjusted p = 0.0015), [redacted] In addition, a post hoc analysis comparing the results for the 40 and 120 µg/kg/day groups showed [redacted] in the proportion of sBA responders between the two odevixibat dose groups (CMH stratified by PFIC type, 2-sided, [redacted]

Figure 17. Serum bile acid response at Week 24



Abbreviations: CI, confidence interval; SBA, serum bile acid
Notes: An SBA response was defined as ≤70 µmol/L at week 24 or a reduction from baseline to week 24 of ≥70%.
Source: Thompson et al, 2020[17]

Figure 18. Mean (±SE) Change from baseline in sBA concentration (µmol/L) by visit

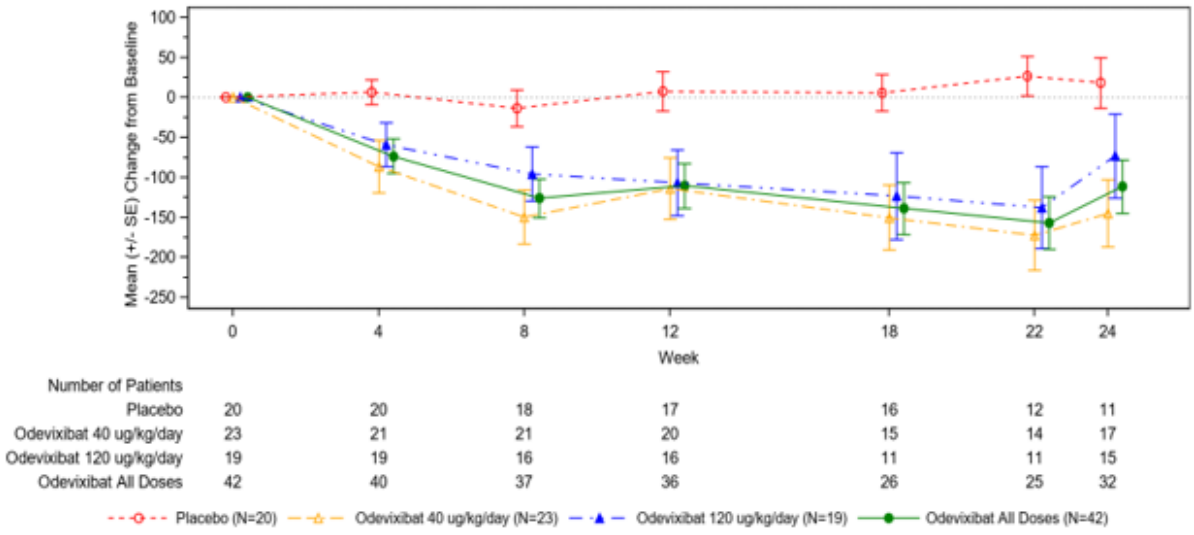
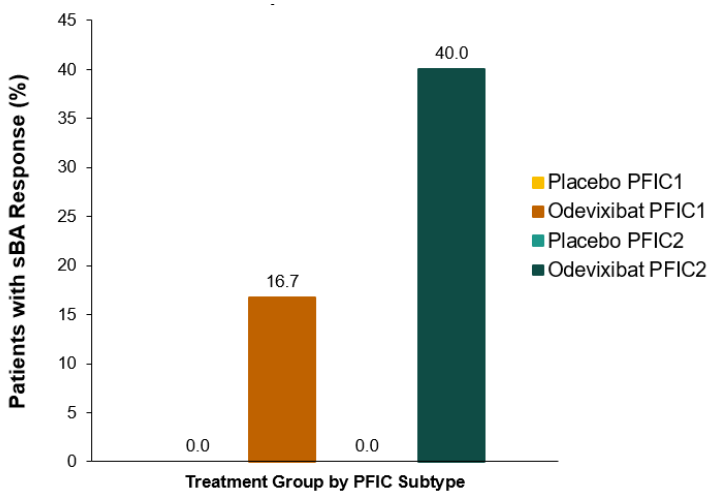


Figure 19. sBA response at Week 24 (A) and sBA over Time (B) in Patients according to PFIC type

A



B

[redacted]

Abbreviations: PFIC, progressive familial intrahepatic cholestasis; SBA, serum bile acid

Pruritus

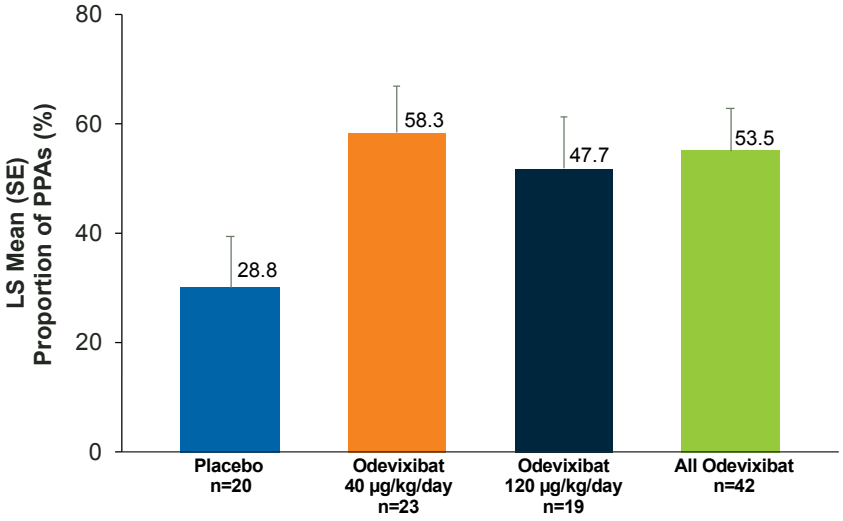
Treatment with odevixibat overall and at doses of 40 µg/kg/day and 120 µg/kg/day led to statistically significant improvements in pruritus compared with placebo over the 24-week treatment period based on the Albireo ObsRO instrument (Table 16; Figure 20). The mean proportion of positive pruritus assessments (i.e., a scratching score of ≤1 or at least a 1-point drop from baseline) at the patient level was 53.5% across all odevixibat-treated patients, [redacted] in the odevixibat 40 µg/kg/day and 120 µg/kg/day dose groups, respectively, compared with 28.7% in the placebo group.[16] Greater than a fall of one point in the mean score is considered clinically meaningful (see section 9.4.1.4).

The magnitude of the treatment effect was similar in patients with PFIC1 and PFIC2 and was persistent over time (Figure 21).

A *post hoc* analysis comparing the results for the 40 and 120 µg/kg/day groups showed [redacted] between the two odevixibat dose groups for the proportion of positive pruritus assessments at the patient level over the 24-week treatment period (ANCOVA, 2-sided p = [redacted]

Figure 20. Proportion of positive pruritus assessments at the patient level over 24 weeks (A) and by timepoint (B)

A



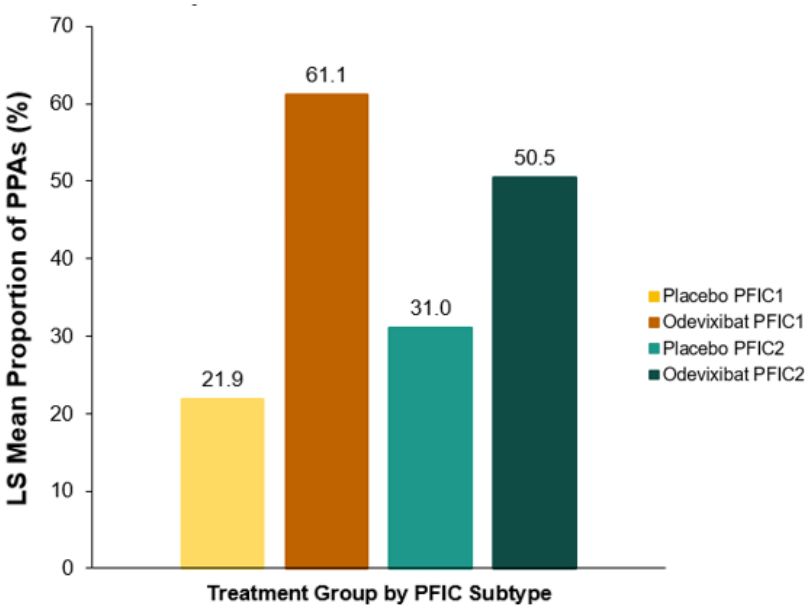
B

[redacted]

Abbreviations: CI, confidence interval; LS, least squares; PPA, positive pruritus assessment
Notes: PPAs defined as a scratching score of ≤1 or ≥1 point drop from baseline on an observer-reported instrument.
Source: PEDFIC1 CSR[16]; Thompson et al, 2020[17]

Figure 21. Proportion of positive pruritus assessments over 24 weeks (A) and by timepoint (B) according to PFIC type

A



B

[redacted]

Abbreviations: LS, least squares; PFIC, progressive familial intrahepatic cholestasis; PPAs, positive pruritus assessments
Notes: PPAs defined as a scratching score of ≤1 or a ≥1-point drop from baseline on an observer-reported instrument

Proportion of Patients Achieving a Positive Pruritus Assessment for >50% of the Time During the 24-Week Treatment Period (secondary endpoint)

Multiple pruritus assessment were completed in PEDFIC1 with results were [redacted]. Results for the secondary efficacy endpoint of the proportion of patients achieving a positive pruritus assessment for >50% of the 24-week treatment

period, [redacted] is provided here and utilised in the health economic analysis (see section 12.2).

[redacted] of patients who received odevixibat overall and in both dose groups were [redacted] in pruritus severity compared with the placebo group (Table 19).

Table 19. Analysis of the Number (%) of Patients Achieving a Positive Pruritus Assessment for More Than 50% of the Time (ObsRO Instrument, Full Analysis Set)

		Odevixibat		
	Placebo N=20	**40 µg/kg N=23**	**120 µg/kg N=19**	**All doses N=42**
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion Difference Adjusting for Stratification Factors (Odevixibat – Placebo)		[redacted]	[redacted]	[redacted]
95% CI[b]		[redacted]	[redacted]	[redacted]
Odds Ratio (Odevixibat/Placebo)		[redacted]	[redacted]	[redacted]
95% CI[c]		[redacted]	[redacted]	[redacted]
One-Sided Unadjusted p-value[d]		[redacted]	[redacted]	[redacted]

CI: confidence interval; ObsRO: observer-reported outcome.
a. Clopper-Pearson exact CI is reported.
b. Miettinen-Nurminen (score) CI is reported.
c. The exact CI is reported based on Vollset, Hirji, and Elashoff (1991).
d. Based on the Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors.
Source: PEDFIC1 CSR[16]

Key secondary endpoints

The overall treatment benefits and wellbeing of patients with PFIC1 and PFIC2 was demonstrated by the totality of evidence across multiple secondary and exploratory endpoints, including improvement in many of the measured sleep parameters and QoL for both patients and their families.

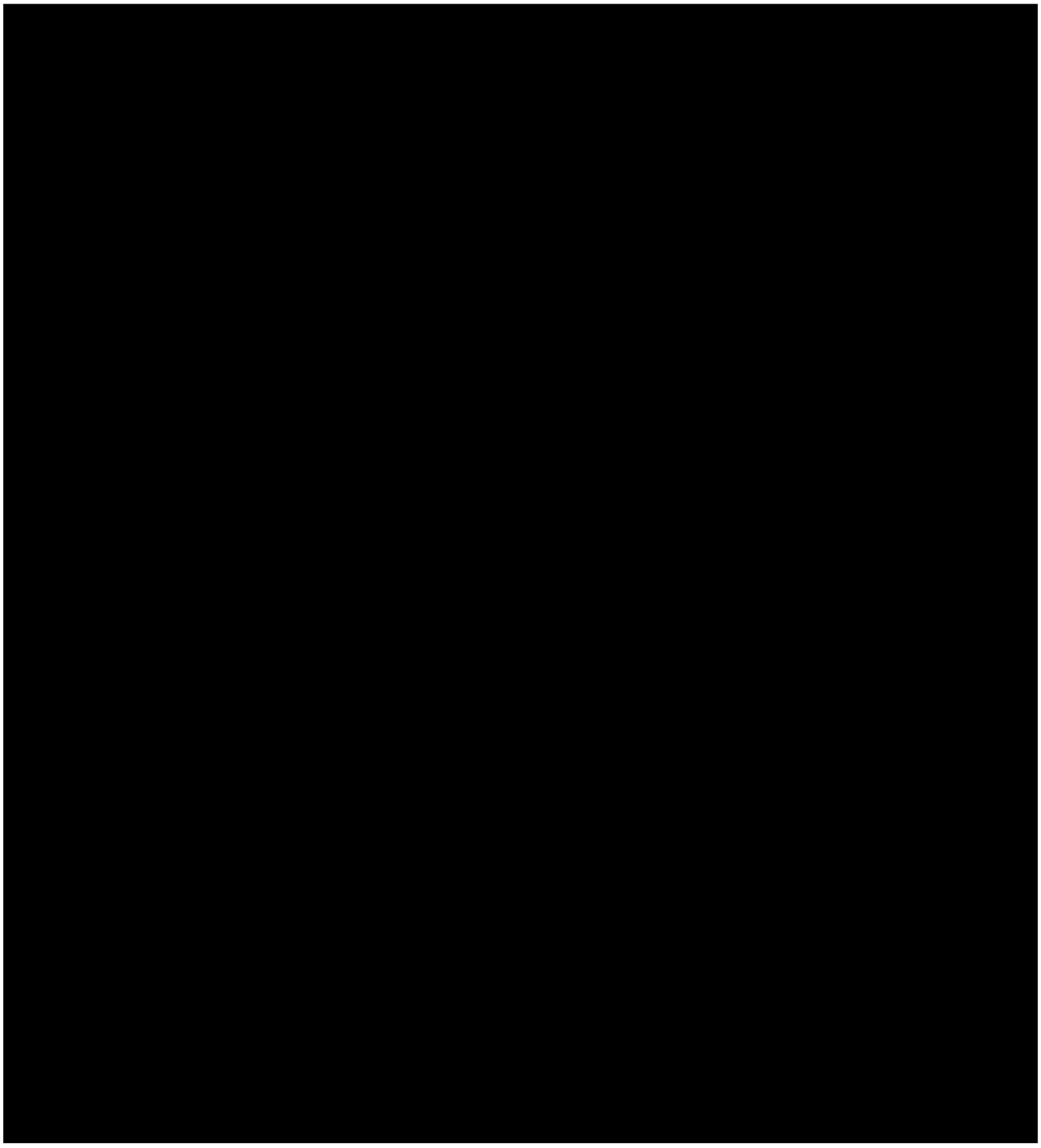
Sleep analysis

Treatment with odevixibat led to improved sleep for patients based on ObsRo (

Figure 22).

Among odevixibat-treated patients, mean reductions from baseline were observed early in the course of treatment relative to placebo for the percentage of days requiring help falling asleep, percentage of days with soothing, and percentage of days sleeping with the caregiver; for the placebo-treated patients, [redacted]changes from baseline were observed for these sleep parameters. Additionally, a [redacted] in daytime tiredness score, which ranges from 0 to 4, was observed for odevixibat-treated patients compared with the placebo group. No clear differences were noted between odevixibat- and placebo-treated patients for percentage of days seeing blood due to scratching or number of awakenings. For these latter two parameters, there [redacted] at both baseline and Weeks 21–24 (ranging from approximately 0 to 100) indicating that a [redacted]

Figure 22. Mean (±SE) change in sleep parameters over time



Results for changes from baseline over time in sleep parameters based on the PRO, including difficulty falling asleep and difficulty staying asleep, and the exploratory endpoints of tiredness and percentage of days waking up, odevixibat-treated patients compared with those who received placebo.

Growth analysis

Patients in the placebo and 120 µg/kg/day groups had [redacted], including both height and weight, compared with patients in the 40 µg/kg/day group. The impact of this on subsequent growth is not known.

The most pronounced effect on growth at Weeks 12 and 24 was observed in the [redacted] in mean height z-score [redacted] and weight z-score ([redacted], respectively) relative to the placebo group which showed [redacted] in height z-score at both time points ([redacted], respectively) with some [redacted] in weight z-scores ([redacted], respectively).

The 24-week treatment duration may not be long enough to assess the full treatment benefit – continued improvements were observed the extension study.

Hepatic analysis

Following 24 weeks of treatment with odevixibat, reductions in hepatic biochemical parameters were observed in both odevixibat dose groups with minimal changes observed in the placebo group.

By Week 12, mean changes from baseline for the secondary efficacy endpoint of ALT were [redacted] in the 40 and 120 µg/kg/day dose groups, respectively, compared with a [redacted] in the placebo group. Further decreases in ALT were observed to Week 24 with mean changes from baseline of [redacted] in the 40 and 120 µg/kg/day dose groups, respectively, compared with a [redacted] in the placebo group.

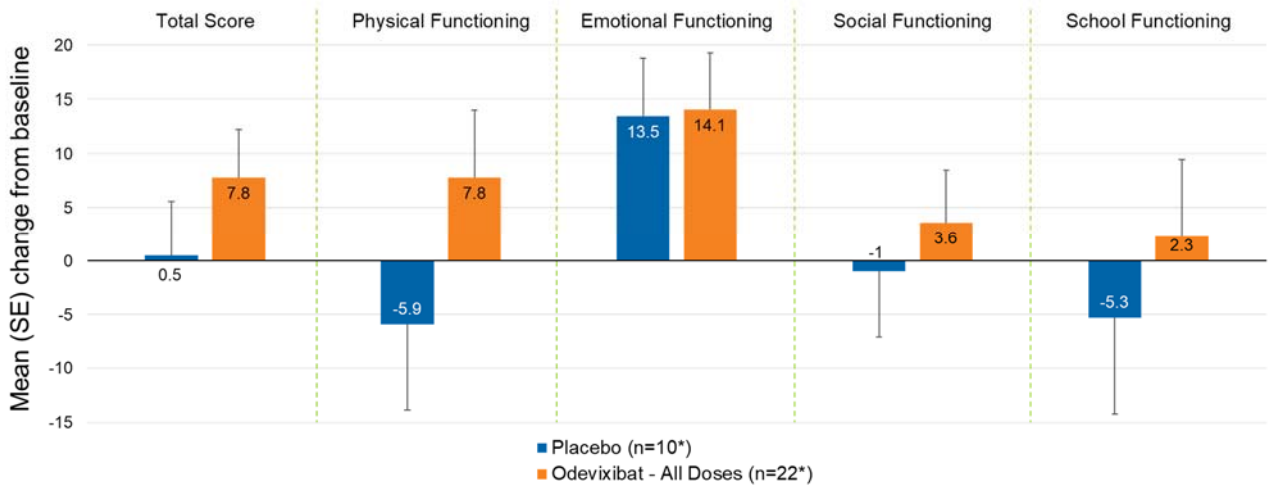
For total bilirubin, mean changes from baseline to Week 24 [redacted] for the 40 µg/kg/day and 120 µg/kg/day groups, respectively, and [redacted] for placebo. [redacted] in GGT were also observed at Week 24 in patients on odevixibat, compared with a mean [redacted] in the placebo group.

PedsQL (exploratory endpoint)

Caregiver-reported total scores on the PedsQL [redacted] from baseline to Week 24 for patients treated with odevixibat indicating improvement in QoL with mean [redacted] from baseline of [redacted] for odevixibat overall and [redacted] for the 40 and 120 µg/kg/day groups, respectively; [redacted] change from baseline was observed for the placebo group [redacted].

Among PedsQL domains, improvements were observed with odevixibat, whereas with placebo, 3 of 4 domains showed worsening (mean changes from baseline to week 24: physical, 7.8 vs –5.9; emotional, 14.1 vs 13.5; social, 3.6 vs –1.0, school functioning, 2.3 vs –5.3, respectively; Figure 23).[16]

Figure 23. Change From Baseline to Week 24 in PedsQL Total and Domain Scores

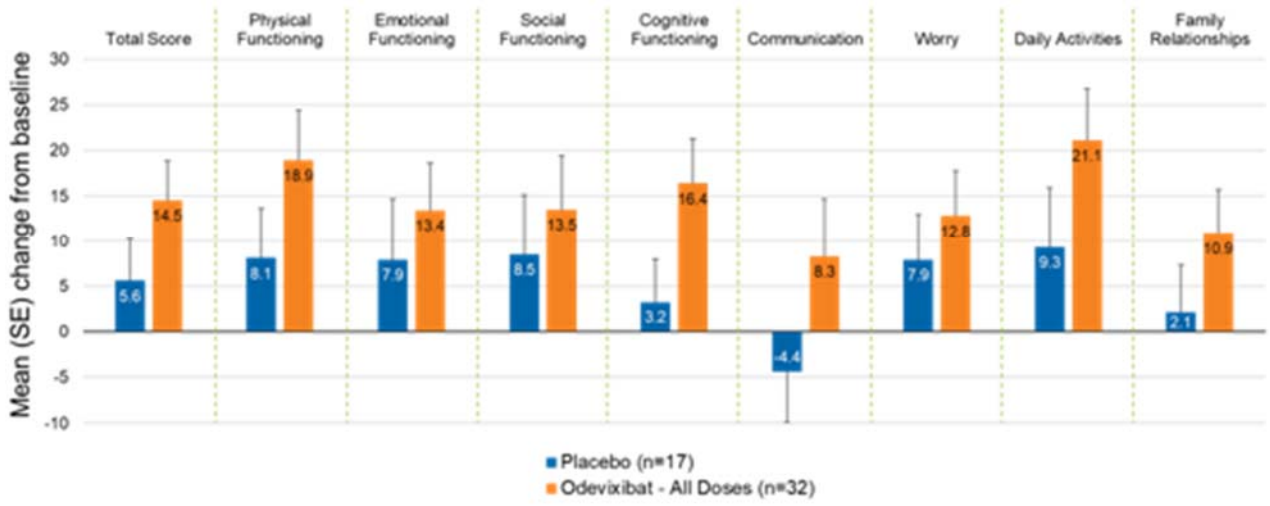


*For School Functioning, n=6 for placebo and n=15 for odevixibat – all doses.
n, number of patients with available assessments; PedsQL, Pediatric QoL Inventory; SE, standard error.
Source: PEDFIC1 CSR[16]

Larger mean improvements were observed with odevixibat vs placebo in Family Impact Module total score; the mean changes were larger in odevixibat-treated patients compared with those who received placebo. Mean changes to Week 24 were 14.5. [redacted] for odevixibat overall, the 40 µg/kg/day, and the 120 µg/kg/day groups, respectively, and was 5.6 for the placebo group. Results across the domain scores were consistent for the odevixibat-treated patients showing improvements whereas both improvements and declines were noted in the placebo group.

Results were consistent across all domains with improvement for the overall odevixibat group for physical, emotional, and social functioning, and cognitive, communication, worry, daily activities, and family relationships (Figure 24).

Figure 24. Change From Baseline to Week 24 in PedsQL Family Impact Module Total and Domain Scores



n, number of patients with available assessments; PedsQL, Pediatric Quality of Life Inventory; SE, standard error.
Source: PEDFIC1 CSR[16]

Global Impression of Symptoms and Change at Weeks 4, 12 and 24 (Exploratory endpoint)

Results for the global impression of change (GIC) and global impression of symptoms (GIS) as completed by the caregivers indicated improvements over time on treatment with odevixibat for scratching and sleep, consistent with the reported changes from baseline in scratching scores and sleep disturbance scores based on the ObsRO.

By Week 24, improvements in scratching and sleep based on the CaGIC were reported in [redacted] of patients receiving odevixibat, respectively, compared with [redacted] of patients, respectively, who received placebo. Across the odevixibat dose groups, [redacted] of patients in the 40 µg/kg/day group were reported as improved from baseline to Week 24 in both scratching and sleep and in the 120 µg/kg/day group [redacted] respectively, had improved.[16]

Exit Survey

An exit survey was added to the protocol on 5 September 2019 [redacted]. Overall the survey was completed by [redacted], including [redacted] for patients who received odevixibat and [redacted] for patients who received placebo.

A [redacted] of caregivers of patients who received odevixibat reported meaningful change in the patient since the start of treatment. In the overall odevixibat group, meaningful change was reported in [redacted] of patients, including [redacted]

patients in the 40 and 120 µg/kg/day groups, respectively, compared with [redacted]% of patients who received placebo.[16]

9.6.1.4 PEDFIC2

Baseline demographics and characteristics

Patient characteristics for PEDFIC2 are displayed in Table 20.

Table 20. Summary of patient characteristics for PEDFIC2

	Cohort 1 PEDFIC1			Cohort 2 Treatment naive
	Placebo N=19	Odevixibat 40 µg/kg/day N=19	Odevixibat 120 µg/kg/day N=15	Odevixibat 120 µg/kg/day N=16
Age, years (range)	4.34 (1.0 – 15.6)	3.82 (1.2 – 10.5)	5.5 (1.6 – 13.9)	7.89 (1.3 – 19.5)
Sex (% female)	36.8	52.6	53.3	56.3
PFIC type, n (%)	Type 1: 5 (26.3) Type 2: 14 (73.7)	Type 1: 6 (31.6) Type 2: 13 (68.4)	Type 1: 4 (26.7) Type 2: 13 (73.3)	Type 1: 3 (18.8) Type 2: 13 (43.8) Type 3: 5 (31.1) Other: 1 (6.3)
Bile acids and range (µg/mL)	270.79 (11 – 528)	104.89 (1 – 327)	155.87 (2.5 – 439)	221.53 (10.5 – 465)
UDCA, n (%)	17 (89.5)	14 (73.7)	9 (60.0)	13 (81.3)
Rifampicin, n (%)	17 (89.5)	8 (42.1)	7 (46.7)	7 (43.8)
ALT and range (U/L)	71.26 (14 – 231)	74.42 (9 – 352)	73.20 (14 – 239)	69.75 (14 – 231)
Total bilirubin and range (mg/dl)	53.34 (3.3 – 39.3)	22.55 (2.5 – 112.6)	37.35 (2.2 – 210.4)	41.48 (11.2 – 119.2)

Source: PEDFIC2 CSR[18]; Thompson et al, 2020[19]

The median age at study entry was 4.1 years and ranged from 1 to 19.5 years, with equal representation of males (51%) and females (49%). Distribution of PFIC subtype was PFIC1 16%, PFIC2 65% and PFIC3 7%. One patient was classified as 'other'.

Patients in Cohort 2 were slightly older (median age 6.3 years) as compared with patients in Cohort 1 (median age ≤ 3.6 years), as might be expected since PFIC3 patients were allowed to be enrolled in this cohort. There was equal representation of males (51%) and

females (49%) and the majority of patients were white (60, 87%) and not Hispanic or Latino (63, 91%). Most patients were enrolled at sites in [redacted] were enrolled at sites in the [redacted] in the rest of world.

Overall, 45 (65%) patients had PFIC2, 18 (26%) had PFIC1, 5 (7%) had PFIC3, and 1 (1%) patient was classified as other PFIC type (MYO5B deficiency). The majority of patients (58, 84%) were receiving UDCA and/or rifampicin at study entry with 53 (77%) patients on UDCA and 39 (57%) on rifampicin.

Primary endpoint results

Serum bile acids

Interim results showed that at Week 24, treatment with odevixibat at a dose of 120 µg/kg/day led to continued improvement in serum bile acid levels for patients who had received active treatment in PEDFIC1 and those who were treatment-naïve at study entry.

For patients in Cohort 1 who had received odevixibat in PEDFIC1 and who entered PEDFIC2 with improved serum bile acids levels, further reductions from baseline were observed during longer-term treatment. Mean changes in serum bile acids levels from PEDFIC2 baseline to Week 22/24 were [redacted], in patients who had received 40 µg/kg/day in PEDFIC1, and [redacted], in patients who had received 120 µg/kg/day.

For patients who had received placebo in PEDFIC1, mean change to Week 24 following the start of treatment with odevixibat 120 µg/kg/day was [redacted] and for patients in Cohort 2 was [redacted] in Cohort 2 had data available at Week 22/24 at the time of the data cut-off.

Table 21. Summary of change in serum bile acids (µmol/L) after 24 Weeks of treatment

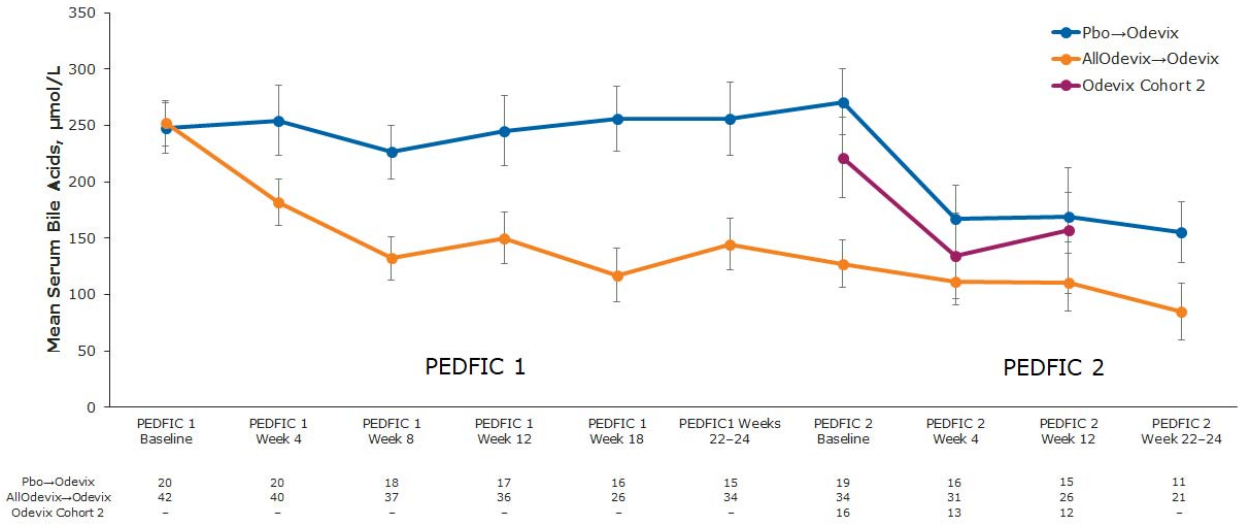
	Odevixibat 120 µg/kg, Once Daily Dosing					
	Cohort 1[a]				Cohort 2 [redacted]	Cohort 2 + Placebo[b] [redacted]
	40 µg/kg [redacted]	120 µg/kg [redacted]	All Doses [redacted]	Placebo [redacted]		
Baseline[c], n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	248.27 (22.604)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.5, 528
Week 22/24, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Odevixibat 120 µg/kg, Once Daily Dosing					
	Cohort 1[a]				Cohort 2	Cohort 2 + Placebo[b]
	40 µg/kg	120 µg/kg	All Doses	Placebo		
Mean (SE)			85.10 (25.123)	155.59 (26.810)		
Median						
Min, max						
Change from baseline, n						
Mean (SE)						
Median						
Min, max						
% change from baseline, n						
Mean (SE)						
Median						
Min, max						

Abbreviations: Max: maximum; min: minimum; SE: standard error.
Notes:
a, For patients in Cohort 1, dose indicated is dose administered during participation in Study A4250-005.
b, Cohort 2 + Placebo = Patients enrolled in Cohort 2 and patients who were assigned to placebo during participation in Study A4250-005.
c, Baseline for Study A4250-008/end of treatment for Study A4250-005.

Source: PEDFIC2 CSR[18]

Figure 25. Mean (±SE) change in serum bile acid concentration (µmol/L) during PEDFIC1 and PEDFIC2 Week 24



Source: Thompson et al, 2020[19]

Pruritus

Interim results displayed in Figure 26 show treatment with odevixibat at a dose of 120 µg/kg/day led to continued improvement in pruritus symptoms for patients who had received active treatment in PEDFIC1 and those who were treatment-naïve at study entry.

The mean proportion of positive pruritus assessments for this group of patients was [redacted] after 24 weeks of treatment at 120 µg/kg/day in PEDFIC2. The proportion of positive pruritus assessments was [redacted] for patients who had received 40 µg/kg/day in PEDFIC1 and transitioned to 120 µg/kg/day in Study PEDFIC2 [redacted] than for patients who had received 120 µg/kg/day (26.6%) throughout both studies.

The mean proportion of positive pruritus assessments over the 24-week treatment period in treatment-naïve patients [redacted] than that observed for patients previously treated with odevixibat.

- Following transition from placebo in PEDFIC1 to 120 µg/kg/day in PEDFIC2, the proportion of positive pruritus assessments at the patient level was [redacted] over the 24-week treatment period.
- Similarly, in Cohort 2, the proportion of positive pruritus assessments at the patient level was [redacted] over the 24-week treatment period, although limited data were available for this cohort at that time.

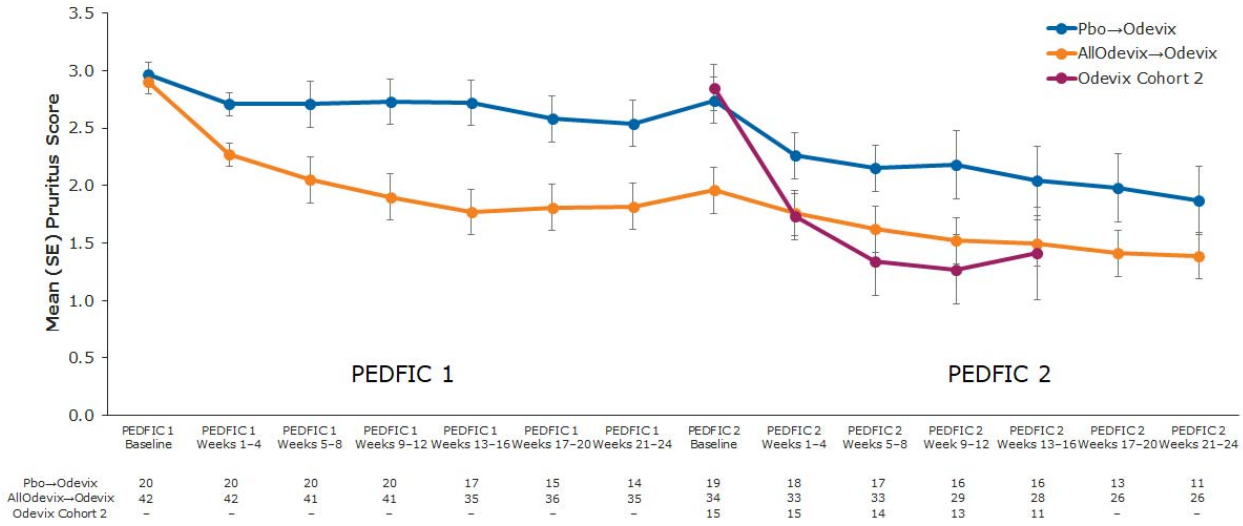
Table 22. Summary of proportion of positive pruritus assessments over the 24-Week treatment period

	Odevixibat 120 µg/kg, once daily dosing					
	Cohort 1[a]				Cohort 2 [redacted]	Cohort 2 + placebo[b] [redacted]
	40 µg/kg [redacted]	120 µg/kg [redacted]	All doses [redacted]	Placebo [redacted]		
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Max: maximum; min: minimum; ObsRO: observer-reported outcome; SE: standard error.
Notes:
a, For patients in Cohort 1, dose indicated is dose administered during participation in PEDFIC1.
b, Cohort 2 + Placebo = Patients enrolled in Cohort 2 and patients who were assigned to placebo during participation in Study PEDFIC1.

Source: PEDFIC2 CSR[18]

Figure 26. Mean (±SE) of the proportion of positive pruritus assessments by grouped weeks



Source: Thompson et al, 2020[19]

[redacted] the improvements observed in the proportion of positive pruritus assessments over time at the patient level, [redacted] in scratching severity was observed in all study groups in Cohort 1 and in Cohort 2.

For previously odevixibat-treated patients, continued decreases in scratching severity scores were observed through Week 24 in PEDFIC2 (

Figure 27). Mean changes from PEDFIC2 baseline to Week 24 for this group of patients was [redacted] overall and was [redacted] for the 40 to 120 µg/kg/day group and [redacted] for the 120 to 120 µg/kg/day group. An analysis of this endpoint was also conducted based on PEDFIC1 baseline. After 24 weeks of treatment with 120 µg/kg/day in PEDFIC2, [redacted] changes from PEDFIC1 baseline in scratching scores were observed in odevixibat-treated groups in Cohort 1, including odevixibat overall [redacted] 40 to 120 µg/kg/day group [redacted] and 120 to 120 µg/kg/day group [redacted]

Other sleep parameters also [redacted] during PEDFIC2 (

Figure 27).

Figure 27. Mean change in observer-reported sleep parameters during PEDFIC1 and PEDFIC2

Secondary endpoints

Biliary diversion surgery or liver transplantation[78]

- There were [redacted] treated with odevixibat in PEDFIC1 that underwent surgery.
- [redacted] patients, both with PFIC2 in Cohort 1 who had received placebo during PEDFIC1, underwent [redacted]
- [redacted] enrolled in PEDFIC1 was listed for [redacted] and was [redacted]. The patient received placebo in PEDFIC1 but rolled over to PEDFIC2 early due to [redacted] after the patient had started treatment with odevixibat 120 µg/kg/day, and the patient continued on odevixibat 120 µg/kg/day.
- [redacted] enrolled in PEDFIC1 were listed for liver transplant and [redacted] added to the list for liver transplant during their participation in the study.

Growth analysis

Improvement in height and weight scores was noted during treatment with odevixibat 120 µg/kg/day (Figure 28 and Figure 29).

For patients in Cohort 1 who had previously received odevixibat in PEDFIC1, mean (SE) change from baseline to Week 24 in height z-score was 0.34 (0.111), with greater improvement noted for those who had received 120 µg/kg/day [redacted] than those who had received 40 µg/kg/day [redacted] Mean (SE) changes from baseline to Week 24 in weight z-scores were [redacted] for patients who had received odevixibat 40 µg/kg/day and 120 µg/kg/day, respectively.[18]

For patients in Cohort 1 who had received placebo in PEDFIC1, mean (SE) changes in height and weight z-scores were 0.40 (0.178) and 0.47 (0.193). Only one patient in Cohort 2 had growth data available at Week 24.[18]

Figure 28. Mean height z-scores over time on treatment for PEDFIC1 and PEDFIC2

Figure 29. Mean weight z-scores over time on treatment for PEDFIC1 and PEDFIC2

Subgroup analysis

Results of all subgroup analyses were consistent with that of the primary analyses showing clinically meaningful decreases in serum bile acids levels and improvement in pruritus score from baseline for all subgroups. While conclusions in some subgroups were limited by sample size, [redacted] the magnitude of efficacy response to odevixibat were observed.

Age (≤5 years, 6 to 12 years and ≥12 years), sex, race, ethnicity, region, PFIC type and subclassification of BSEP1 and BSEP2, baseline serum bile acids levels (≥250 or ≤250 µmol/L) or pruritus severity score (≥3 or ≤3) at baseline [redacted] proportion of patients who met the serum bile acid level responder analysis. Use of conventional therapies, i.e., UDCA and/or rifampicin did not attenuate the treatment response.

Age, sex, race, ethnicity, region, and baseline serum bile acids levels [redacted] treatment effects on pruritus assessed as the proportion of positive pruritus assessments at the patient level after 48 weeks of treatment. The observed treatment effects [redacted] PFIC subtype, hepatic status, and for the rifampicin subgroup, described below.

The treatment effect was not affected by use of UDCA, as the observed proportion of positive assessments in patients on stable doses of UDCA and those not on UDCA was comparable (65.4% vs. 71.5%, respectively). Similarly, when comparing the clinical response in patients on UDCA or rifampicin vs. not on these therapies, [redacted]. A [redacted] when comparing the subgroup on rifampicin vs. those who were not. For this analysis, the proportion of positive pruritus assessment was [redacted] in patients on stable doses of [redacted] compared with patients who were not receiving [redacted] at baseline [redacted]. A potentially [redacted] severity score in patients on rifampicin could be one plausible explanation for the observed differences.

The proportion of positive pruritus assessment at the patient level was higher in patients with PFIC2 (N=23) compared with patients with PFIC1 (N=9), although both groups experienced a clinically meaningful response of 73.5% and 47.8%, respectively. It is important to note that there was a smaller number of patients in the PFIC1 subgroup.

Five female patients with PFIC3 were enrolled in Cohort 2 of PEDFIC2. The patients ranged from [redacted] years of age and [redacted] patients experienced improvement in pruritus and reduction in serum bile acid levels, observed as [redacted], with continued or sustained effects to their last visit as of the data cut-off. Four of the five patients met the serum bile acid responder definition reaching a level ≤70 µmol/L or having a ≥70% reduction from baseline and all had ≥94% positive pruritus assessments at the last assessment prior to data cut off

One patient with PFIC6 (Myo5B deficiency) was enrolled in PEDFIC2 Cohort 2. The patient had improvement in both pruritus scores and sBA reduction at weeks 9-12.[18]

[redacted] were included in Cohort 2 of PEDFIC 2 – these patients had [redacted] in pruritus or sBA at week 9-12.

Figure 30. Post Hoc Analysis: Mean Change in Pruritus Scores and Serum Bile Acids by PFIC Genotype Subtype to PEDFIC 2 Week 12 – Cohort 2

[redacted]

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

All analyses were carried out on the intent-to-treat population.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The studies presenting rates of adverse events with odevixibat have been identified as described in Section 9.1 to Section 9.6 (PEDFIC1 and PEDFIC2).

Safety data are also presented for the Phase 2 exploratory study A4250-003; study details are presented in Appendix 5.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in Table C10.

9.7.2.1 Phase 2 exploratory study A4250-003 (EudraCT 2015-001157-32)

Odevixibat was well tolerated in all dose groups from 0.01 mg/kg up to 0.2 mg/kg. There were no treatment-related SAEs and only one reported AE with possible relation to the study drug. All patients completed treatment without any dose adjustments.

There were no AEs that lead to discontinuation of the study treatment or discontinuation of study participation. Two SAEs that required hospitalisation were reported and neither led to discontinuation of study treatment. Both events were assessed as not related to the study treatment and resolved.

There were individual changes in liver enzyme values (ALP, ALT, AST, GGT, and bilirubin) during the study period and at all dose levels. Liver-related AEs reported were not assessed to be related to the study treatment and there were no overall treatment-related trends observed.

PK analysis after single-dose administration showed low systemic exposure with levels well below the stopping threshold of Cmax <7 nmol/L.

Two SAEs of gastroenteritis and influenza experienced by two patients were reported during the study and required hospitalization; [redacted] led to discontinuation of study treatment. Both events were assessed as not related to study treatment. There were [redacted] AEs that led to discontinuation of the study treatment or discontinuation from study participation.

Of the 24 patients enrolled, 18 patients (75%) experienced an AE during the study. The most frequently reported SOC was [redacted] reported an AE [redacted] This was followed by SOC [redacted] where [redacted] patients reported an AE [redacted]

Table 23. Overall summary of adverse events (Safety Set)

	Number of patients (%)					
	0.01 mg/kg	0.03 mg/kg	0.06 mg/kg	0.1 mg/kg	0.2 mg/kg	Total
	n=4	n=6	n=4	n=6	n=4	n=24

Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Possibly related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe (Grade 3) TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; SAE, serious adverse event, TEAE, treatment-emergent adverse event
Source: Phase 2 CSR[70]

In total, [redacted] AEs occurred during the study, with [redacted] events in the 0.2 mg/kg dose group [redacted] while the 0.03 mg/kg and 0.1 mg/kg groups had the [redacted] number of events [redacted] events per group). The most commonly reported AE was pyrexia (six events), followed by ear infection (3 events). Of all patients with any reported AE, [redacted] patients [redacted] had causality assessed as "not related." [redacted] patients [redacted] experienced events that were assessed as "unlikely related" while one patient (4.2%) had an AE (diarrhoea) with causality "possibly related." The diarrhoea was reported as mild, transient, and occurred after single-dose administration. The diarrhoea did not reoccur during the 4-week treatment period. Liver-related AEs reported were not assessed to be related to the study treatment and there were no overall treatment-related trends observed.

The number of bowel movements, abdominal discomfort, diarrhoea symptoms, and Bristol Stool Form Scale (BSFS) were [redacted] with odevixibat, [redacted] in global symptom relief, international normalised ratio (INR), serum albumin or insulin like growth factor-binding protein 3 (IGFBP3).

Average increases in [redacted] was seen in FGF19. There was [redacted] seen for p-C4, FGF19, or autotaxin.

Table 24. Summary of patients with any AE (Safety Set)

	Number of patients (%)					
	0.01 mg/kg	0.03 mg/kg	0.06 mg/kg	0.1 mg/kg	0.2 mg/kg	Total
	n=4	n=6	n=4	n=6	n=4	n=24
Any AE						
GI disorders						
Respiratory, thoracic and mediastinal disorders						
General disorders and administration site conditions						
Ear and labyrinth disorders						
Infections and infestations						
Injury, poisoning and procedural complications						
Investigations						
Blood and lymphatic system disorders						
Metabolism and nutrition disorders						
Skin and subcutaneous tissue disorders						

Source: Phase 2 CSR[70]

9.7.2.2 PEDFIC1

Patients on treatment or placebo experienced similar rates of having at least one TEAE. However, most TEAEs were mild to moderate in severity and assessed as unrelated to study treatment. Treatment-emergent serious AEs were reported in 7% patients who received odevixibat and in 25% placebo patients.

Only one patient in the 120 µg/kg/day dose group discontinued treatment due to diarrhoea. There were no deaths during the study.

Table 25. Summary of treatment emergent adverse events

	Placebo N=20	Odevixibat		
		40 µg/kg N=23 n (%)	**120 µg/kg N=19 n (%)**	**All doses N=42 n (%)**
TEAE	17 (85.0)	19 (82.6)	16 (84.2)	35 (83.3)
Drug-related TEAE[a]	3 (15.0)	7 (30.4)	7 (36.8)	14 (33.3)
Severe TEAE[b]	2 (10.0)	1 (4.3)	2 (10.5)	3 (7.1)
Serious TEAE	5 (25.0)	0	3 (15.8)	3 (7.1)
Drug-related serious TEAE	0	0	0	0
TEAE leading to study treatment discontinuation	0	0	1 (5.3)	1 (2.4)
TEAE leading to death	0	0	0	0

Abbreviations: TEAE, treatment-emergent adverse events; SAE, serious adverse event
Notes: a, Patients reporting more than one event are counted only once at the highest relationship reported; b, Patients reporting more than one event are counted only once at the maximum severity reported.

Source: PEDFIC1 CSR[16]; Thompson et al, 2020[17]

TEAEs were reported in ≥5% of patients who received odevixibat vs placebo: [redacted]

The incidence of these commonly reported events was similar in the odevixibat 40 and 120 µg/kg/day dose groups.

Table 26. Common treatment-emergent adverse events

MedDRA SOC preferred term	**Placebo N=20**	**Odevixibat 40 µg/kg N=23 n (%)**	**Odevixibat 120 µg/kg N=19 n (%)**
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Infections and infestations	12 (60.0)	11 (47.8)	11 (57.9)
Upper respiratory tract infection	3 (15.0)	3 (13.0)	5 (26.3)
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	1 (5.0)	3 (13.0)	3 (15.8)
Blood bilirubin increased	2 (10.0)	3 (13.0)	2 (10.5)
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]

Pyrexia	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]

Abbreviations: MedDRA, Medical Dictionary for regulation Authorities; SOC, system organ class
Source: PEDFIC1 CSR[16]

Among patients who received odevixibat, the most commonly reported drug-related TEAEs were [redacted] All other drug-related TEAEs were reported in [redacted] who received odevixibat (Table 27).

In the placebo group, drug-related TEAEs included [redacted]

Table 27. Treatment-emergent drug-related adverse events

MedDRA SOC preferred term	Placebo N=20	Odevixibat		
		40 µg/kg N=23 n (%)	120 µg/kg N=19 n (%)	All doses N=42 n (%)
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MedDRA, Medical Dictionary for regulation Authorities; SOC, system organ class
Source: PEDFIC1 CSR[16]

The majority of adverse events were mild to moderate in severity. [redacted] experienced SAEs over the course of the 24-week treatment period, including [redacted] patients on odevixibat 120 µg/kg/day and [redacted] patients on placebo. [redacted] treatment-emergent SAEs were reported in the 40 µg/kg/day treatment group. All SAEs were assessed as unrelated to study treatment.

9.7.2.3 PEDFIC2

Of the 69 patients who received odevixibat, 50 (73%) experienced at least one TEAE (Table 28). The overall incidence of TEAEs was similar across the treatment groups in Cohort 1 (74% to 84%), including those patients who had received placebo in PEDFIC1.

The overall incidence of TEAEs was lower among the 16 patients in Cohort 2 (50%); most of these patients had been dosed for 12 weeks at the data cut for the interim analysis

(15 July 2020). Most TEAEs were mild to moderate and assessed as unrelated to study treatment. Treatment-emergent SAEs were reported in four (6%) of the 69 patients, including three patients in Cohort 1 (previously treated with placebo in A4250-005) and in one patient in Cohort 2. Overall, three patients (4%) discontinued treatment due to TEAEs.

No deaths occurred during the study.

Table 28. Overall summary of treatment-emergent adverse events for PEDFIC2

	Odevixibat 120 µg/kg			
	Cohort 1			Cohort 2 N=16
	40 µg/kg N=19	120 µg/kg N=15	Placebo N=19	
TEAE	16 (84.2)	12 (80.0)	14 (73.7)	8 (50.0)
Drug-related TEAE[c]	6 (31.6)	4 (26.7)	5 (26.3)	5 (31.3)
Severe TEAE[d]	0	1 (6.7)	1 (5.3)	3 (18.8)
Serious TEAE	0	0	3 (15.8)	1 (6.3)
Drug-related serious TEAE	0	0	0	0
TEAE leading to death	0	0	0	0
TEAE leading to treatment discontinuation	0	0	1 (5.3)	2 (12.5)

Source: PEDFIC2 CSR[18]

The most commonly reported TEAEs (>10% overall) were upper respiratory tract infection (20%), cough (15%), and pyrexia and blood bilirubin increased (each 13%); diarrhoea and pruritus were each reported in 9% of the 62 patients (**Error! Not a valid bookmark self-reference.**). In general, the incidence of these commonly reported events was similar across the treatment groups in Cohort 1.

Table 29. Common treatment-emergent adverse events

System organ class preferred term	Odevixibat 120 µg/kg			
	Cohort 1			Cohort 2 N=16
	Placebo N=19	40 µg/kg N=19	120 µg/kg N=15	
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	5 (26.3)	5 (26.3)	4 (26.7)	0
Otitis media	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	2 (10.5)	3 (15.8)	1 (6.7)	3 (18.8)
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]

Diarrhoea	0	4 (21.1)	2 (13.3)	0
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cough	2 (10.5)	3 (15.8)	5 (33.3)	0
General disorders and administration site conditions	4 (21.1)	[redacted]	[redacted]	[redacted]
Pyrexia	4 (21.1)	3 (15.8)	4 (26.7)	2 (12.5)
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	2 (10.5)	2 (10.5)	2 (13.3)	0
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Splenomegaly	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEDFIC2 CSR[18]

The most commonly reported drug-related TEAEs across the 62 patients were blood bilirubin increased (10%), hepatic enzyme increased and INR increased (each in two patients, 3%) (Table 30). All other drug-related TEAEs were reported in only one patient.

Table 30. Drug-related treatment-emergent adverse events

	Odevixibat 120 µg/kg		
Drug-related TEAEs occurring in 6 or more patients overall, by preferred term (listed in alphabetical order)	Cohort 1 (all doses) **n=34**	Cohort 1 (placebo) **n=19**	**Cohort 2 n=16**
Blood bilirubin increased	4 (11.8)	2 (10.5)	3 (18.8)
Cough	8 (23.5)	2 (10.5)	0
Diarrhoea	6 (17.6)	1 (5.3)	0
INR increased	2 (5.9)	2 (10.5)	2 (12.5)
Pruritus	4 (11.8)	2 (10.5)	0
Pyrexia	7 (20.6)	4 (21.1)	2 (12.5)
Upper respiratory tract infection	9 (26.5)	5 (26.3)	0

Source: PEDFIC2 CSR[18, 19]

Discontinuation of treatment

Overall, three patients discontinued treatment due to TEAEs, one patient underwent SBD following SAE of cholestasis (received placebo in PEDFIC1), one with acute pancreatitis and one patient due to pruritus, hypophagia, jaundice, splenomegaly and weight loss.

Updated safety data December 2020

Longer- term analysis of PEDFIC2 [redacted] has recently been completed as part of the EMA assessment. The safety and tolerability profile of odevixibat in patients with PFIC xxxxx xxxxxx [redacted] x xx.[79]

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

The observed safety and tolerability profile of odevixibat was acceptable with no new or major safety findings identified in the current safety data set which includes a total of [redacted] patients with PFIC who received odevixibat in Phase 2 and 3 studies; [redacted] patients who received treatment for ≥ 6 months and [redacted] patients who received odevixibat for ≥ 12 months. Overall, 77 patients received at least one dose of odevixibat across the Phase 3 studies. Demographics, baseline and disease characteristics were representative of the targeted patient population Ursodeoxycholic acid (UDCA) and rifampicin were the [redacted] used conventional therapies for PFIC. [redacted] patients were receiving vitamin supplementation for treatment of fat-soluble vitamin deficiency or as prophylactic therapy.

The safety profile demonstrated for odevixibat was consistent across the Phase 2 and 3 trials and was as expected based on nonclinical data and given that odevixibat acts locally in the intestine with minimal systemic exposure.

[redacted] on the observed treatment-emergent adverse events (TEAEs; incidence or severity) between 40 and 120 µg/kg/day. Transitioning from 40 µg/kg/day or placebo to 120 µg/kg/day was well tolerated. The safety profile was [redacted] between the Pooled Phase 3 group (patients in Studies A4250-005 and A4250-008) and that in Study A4250-005, indicating [redacted]

Odevixibat was well tolerated in patients with PFIC1, 2, and 3 and in patients with a medical history of biliary diversion surgery. The discontinuation rate due to TEAEs was low with three (on 120 µg/kg/day) of 77 patients across the Pooled Phase 3 group discontinued due to a TEAE of diarrhoea, worsening of cholestasis or worsening of pruritus and weight loss.

There were no deaths reported across the odevixibat clinical programme. Treatment-emergent serious adverse events (SAEs) were reported in [redacted] patients in the Pooled Phase 3 group; these were primarily reports of [redacted] The only SAEs reported in more than one patient overall across the Phase 2 and

3 studies were [redacted] In Study A4250-005, there were no SAEs reported in patients who received 40 µg/kg/day; three patients (16%) in the 120 µg/kg/day group and 5 patients (25%) in the placebo group experienced SAEs. Two (20%) of the patients with PFIC in Study A4250-003 experienced SAEs. None of the treatment-emergent SAEs were assessed by the investigator as related to study drug. No patients experienced an event of liver decompensation.

[redacted] were observed in clinical chemistry and haematology parameters measured, including serum creatinine, albumin, platelets, international normalised ratio (INR), and fat-soluble vitamin levels, or effects on urinalysis parameters, but excluding hepatic biochemical parameters. [redacted] based on review of vital signs or physical examination data.

In longer- term analysis of PEDFIC2 [redacted] the safety and tolerability profile of odevixibat in patients with PFIC [redacted]

9.8 Evidence synthesis and meta-analysis

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

9.8.2.1 Rationale for qualitative synthesis

Based on the data available for off-label oral therapies and biliary diversion surgery, that included only uncontrolled, mainly retrospective studies (see Appendix 17.6) for the studies identified in the systematic literature review), it was not possible to carry out an indirect comparison.

In order to investigate the relative effectiveness of odevixibat compared to patients who have received current standard of care therapies, Albireo is planning to perform the [redacted] study. The [redacted] study will compare clinical outcomes in odevixibat to comparable

external controls [redacted] The study will compare firstly odevixibat versus external controls without prior PEBD (Part A) ,and then odevixibat without prior PEBD versus external controls receiving PEBD (Part B). The study results are expected in [redacted].

- The primary endpoint (Part A only) is planned as [redacted]
- The secondary endpoints will include:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Exploratory
  - [redacted]
  - [redacted]
  - [redacted]

The [redacted] study is a [redacted] provided feedback on the sufficient duration to detect a meaningful difference in the clinical outcomes between the odevixibat cohort and the external control. Based on the [redacted] was revised and finalised in [redacted] database is planned to be locked after all patients [redacted] or discontinue from the study and interim database lock from the ongoing [redacted]

The primary analysis will be performed after [redacted]. It is estimated that study will have at least 90% power to detect a hazard [redacted]. The power is at least [redacted] for the External Control Cohort. To maintain data integrity and minimise potential bias, [redacted]

At this stage Albireo is unable to carry out interim analyses of the [redacted] for the below reasons:

- Following a meeting with [redacted]
- [redacted]
- [redacted]

9.8.2.2 NAPPED

As described in section 6.1.3, the NAPPED study aims to determine the natural history of PFIC and outcomes following SBD by assembling the largest genetically defined cohort of patients with severe BSEP deficiency to date.

Albireo provides support for the NAPPED natural history study, where the data will support the Phase 3 programme by further demonstrating the importance of bile acid reduction for symptoms and disease modification as well as serving as a “control” arm for the open-label extension study (PEDFIC2).

The aims of NAPPED were to:

- Characterise the natural course of disease in PFIC1 and PFIC2
- Determine associations between genotype and phenotype
- Assess effects of surgical biliary diversion on native liver survival
- To identify an early surrogate marker for long-term native liver survival

Since its start in 2017, NAPPED has collected retrospective data on patients with PFIC1 and PFIC2 (severe BSEP deficiency caused by mutations in ABCB11). The Childhood Liver Disease Research Network (ChiLDReN) collected data prospectively[12].

NAPPED currently comprises 68 referral centres from Europe, North America, South America, Africa, Asia, and Australia[12].

Data collection and management used a prespecified case-record form and was captured using Research Electronic Data Capture (REDCap). Demographic, clinical, and outcome data were collected by investigators within each centre, who identified all consecutive patients who had ever been under paediatric care (age 0-18 years) since 1981. From

ChiLDReN, all cases of PFIC1 enrolled in the Longitudinal Study of Genetic Causes of Intrahepatic Cholestasis (LOGIC) since 2007 were included.

Table 31. Summary of methodology for NAPPED

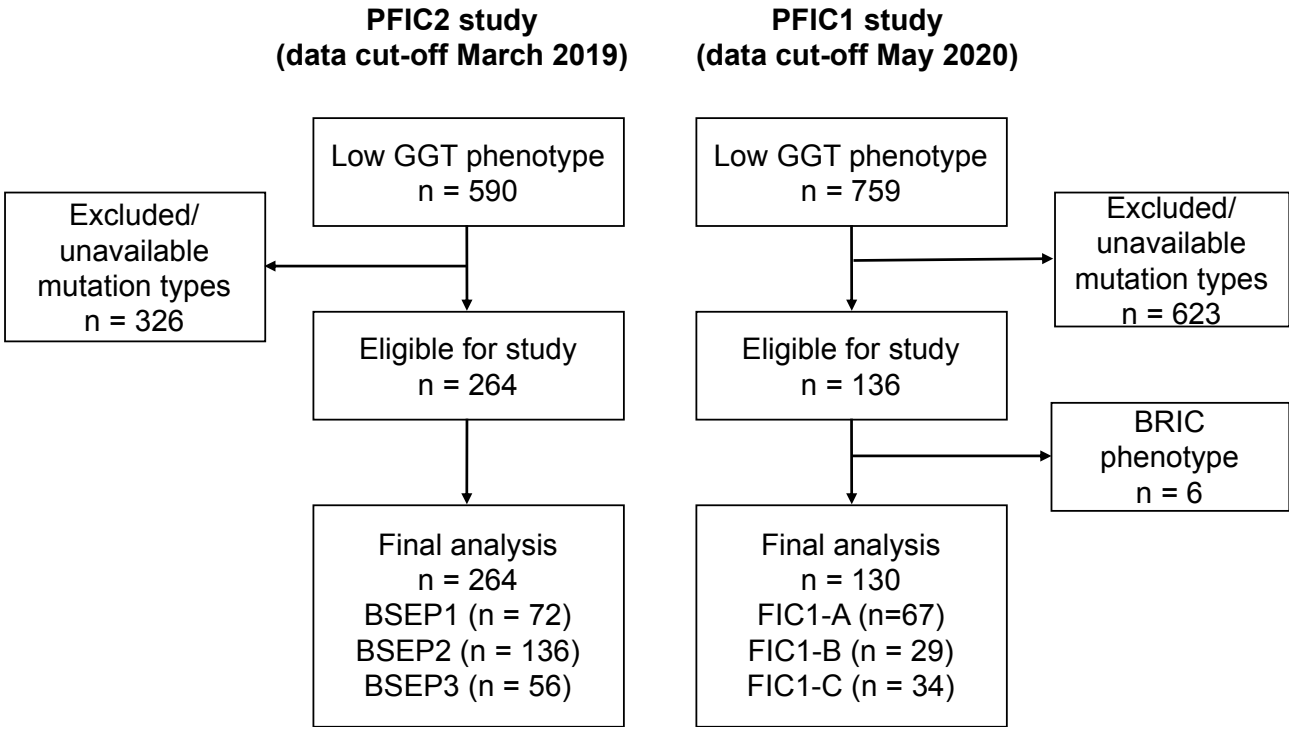
Study name	NAPPED (NAtural course and Prognosis of PFIC and Effect of biliary Diversion)
Objective	• Characterise the natural course of disease in PFIC1 and PFIC2 • Determine associations between genotype and phenotype • Assess effects of surgical biliary diversion on native liver survival • To identify an early surrogate marker for long-term native liver survival
Location	European, North American, South American, African, Asian and Australian centres
Design	Retrospective study
Duration of study	Data collection ran from 2017. Most recent published analysis of the PFIC1 population has a data cut-off in May 2020[12]. Most recent published analysis of the PFIC2 population has a data cut-off in March 2019[10]
Patient population	Patients with a clinical phenotype of progressive low- GGT cholestasis, including all consecutive patients who had ever been under paediatric care (age 0–18 years) since 1977
Sample size	PFIC1 N=130 (van Wessel 2021[12]); PFIC2 N=264 (van Wessel, 2020[10])
Inclusion criteria	Patients with PFIC1 and PFIC2 are included in the NAPPED study. • PFIC1: Patients with pathological compound heterozygous or homozygous ATP8B1 mutations • PFIC2: Patients with compound heterozygous or homozygous pathological ABCB11 mutations were selected.
Exclusion criteria	PFIC1 population: Patients without available genetic reports or with mutations of no identifiable pathological significance were excluded. PFIC2 population: Patients were excluded if genetic reports were unavailable, if they had ABCB11 mutations of no or unknown pathogenicity, or mutations in ATP8B1 or TJP2
Intervention(s) (n =) and comparator(s) (n =)	Not applicable. Patients were receiving standard of care therapies.
Baseline differences	Not applicable
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow-up ended at last visit, liver transplantation or death.
Outcomes (including scoring methods and	**PFIC1** (van Wessel 2021[12]): Biochemistry at presentation in the tertiary centre, as well as prior to SBD and between 2 months and 1 year after

timings of assessments)	SBD, were analysed. If such information was available from the medical file, pruritus was scored as “absent,” “mild to moderate,” or “severe” at the discretion of the participating centre, which, for statistical purposes, was dichotomized later into “absent” or “present.” Effect of SBD on pruritus was noted as “no improvement in pruritus,” “transient (partial or complete) relief of pruritus,” or “sustained (partial or complete) relief of pruritus.” Analyses were performed with regard to important clinical events in the form of SBD, LT, or death. **PFIC2** (van Wessel, 2020[10]): Outcome parameters were diversion-free survival (years between birth and SBD, last visit, LTx or death) and native liver survival (NLS, years between birth and either LT, death, or last visit, whichever occurred first)

9.8.2.3 Patient disposition

The number of patients included in each part of the study are shown in Figure 31. Of note, The PFIC2 NAPPED study included patients of the BSEP3 subtype (with mutations leading to non-functional protein).

Figure 31. Patient disposition in NAPPED – PFIC1 and PFIC2 studies



Source: van Wessel 2020[10]; van Wessel 2021[12]

9.8.2.4 Baseline characteristics

Baseline characteristics of the two studies are shown in Table 32.

Table 32. Baseline characteristics of PFIC1 and PFIC2 patients in NAPPED

	PFIC1 Patients (n = 130)	PFIC2 Patients (n = 264)
Year of birth, years Available n (%)	2007 (1999-2012) 130 (100)	2004 [1995-2012] 263 (99)
Year of birth time frame	1981-2019	1964-2018
Males, n (%) Available n (%)	71 (55) 130 (100)	125 (50) 252 (95)
Age at first visit, years Available n (%)	0.6 (0.3-2.2) 130 (100)	0.7 [0.2-1.9] 251 (95)
Year of first visit, years Available n (%)	2010 (2006-2014) 130 (100)	2007 [1997-2013] 251 (95)
Year of first visit time frame	1982-2019	1977-2018
Prior to presentation ever treated with:		
UDCA, n (%)	41/103 (40)	122/264 (46)
Rifampicin, n (%)	16/103 (16)	52/264 (20)
Phenobarbital, n (%)	10/103 (10)	16/264 (6)
Cholestyramine, n (%)	12/103 (12)	40/264 (15)
Antihistamines, n (%)	9/103 (9)	21/264 (8)
Laboratory data at presentation:		
sBAs, μmol/L Available n (%)	179 (122-220) 69 (53)	252 (161-363) 141 (53)
Total serum bilirubin, μmol/L Available, n (%)	129 (64-220) 103 (79)	107 (43-162) 200 (75)
ALT, IU/L Available, n (%)	48 (31-82) 102 (78)	199 (83-386) 189 (71)
AST, IU/L Available, n (%)	66 (50-86) 89 (68)	242 (97-422) 169 (64)
GGT, IU/L Available, n (%)	23 (17-35) 90 (69)	24 (16–36) 182 (69)
Platelet count, 109/L Available, n (%)	461 (313-569) 57 (44)	384 (275-517) 176 (67)

Abbreviations: ALT Alanine aminotransferase; AST Aspartate aminotransferase; GGT Gamma-glutamyltransferase;
Source: van Wessel 2020[10]; van Wessel 2021[12]

In patients with PFIC1,[12] half of the patients with an FIC1-A genotype had used or were using UDCA (50%) prior to or at presentation, which was a larger proportion of patients than in the FIC1-B (39%) or FIC1-C (26%) genotypes (P = 0.01). The difference in use of UDCA did not seem result in markedly improved biochemistry in comparison to the other patient groups. In FIC1-A patients, significant differences in biochemistry at presentation were not observed between patients who had used or were using UDCA and those who never used UDCA (not performed for FIC1-B and FIC1-C due to lower numbers). In PFIC2 patients 46% had been treated with UDCA at presentation in the referral centre, which was similar across the subtypes.[10]

9.8.2.5 Key results

PFIC2 (van Wessel 2020[10])

During follow-up of a median 4.1 (1.5–12.3) years, 61 patients had undergone SBD and 120 patients had undergone LT.

In total, 16 patients (BSEP1 n = 3/72 [4%], BSEP2 n = 8/136 [6%], BSEP3 n = 5/ 56 [9%]) died prior to LTx (age 1.6 [1.1–3.5] years). Deaths were all related to liver disease.

At 18 years of age, 32% of patients were alive with native liver. During adulthood (age ≥18 years), 5 patients underwent LTx (aged 19.6–27.5 years).

Patients with BSEP1 had better long-term outcomes than those with BSEP2 or BSEP3, with a median NLS of 20.4 years, vs. 7.0 years and 3.5 years, respectively (BSEP1 vs. BSEP2 p = 0.009; BSEP1 vs. BSEP3 p <0.001; BSEP2 vs. BSEP3 p = 0.02).

SBD was more often performed in BSEP1, as opposed to BSEP2 and BSEP3 (p <0.001, % of patients with SBD at 15 years: 74%, 38% and 28% respectively; BSEP1 vs. BSEP2 p <0.001, BSEP1 vs. BSEP3 p = 0.004, BSEP2 vs. BSEP3 p = 0.90).

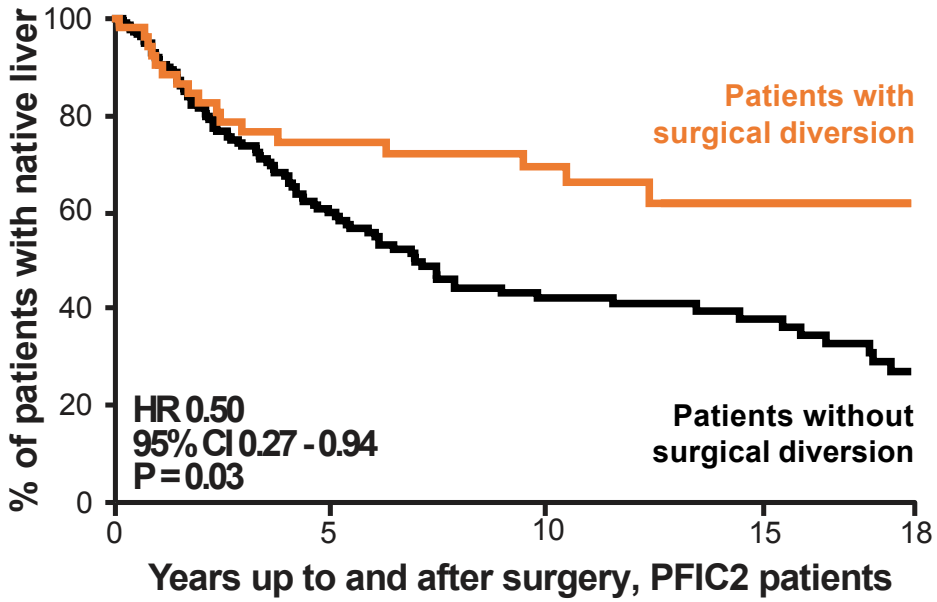
Median age at time of SBD was 2.3 (1.2–4.7) years (n = 61). Follow-up after SBD was 8.4 (1.6–12.0) years. The diversion was surgically closed in 6 patients (BSEP1 n = 2, BSEP2 n = 3, BSEP3 n = 1) at 2.0 (0.1–4.0) years after SBD. LTx followed closure in 5/6 patients, 6.2 (0.8–10.2) years after initial SBD. LTx was performed in 18 (30%) of the 61 patients at 2.4 (1.3–10.0) years after SBD.

Prior to SBD, pruritus was present in 36 (97%) of the 37 patients for whom paired data was available pre- and post-SBD. After SBD, 17 patients (46%) experienced pruritus (p <0.001). The improvement of pruritus post-SBD was semi-quantified: 12/41 patients (29%) had no improvement of pruritus, whereas 7/41 (17%) had transient partial or complete relief of pruritus and 22/41 patients (54%) had sustained partial or complete relief of pruritus.

SBD was associated with a decrease in sBAs (363 [254–452] to 48 [4–258] µmol/L; median 90% decrease; p <0.001). 63% (24/38) had a ≥ 75% decrease in sBA.

SBD was associated with significantly higher NLS (HR 0.50; 95% CI 0.27–0.94; p = 0.03; Figure 32) in BSEP1 and BSEP2.

Figure 32. Observed native liver survival in PFIC2 (BSEP1 and BSEP2) patients undergoing SBD or not

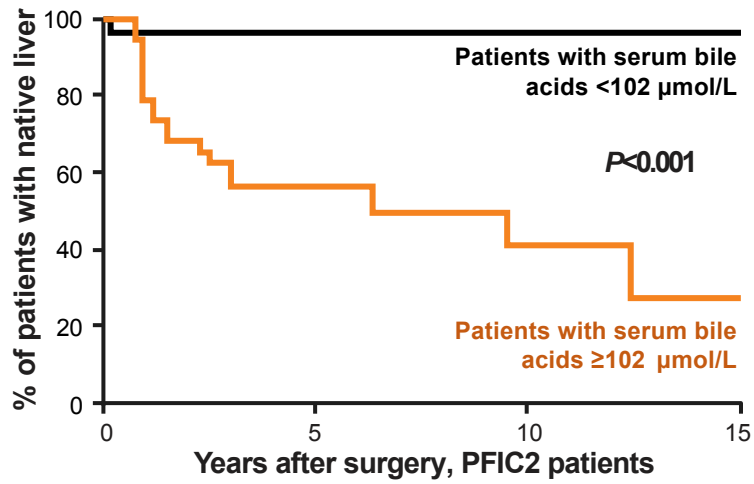


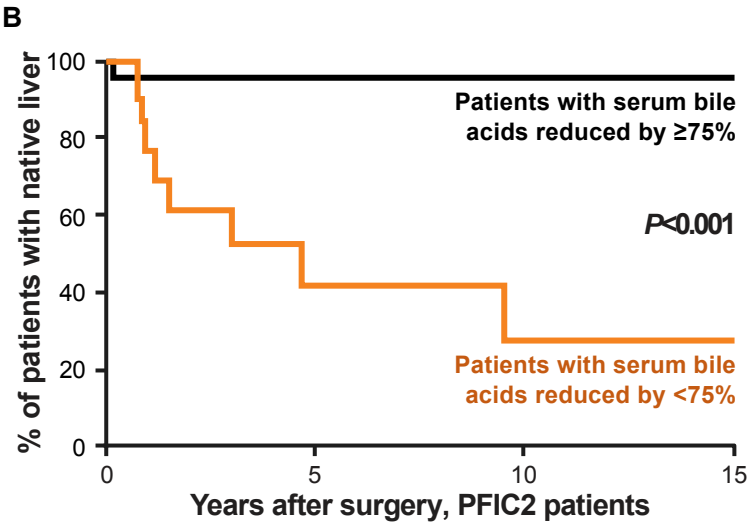
Source: Adapted from Van Wessel et al. 2020[10]

Furthermore, serum bile acid levels after diversion were associated with native liver survival. A post-SBD sBA level <102 µmol/L was associated with prolonged NLS after SBD (Figure 33; p <0.001, AUC sBAs: 0.778; cut-off 102 µmol/L: sensitivity 80%, specificity 75%). Additionally, a decrease of at least 75% in sBAs was associated with improved NLS after SBD (p <0.001; AUC % change sBAs 0.774; cut-off 75%: sensitivity 73%; specificity 78%).

Figure 33. Observed native liver survival after surgical biliary diversion, stratified for post-surgical SBA cut-offs (PFIC2 patients)

A





Source: Adapted from Van Wessel et al. 2020[10]
Notes: A – Patients with a post-surgical SBA concentration < or ≥ 102 µmol/L; B – patients with a relative decrease in SBAs of < or ≥75% Log-rank test

PFIC1 (van Wessel 2021[12])

During follow-up of a median of 4.2 (2.2-9.8) years, 62 of 130 patients (48%) had undergone an SBD and 38 of 130 patients (29%) had undergone LT.

A total of 8 patients (6%) died prior to LT, of which 3 underwent SBD during follow-up. Deaths were related to liver disease in 7 patients (age at death 5.0 years [range, 3.2-10.7]) and unrelated to liver disease in 1 patient.

Survival analysis showed that at 18 years of age, 44% of patients were alive with their native liver. During adulthood (i.e., ≥18 years of age), 2 patients underwent LTx (ages 20.0 and 20.2 years, indications for LT; pruritus [n = 1], unknown [n = 1]).

A total of 62 patients underwent an SBD during follow-up, at a median age of 5.9 years. Based on the limited information available (n = 22), it seemed that the main indication for SBD had been pruritus (21/22 [95%]). Of the 62 patients who underwent SBD, 49 underwent partial external biliary diversion (PEBD) (79%), 6 underwent gallbladder-colic diversion (CLD) (10%), 4 underwent ileal exclusion (IE) (5%), 1 underwent total biliary diversion (TBD) (2%), 1 underwent cholecystojejunostomy (2%), and 1 underwent an unknown procedure (2%).

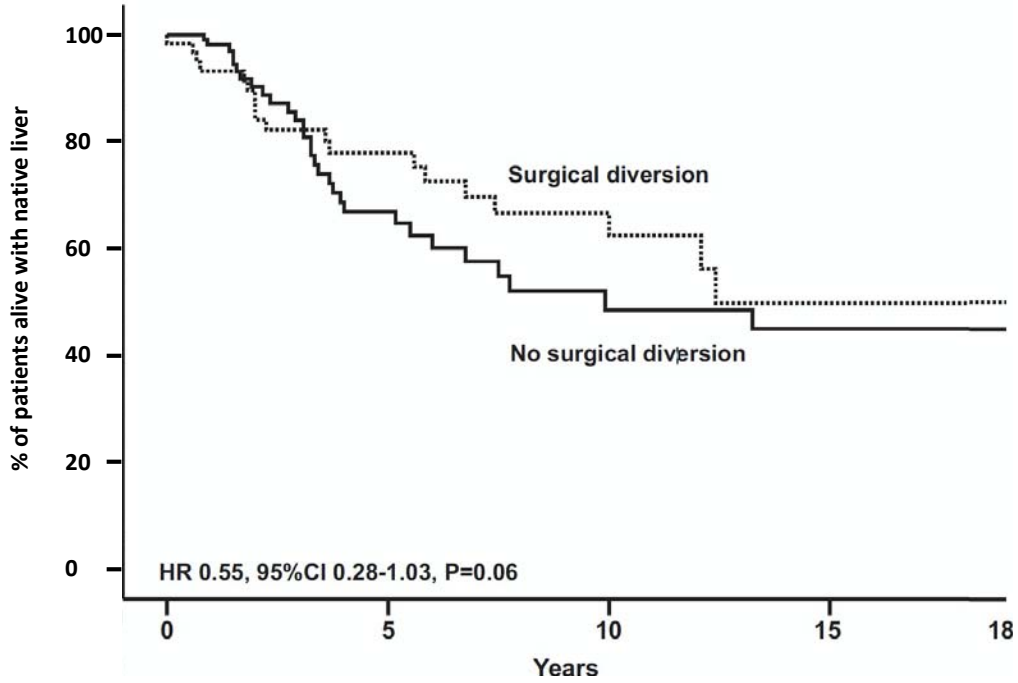
Prior to SBD, pruritus had been present in 28 of 29 patients (97%). Post-SBD (i.e., at least 2 months and maximum 1 year after SBD), pruritus was present in 23 of 29 patients (79%) (P = 0.13). Retrospective analysis on pruritus data should be interpreted with caution, however, data derived from the patient files indicated that in those patients for whom long-term pruritus data were available (n = 23), half seemed to (partially) benefit from SBD: In 11 of 23 patients (48%), no improvement of pruritus was reported, whereas 6 of 23

patients (26%) had transient relief and 6 of 23 patients (26%) had sustained (partial or complete) relief of pruritus.

SBD was associated with a decrease in sBAs (230 [125-282] to 74 [11-177] µmol/L; median 49% decrease; P = 0.005). 52% (12/23) patients had a reduction in sBA to < 65 µmol. Although numbers were small, the post-SBD sBA levels associated with post-SBD presence of pruritus: patients with a post-SBD sBA <65 µmol/L were less likely to experience pruritus (n = 7/11 [63%]) compared to patients with a post-SBD sBA ≥65 µmol/L (n = 9/9 [100%]) (P = 0.04).

SBD tended to be associated with NLS (overall HR, 0.55; 95% CI, 0.28-1.03; P = 0.06; Figure 34). However, the association between SBD and NLS was not similar across the three subgroups: An FIC1-B genotype was associated with a significantly lower NLS (HR, 2.13; 95% CI, 1.09-4.16; P = 0.03).

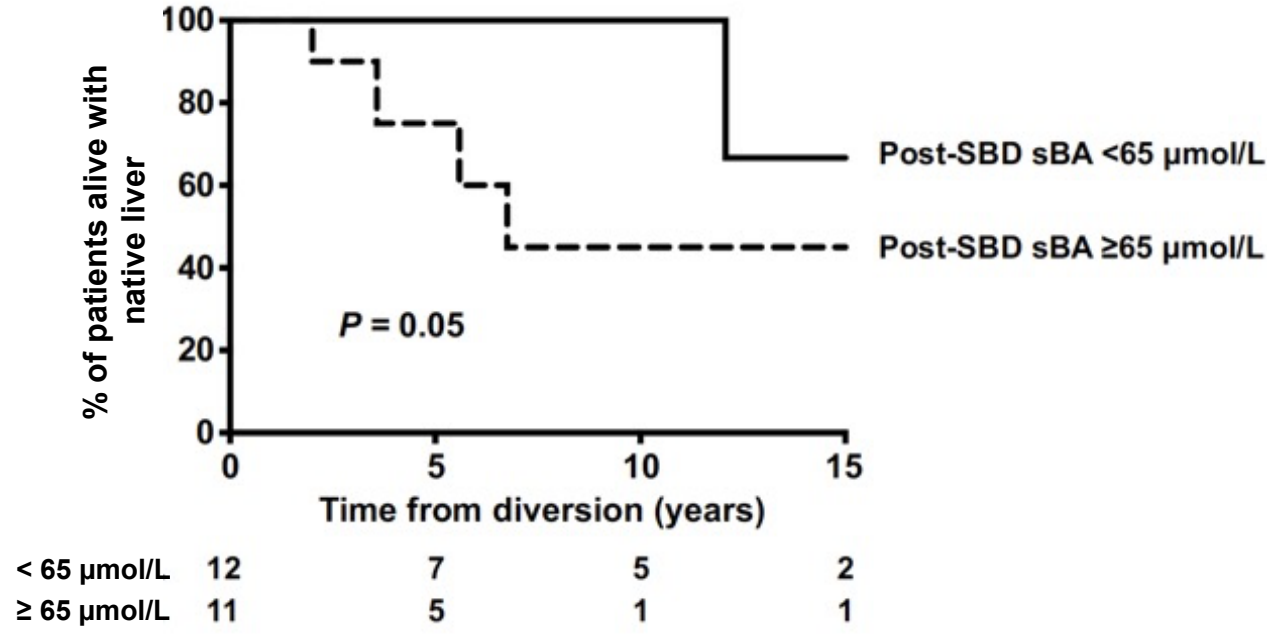
Figure 34. Observed native liver survival in PFIC1 patients undergoing SBD or not



Source: Adapted from Van Wessel et al. 2021[12]

As in PFIC2, serum bile acid levels after diversion were associated with native liver survival. A post-SBD sBA level <65 µmol/L tended to be associated with prolonged NLS after SBD (P = 0.05; AUC sBAs: 0.589; sensitivity 80%, specificity 61%; Figure 35). A decrease of at least 76% (based on ROC) in sBAs was not associated with improved NLS after SBD (P = 0.21; AUC % change sBAs: 0.525; cut-off 76%: sensitivity 80%, specificity 44%).

Figure 35. Observed native liver survival after surgical biliary diversion, stratified for post-surgical sBA cut-offs (PFIC1 patients)



Source: Adapted from Van Wessel et al. 2021[12]

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

PFIC is a rare and devastating disease; the two major complications are cholestasis leading to progressive hepatic damage, and unrelenting pruritus. The majority of patients with PFIC undergo liver transplantation in childhood[26] with the indication for transplantation being identified as either end-stage liver disease or intractable pruritus. Elevated sBAs have been associated with, and are thought to contribute to, the progressive hepatic damage seen in these children,[10] and to mediate cholestatic pruritus, although the exact mechanism has not yet been established.[26]

There is currently no approved pharmacological therapy for the treatment of PFIC in the UK and in many cases the frequently-used off-label medications and surgical biliary diversion do not prevent the progressive hepatic damage that results in end stage liver disease and the need for liver transplantation. A new medical therapy is desperately needed for this patient population that has a serious unmet need.

The primary evidence of the efficacy and safety of treatment with odevixibat in the proposed indication is based on the two Phase 3 studies conducted in patients with PFIC: PEDFIC and PEDFIC2.

Treatment with odevixibat led to statistically significant reductions in pruritus severity over the 24-week treatment course of PEDFIC1. The primary pruritus endpoint evaluated the proportion of positive pruritus assessments, where a positive assessment was defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the ObsRO instrument. (The ≥1 point reduction in scratching score used in the primary analysis was determined to be clinically meaningful based on a blinded psychometric analysis conducted by an independent group.[71])

- A significantly higher mean proportion of positive pruritus assessments at the patient level was observed over the 24-week treatment period in both the 40 µg/kg/day group and the 120 µg/kg/day group compared with placebo.
- The observed difference in the proportion of positive pruritus assessments between the 40 and 120 µg/kg/day groups was not statistically significant and the outcomes in the two treatment groups are considered comparable.
- The durability of the improvement in pruritus, in some patients for over a year, was demonstrated by continued observation of patients who rolled over to receive odevixibat at 120 µg/kg/day in PEDFIC2.
- Importantly for patients, the improvement in pruritus symptoms occurred rapidly, i.e., within 4 weeks. This reduction was maintained through 24 weeks in PEDFIC1 and during continued treatment in PEDFIC2 with some patients treated for 72 weeks and longer.[79]

A key objective in patients with PFIC is to reduce the intense pruritus that occurs at night and disturbs the child's sleep leading to tiredness, poor attention, and impact on school performance. Consistent with the primary endpoint, which evaluated the combined night-time and daytime scores, treatment with odevixibat also led to greater improvements in both night-time pruritus symptoms and daytime pruritus symptoms compared with placebo and these improvements continued during long-term treatment.

As noted above, patients with PFIC often experience intense pruritus at night that disturbs their sleep (for the younger children, this also impacts the sleep of the caregiver). Improvements in several observer-reported sleep parameters were observed in PEDFIC1, consistent with the improvements in pruritus. A greater improvement in daytime tiredness

score also was observed for patients who received odevixibat compared with those who received placebo. These improvements in daytime and night-time pruritus and sleep disturbance were maintained during continued treatment with odevixibat in PEDFIC2.

Treatment with odevixibat at doses of 40 and 120 µg/kg/day was shown to be effective in reducing sBA in patients with PFIC.

- Both doses of odevixibat led to a statistically significantly higher proportion of patients experiencing at least a 70% reduction in SBA concentration from baseline or reaching a level of ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment in PEDFIC1 compared to placebo.
- Although the proportion of responders was numerically higher in the 40 µg/kg/day group, the difference in the responder rate between the odevixibat treatment groups was not statistically significant and the results between the 40 and 120 µg/kg/day groups were determined to be comparable.
- Analyses of secondary and exploratory endpoints demonstrated that mean reductions in sBA levels from baseline to the end of treatment were observed for both odevixibat treatment groups compared to an increase from baseline observed in the placebo group.
- The reductions in sBA produced by odevixibat occurred rapidly, within 4 weeks following initiation of treatment, with maximum improvements after 8 weeks. The reductions were maintained during continued treatment with odevixibat in PEDFIC2; some patients have continued to receive odevixibat for up to 1 year and reductions in sBAs have been maintained.

The clinical relevance of this decrease in sBAs with respect to long term benefit has recently been established.[10,12,35] Elevated bile acid levels in the liver evoke progressive liver damage, therefore reducing these levels slows progression of liver damage. In the NAPPED study, a greater proportion of patients (PFIC2) with lower sBAs after surgery survived with their native liver intact for up to 15 years versus those who had elevated sBAs post-surgery.[10] Reduction of bile acid levels below 102 µmol/L, or a 75% reduction from pre-diversion values, significantly increased native liver survival after SBD.[10] An analysis of patients with PFIC1 in NAPPED showed that post-SBD sBA level <65 µmol/L tended to be associated with prolonged NLS after SBD over 15 years ($p = 0.05$), although a decrease of at least 76% (based on ROC) in sBAs was not associated with improved NLS after SBD[12]. In addition, in a study of the investigational treatment maralixibat,

another iBAT inhibitor under investigation for the treatment of PFIC, in patients who responded to treatment, defined as achieving an sBA <=100umol, none were listed for LTx after >4.5 years treatment.[80]

Since reduction in sBA can be correlated with increase in native liver survival, treatment with odevixibat alters the course of PFIC disease progression, with the potential to delay liver transplants in patients who would otherwise have been transplanted due to uncontrolled severe pruritus.

In PEDFIC1 there were [redacted] patients treated with odevixibat that underwent surgery, whilst [redacted] who had received placebo underwent surgical intervention due to lack of improvement in pruritus. [redacted] enrolled in PEDFIC1 was listed for [redacted] due to [redacted] pruritus following odevixibat treatment in PEDFIC2.[18]

Improvements relative to placebo were also observed for other clinically meaningful secondary endpoints, including sleep parameters and growth. Among odevixibat-treated patients, mean reductions from baseline were observed early in the course of treatment for both dose groups for the percentage of days with help falling asleep, percentage of days requiring soothing, and percentage of days sleeping with the caregiver; for the placebo-treated patients, minimal changes from baseline were observed for these sleep parameters.

In addition to their chronic illness and severe symptomatology, patients with PFIC have fat malabsorption which contributes to growth retardation with weight and height below normal centiles for their age-matched peers. Growth was monitored in both PEDFIC1 and PEDFIC2. Substantial improvement in growth was observed in patients continuing treatment in the open label extension study. Mean height and weight z-scores improved by approximately 0.5 during treatment with odevixibat with both approaching a z-score of 0 (50th percentile) indicating a substantial catch-up in growth to that expected in healthy children.

In parallel with improvements in clinical signs and symptoms of the underlying disease, odevixibat improved patient and family QoL, Results of the PedsQL total score and family impact scores showed [redacted] at Week 24 for patients who received odevixibat and [redacted] for patients who received placebo.[16] Among PedsQL domains, [redacted] in physical, emotional, social and school functioning, whereas with placebo, [redacted]. PEDFIC1 also included as exploratory endpoints the use of global symptom relief instruments (GIS and

GIC) to further evaluate odevixibat's impact on pruritus and sleep. Caregivers of patients who received odevixibat reported [redacted] in both itch and sleep of patients at Week 24 compared with caregivers of patients who received placebo. Consistent with these assessments of the impact of odevixibat on the overall well-being of patients and families, responses to an exit survey demonstrated [redacted] who received odevixibat reported meaningful change in the patient since the start of treatment compared with placebo. In the overall odevixibat group, meaningful change was reported in [redacted] of patients receiving odevixibat compared with [redacted] patients who received placebo.[77]

In summary, treatment with odevixibat led to a statistically significant and clinically meaningful reduction in pruritus as well as a statistically significant and clinically relevant reduction in sBAs .

Pruritus is one of the two indications for liver transplantation in children with PFIC. Indeed, confidential data from the NAPPED study show that [redacted], with approximately [redacted] of the PFIC1 and PFIC2 patients being [redacted].[29] This means that, by reducing pruritus, odevixibat has the potential to delay, or perhaps even prevent, liver transplantation in this patient population.

The second indication for liver transplantation in PFIC patients is end-stage liver disease resulting from prolonged cholestasis. To the extent that bile acids contribute to the ongoing liver damage, reduction of bile acid levels by odevixibat could also result in improved hepatic health and subsequent delay of liver transplantation; this potential is supported by the improvement in hepatic biochemical parameters observed in patients receiving odevixibat.

The impact of odevixibat on the overall health and well-being of patients was demonstrated by the totality of evidence across multiple endpoints, including improvement in growth, improvement in many of the measured sleep parameters, and in QoL for both patients and their families.

Odevixibat has been generally well tolerated in all completed studies. Adverse events (AEs) reported have primarily been of mild to moderate intensity.

Recent data from PEDFIC2 ([redacted]) provided to the EMA show that treatment with odevixibat 120 µg/kg/day resulted in [redacted]

[redacted]as assessed by serum bile acids and hepatic biochemical parameters, [redacted] in pruritus severity, and [redacted] in sleep parameters, and growth. The safety and tolerability profile of odevixibat in during the update period is [redacted].[79]

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

9.9.2.1 PEDFIC1

The efficacy and safety of odevixibat in children with PFIC1 and PFIC2 have been demonstrated in a multicentre, multinational, double-blind, randomized, placebo-controlled, Phase 3 study that included 62 patients. PEDFIC1 is the largest phase 3 PFIC randomised study to date ever conducted.

Placebo as comparator: Currently, there is no medical treatment approved for PFIC1 and PFIC2 and therefore placebo was the appropriate comparator. Concomitant treatment with conventional therapies, including UDCA and rifampicin, was permitted during the study provided the dose remained stable during the treatment period.

Endpoint measurement: The study met both primary endpoints. Given the expected impact of odevixibat to lower serum bile acid levels, measurement of this key efficacy endpoint was conducted at a central laboratory and the results were not submitted to the study sites or sponsor prior to database lock in order to maintain the treatment blind. For the pruritus endpoint, Albireo developed novel clinical outcome assessment tools, including Patient Reported Outcomes (PRO) and ObsRO instruments, to assess pruritus (itching and scratching, respectively). These instruments also evaluated sleep disturbance. The development of the instruments followed industry and regulatory best practice guidelines. Patients and/or their caregivers were provided an electronic diary (eDiary) for twice-daily recording (AM, representing nighttime impact and PM, representing daytime impact) of itching, scratching, and sleep disturbance throughout the study using the PRO (for patients ≥8 years of age) or ObsRO (caregivers of all patients).

Stratification of baseline characteristics: Stratification was used to minimise any potential imbalance in baseline characteristics that could impact treatment effect. Two factors were selected: age (6 months to 5 years, 6 to 12 years, and 13 to ≤18 years) and

PFIC type (Type 1 and 2). Stratification by age was performed due to the progressive nature of the disease. In general, patients with PFIC1 have more systemic manifestations (pancreatic disease, bowel problems and hearing impairment) than those with PFIC2, who primarily present with only liver-associated manifestations.[81] In patients with PFIC2, hepatic decompensation tends to progress more rapidly than in patients with PFIC1.[38]

Subgroup analyses of PEDFIC1 indicate that the positive treatment effects for both reduction in sBA and improvement in pruritus severity were similar across patient subgroups based on demographic and baseline disease characteristics. Importantly, both patients with PFIC1 and with PFIC2 obtained substantial benefit from treatment with odevixibat, including reductions in sBA levels and improvement in pruritus symptoms. Similar results were seen in the five patients with PFIC3 and one patient with MYO5B deficiency (PFIC6) in PEDFIC2.

Length of study: PEDFIC1 was 24 weeks in duration. While 12 months was recommended by US and EU regulators, a feasibility study suggested that it would be difficult to enrol a placebo-controlled study of that duration. Furthermore, a 6-month study was considered adequate to achieve the intended effect on the study endpoints, including significant improvements over placebo. This significant improvement over placebo after 24 weeks of treatment with odevixibat was confirmed based on the efficacy results of PEDFIC1.

Longer-term evaluation of efficacy and of safety is provided by the results of PEDFIC2.

9.9.2.2 PEDFIC2

PEDFIC2 is an open-label, 72-week extension study to investigate the long-term efficacy and safety of the 120 µg/kg/day dose of odevixibat in patients with PFIC. The study includes an optional extension period after 72 weeks for continued access to odevixibat. As well as providing long-term data in patients who participated in PEDFIC1, PEDFIC2 will investigate efficacy in an additional cohort that includes patients of any age with any type of PFIC. PEDFIC2 is ongoing.

Study design: A limitation of PEDFIC2 is its open label design. Clinical laboratory measurement endpoints, such as bile acids, are unlikely to be impacted by the patient's or caregiver's knowledge that the child is receiving active drug; however, the more subjective endpoints, such as assessments of pruritus score and sleep parameters could be influenced. Steps were taken, such as use of a standardised eDiary, collection of pruritus

scores at set times during the day, and extensive training on the use of the eDiary to harmonise scoring and assessments.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

9.9.3.1 Comparator

The key comparator for odevixibat in this assessment is biliary diversion surgery, however there is no direct comparative evidence available. As described in section 9.8.2.1, [redacted] will compare clinical outcomes in odevixibat to comparable external controls [redacted]. The primary analysis will be performed after [redacted]

Some comparative evidence is available from a single case study in which the same patient that participated in the phase 2 study (aged 15 months old) received sequential use of odevixibat and surgical interventions for treatment of PFIC.[82] At baseline of the phase 2 study, the patient's total serum bile acid level was 124.3 µmol/mL which fell by 95% to 6.5 µmol/mL after 4 weeks of odevixibat treatment. Immediately preceding PEBD, the total sBA level was 276 µmol/mL which fell to <1 µmol/mL following PEBD.

Pruritus and sleep disruptions demonstrated similar patterns:[82]

- During the odevixibat study, patient diary data showed reductions in visual analogue scale itch severity (VAS-Itch; 0–10 scale) scores of 5 points with odevixibat treatment (from 8 to 3 points). Following PEBD, VAS-Itch scores were reduced by 6 points (from 8 points before PEBD to 2 points after surgery).
- Pruritus improvements were also documented during the clinical study of odevixibat on the 4-point Whitington-itch scale (reduction from 2 to 1) and in Partial Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD; 0–10 scale) itch score (reduction from 8 to 3).
- A similar improvement (from 8 to 3) was observed in PO-SCORAD sleep disturbance score during odevixibat treatment. Sleep improvements observed after PEBD were qualitatively similar to those observed with odevixibat treatment.

9.9.3.2 Patient benefit

Clinical trial data provide direct evidence for the benefit for patients, in terms of reducing pruritus, improving sleep and improving growth. Whilst limited data are currently available on long-term outcomes, including requirement for surgical interventions, it is reasonable to expect that these will be delayed and even avoided, with long-term control of sBA. Longer-term data is still being collected in PEDFIC2.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The demographic characteristics of the paediatric patients with PFIC studied in the odevixibat Phase 2 and 3 clinical development programme are consistent with the known characteristics of the PFIC patient population.[4] Patients with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein were excluded from the clinical studies, and these patients are not expected to be treated in clinical practice. The SmPC states that patients with PFIC2 who have a complete absence or lack of function of BSEP protein will not respond to odevixibat.[15]

Included patients had sBA ≥100 µmol/L. In the NAPPED study patients also had sBA ≥100 µmol/L (PFIC1 range 122-220 µmol/L; PFIC2 range 161-363 122-220 µmol/L).[10,12]

Therefore, the results observed in the clinical development programme are applicable to the general population of patients with PFIC.

In England there are three highly specialised centres that manage patients with PFIC, and these are study sites for the odevixibat clinical trials. To date, 15 patients have been treated in the UK a part of the clinical trial programme.

Surgery

Patients with liver transplantation were excluded from the clinical studies and these patients are not expected to be treated in clinical practice. To date only 10 patients with previous biliary diversion surgery in cohort 2 of PEDFIC2 have been treated with odevixibat; the expectation is that odevixibat will have limited benefit in these patients.

PFIC subtypes

In clinical practice all patients with PFIC will be eligible for odevixibat treatment (see section 9.9.4). However, patients with types of PFIC other than PFIC1 or PFIC2 were excluded from PEDFIC1.

Data from the phase 2 study show improvements in sBA in a cohort that included two PFIC3 patients (section 9.6.1.2). Interim data from PEDFIC2 showed a [redacted] in pruritus and reduction in sBA in [redacted] patients included in Cohort 2 of the PEDFIC2 study (data at week 12), that included a patient with [redacted] Further evidence is currently being collected within Cohort 2 of the PEDFIC2 study and the ongoing Expanded Access Program.

Despite the current lack of data, clinicians believe all patients with PFIC should have access to treatment.

PFIC3 represents approximately one-third of PFIC cases[27], although this may be lower in the UK, where clinical experts estimate approximately 20% of patients have PFIC3.[8] PFIC3 has insidious onset in late infancy (30%) to early adulthood. PFIC3 represents with similar to PFIC1 and 2. It is a heterogenous disease with increased levels of GGT (cholangiopathy) and lower levels of serum bile acids, compared to patients with PFIC1 and 2.[27] However, similar to PFIC1 and PFIC2, it is characterised by progressive cholestasis. Patients experience end stage liver disease in the 1st to 2nd decade of life ultimately requiring liver transplant.

PFIC4 (TJP2 mutation) is a multisystem disease that has only recently been discovered and is very rare.[83,84]

All PFIC subtypes, regardless of the underlying genetic mutation, result in cholestasis characterised by elevated bile acid concentrations and intense pruritus. These features of PFIC are clinically relevant; elevated bile acid concentrations because they lead to ongoing hepatocyte damage and progressive live disease, and pruritus because it is often the most troubling symptom, frequently leading to liver transplantation in patients with PFIC.

Odevixibat directly addresses the elevated serum bile acids and pruritus by inhibiting IBAT in the terminal ileum, transporters common to patients with all PFIC subtypes. The site of action of odevixibat is distal to the underlying biochemical abnormalities and is independent of the genetic abnormalities responsible for the different PFIC subtypes.

Available evidence demonstrates efficacy of odevixibat in patients with PFIC1 and PFIC2. And although limited, accumulating data provide a strong initial signal for efficacy in patients with PFIC3 and demonstrate success in the single patient with PFIC6 (Figure 36).

The very small numbers of patients with PFIC3, PFIC4, PFIC5 and PFIC6 make conducting a randomized, controlled clinical trial in these population extremely challenging. However, as with PFIC1 and PFIC2, there is a critical unmet medical need in these populations.

The rationale presented here was provided to EMA for including all PFIC subtypes in the prescribing information for odevixibat. It has recently been supported by a publication in a peer-reviewed journal.[85] The authors conclude their review with the statement "*Preclinical and clinical data support IBAT inhibitors as non-invasive options to interrupt the enterohepatic circulation to treat cholestatic liver diseases and other disorders. These orally administered, selective and reversible compounds decrease enteric bile acid reuptake with minimal systemic exposure. They may play an important role in reducing the symptoms of ALGS [Alagille syndrome] and PFIC by pharmacologically interrupting the enterohepatic circulation of bile acids, thus reducing bile acid accumulation in the liver and reducing the potential for hepatobiliary injury*."

Figure 36. Changes in pruritus and sBA observed in subtypes of patients in PEDFIC2

BRIC is a type of PFIC characterised by episodes of cholestasis lasting from weeks to months, with irresistible pruritus. In a proportion of those with BRIC, the disease progresses to complete cholestasis over time with either a severe PFIC1 or PFIC2 phenotype depending on the mutation present.[10,12] Treatment of patients with episodic BRIC will be based on clinical judgment and the severity and duration of symptoms, and it is proposed that those patients most suitable for odevixibat would be those progressing to

continuous cholestasis and hepatocellular damage, or those with significant pruritus symptoms lasting at least three months.

Adult patients

Although not expected to influence the external validity, it should be noted that PEDFIC1 excluded patients aged 18 years or older, whilst the marketing authorisation is expected to be for patients aged 6 months or older. As PFIC presents in childhood, with most patients undergoing LTx before 18 years of age[35], patients in clinical practice are expected to start treatment with odevixibat before 18 years of age. By reducing sBAs, odevixibat is expected avoid surgical biliary diversion and delay or avoid liver transplant. As such, odevixibat is a chronic therapy: patients may continue to receive odevixibat into adulthood.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Patients with all PFIC types who have not yet had a liver transplantation or biliary diversion surgery are expected to benefit from treatment with odevixibat. Although not contra-indicated, patients with PFIC2 who have a complete absence or lack of function of BSEP protein are not expected to respond to odevixibat.[15]

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

There are several aspects of PFIC that have a negative impact on health-related quality of life (HRQL). The most distressing characteristic reported by patients, caregivers and clinicians is the extreme pruritus, which affects all aspects of daily living. This is the area where clinicians feel they have least control and are acutely aware of the effect on the quality of life of the patient and caregiver. The severe pruritus experienced in those with PFIC can be intolerable and often results in self-mutilation (see section 7.1.1). as well as having a significant impact on sleep, including difficulty falling and staying asleep, often requiring soothing from caregivers to sleep (see section 7.1.2).[42]

Growth retardation, failure to thrive and complications relating to vitamin deficiencies are other worrying aspects of the condition and may have a detrimental effect on the patient's HRQL.[7,86]

Other factors that may affect quality of life for patients with PFIC are the multiple medications, frequent medical appointments, and hospitalisations.

As a result of the intractable pruritus associated with PFIC and declining liver function, children with PFIC often require surgery at a very young age. Whilst the aims of surgery include reducing pruritus, sleep disturbances and improving growth, thereby improving HRQL, it is associated with a number of complications and other considerations, such as the requirement for a stoma, that may negatively impact HRQL (see 10.1.2).

Liver transplantation is not a cure, patients require life-long immunosuppressive therapy and experience anxiety related to the risk of complications and transplant rejection (see sections 7.1.1 and 8.2.6).

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

PFIC is a genetic disorder classified by the liver's inability to excrete bile acids. As a result, the acids accumulate in the liver and bloodstream, causing jaundice, nutritional deficiencies, severe itching known as pruritis and liver damage or cirrhosis. PFIC is a life-threatening rare disease affecting young children resulting in premature mortality in patients who have not undergone PEBD or LT.

There are no studies that describe HRQL over the disease course of PFIC. However, as the disease is progressive and without an effective pharmacological treatment the symptoms increase in severity with an associated decline in quality of life, with particularly poor HRQL in patients who experience pruritus.[85] Pruritus symptoms eventually become intolerable, necessitating SBD or LTx.

SBD, usually PEBD, can result in symptomatic improvement; however, post-surgery complications may occur, and the creation of a stoma may lead to feelings of anxiety, depression and anguish. In one study (Yee, 2018[45]) patients who underwent SBD all experienced improvements in HRQL, mainly due to improved sleep (73.4%), improved mood (67.4%) and less itching (63.3%). Another study reported post-surgery HRQL is similar to healthy children. Several important medical aspects, such as stomata or stigmatising scars, and everyday aspects such as the possibility of pursuing certain hobbies like swimming, were not included in the survey.[44]

External stoma bags required following PEBD contribute to negative feelings among patients. Common concerns expressed regarding stoma bags include fears about social life and insecurity by reintegration of previous social roles and functions.[60] The concomitant emotional and psychological burden on patients, their families and caregivers is significant.

Lower HRQL is seen in children with liver transplant compared with healthy children.[87] In addition, LTx is associated with life-long immunosuppressant therapy, potential complications, infections and rejection that would be expected to impact on HRQL. Patients with PFIC may change their lifestyle as a result of their LTx and express anxiety relating to maintaining their health post-transplant. However, if a LTx is successful in a child with PFIC, and is associated with a durable response with reduction in symptoms of pruritus, HRQL is expected to improve overall compared to that prior to transplantation.[44]

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals

HRQL data was collected using the paediatric quality of life inventory (PedsQL), reported by caregivers and patients in PEDFIC1.

Data was not considered appropriate given the small patient numbers and low statistical power. Patient numbers available for this analysis were small, especially in the patient-report group, with only a single observation for the sBA response at baseline. Due to differences at baseline in responders and non-responders, small sample size and marginal

differences in absolute scores that were counterintuitive, it was decided not to apply these values in the economic analysis (see Appendix 17.8).

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Mapping of the PEdsQL in PEDFIC1 was carried out but was not used in the base case analysis (see Appendix 17.8).

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used.

The search strategy for HRQL data is shown in Appendix 17.5. The number of studies included and excluded at each stage are shown in Figure 37. Seven of the 11 references related to odevixibat studies.

Albireo also conducted a burden of illness systematic literature review to identify studies on epidemiology and the wider burden of disease in PFIC. An additional study was identified in this review (Yee et al 2018[45]); however this study only reported that HRQL improved after SBD and did not report any scores.

Figure 37: Quality of life and utility SLR PRISMA

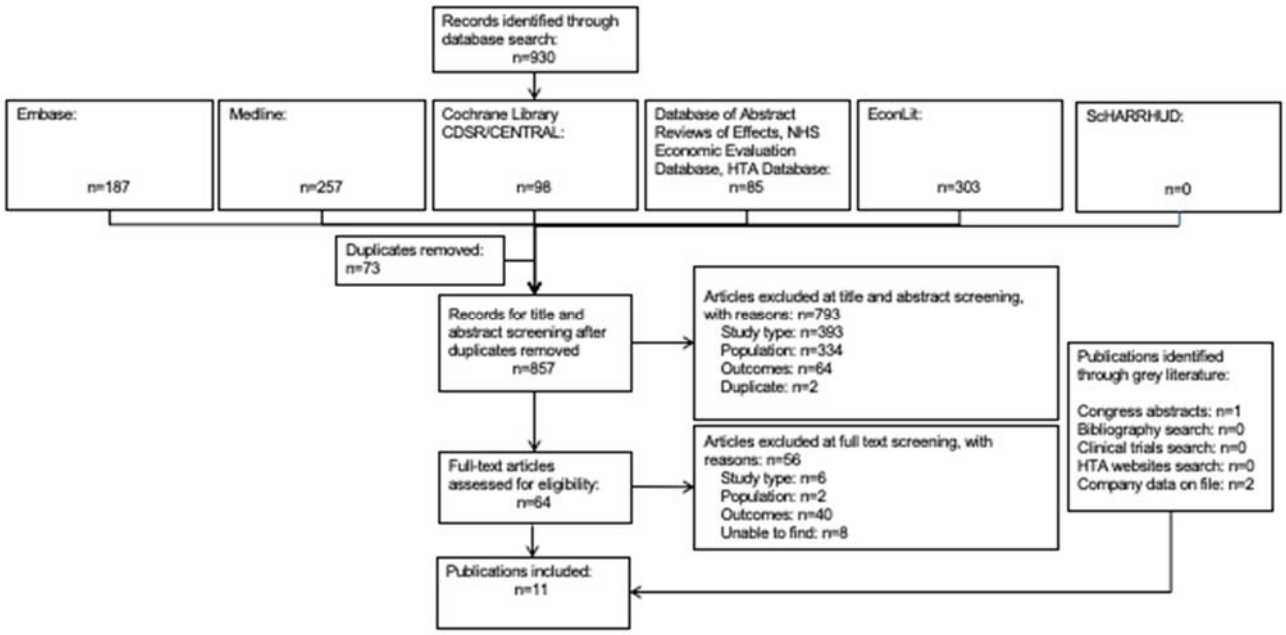


Table 33. List of included quality of life and utility SLR studies

Reference
Foroutan HR, Bahador A, Ghanim SM, Dehghani SM, Anbardar MH, Fattahi MR, Forooghi M, Azh O, Tadayon A, Sherafat A, Yaghoobi AA. Effects of partial internal biliary diversion on long-term outcomes in patients with progressive familial intrahepatic cholestasis: experience in 44 patients. Pediatric surgery international. 2020;63(5):603-610
Kamath BM, Chen Z, Romero R, Murray KF, Fredericks EM, Magee JC. Quality of life in alagille syndrome is associated with growth failure and cardiac defects. Hepatology. 2012;56:732A-733A
Thompson RJ, Kelly DA, McClean P, Miethke AG, Soufi N, Rivet C. Phase 2 open-label efficacy and safety study of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with progressive familial intrahepatic cholestasis: 48-week interim efficacy analysis. Hepatology. 2017 Oct 1;66(S1):57A.
Wassman S, Pfister ED, Kuebler JF, Ure BM, Goldschmidt I, Dingemann J, Baumann U, Schukfeh N. Quality of life in patients with progressive familial intrahepatic cholestasis: no difference between post-liver transplantation and post-partial external biliary diversion. Journal of pediatric gastroenterology and nutrition. 2018 Nov 1;67(5):643-8.
Odevixibat studies
Slavetinsky C, Sturm E. Impact of an ileal bile acid transporter inhibitor versus partial external biliary diversion in progressive familial intrahepatic cholestasis-a case providing direct comparison of medical and surgical therapies. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):892-893
Sturm E, Baumann U, Lacaille F, Gonzales E, Arnell H, Fischler B, Jorgensen MH, Thompson RJ, Mattsson J, Ekelund M, Lindstrom E et al. The ileal bile acid transport inhibitor a4250 reduced pruritus and serum bile acid levels in children with cholestatic liver disease and pruritus: Final results from a multiple-dose, open-label, multinational study. Journal of Pediatric Gastroenterology and Nutrition. 2017; 65(S2): S168-S169
Sturm E, Baumann U, Lacaille F, Gonzales E, Arnell H, Fischler B, Jorgensen MH, Thompson RJ, Mattsson J, Ekelund M, Lindstrom E et al. The ileal bile acid transport inhibitor A4250 reduced pruritus and serum bile acid levels in children with cholestatic liver disease and pruritus: final results from a multiple-dose, open-label, multinational study. Hepatology 2017 Oct 1;66(S1):646A-647A
Baumann U, Lacaille F, Sturm E, Gonzales E, Arnell H, Jørgensen MH, Thompson RJ, Ekelund M, Mattsson JP, Lindström E, Gillberg PG. The Ileal Bile Acid Transport inhibitor A4250 decreases pruritus and serum bile acids in cholestatic liver diseases–an ongoing multiple dose, open-label, multicentre study. Journal of Hepatology. 2017 Jan 1;66(1):S91.
Thompson RJ, Kjems L, Hardikar W, Lainka E, Calvo PL, Horn P. Improved Quality of Life in Children With Progressive Familial Intrahepatic Cholestasis Following 24 Weeks of Treatment With Odevixibat,

an Ileal Bile Acid Transporter Inhibitor- Results From the Phase 3 PEDFIC 1 Study. Value in Health. 2021;24(5):S1.
PEDFIC1 Clinical Study Report (company data on file)
PEDFIC2 Clinical Study Report (company data on file)

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

Eleven publications were included in the review, seven of which related to odevixibat studies. An overview of the four other studies is given in Table 34. One study (Wassman 2018[44]) provided adequate data that could be used to inform the economic model. In other studies utilities were not presented, could not be calculated or were not relevant to health states in the model.

The study by Wassman et al 2018 included 32 children with PFIC and compared patients after PEBD who still lived with their native livers were compared to those after LTx.

Table 34. Quality of life and utility SLR outcomes

	Foroutan 2020	Kamath 2012	Wassman 2018	Thompson 2017
Population in which health effects were measured.	26 children with PFIC types 1 and 2, who underwent PIBD 12 male, 14 female Median (range) age, years: 9 (2–22)	49 children with PFIC Gender NR Mean (SD) age, years: 10.3 (NR)	32 children with PFIC 15 male, 17 female Mean (SD) age, years (at the time of health-related quality of life assessment) Liver transplant group (n=22): 18.9 (7.5) PEBD group (n=10): 15.3 (6.5)	33 children with PFIC types 1 and 2 (baseline data reported for the 33, 24 week data for 26 patients – demographic details for the 26 NR) 14 male, 19 female Median (range) age, years: 3.0 (1–13)
Information on recruitment.	Children with PFIC from Iran and Iraq who were referred to the pediatric surgery clinic of Namazi and Madarokoodak Hospital of Shiraz University of Medical Sciences	Part of the Childhood Liver Disease Research & Education Network (ChiLDREN) prospective study of cholestatic children	The study included all patients who were treated with the diagnosis of a PFIC in the author's clinic (Hannover Medical School, Hannover, Germany) between 1988 and 2010.	NR (phase 2 study)
Interventions and comparators.	PIBD All Patients received UDCA (30 mg/kg), rifampin (10 mg/kg), cholestyramine (200 mg/kg), and phenobarbital (5 mg/kg) for about 6 months before surgery	NR	Patients with PFIC after PEBD who still lived with their native livers were compared to those after liver transplant	Maralixibat — doses were escalated from 14 to 280 µg/kg/day over 13 weeks (depending on tolerability) and maintained for ≤59 weeks
Sample size.	n=44	n=49	n=32	n=33 (follow-up 26)
Response rates.	NR	NR	1/33 patients did not answer the questionnaire	NR
Description of health states	Patients with PFIC, whose pruritus was unresponsive to medication, who underwent PIBD. Patients with end-stage liver disease and those who were not fit enough to undergo PIBD were excluded.	Mean total bilirubin level, mg/dL: 3.0	Twenty-two patients had undergone liver transplant at a mean of 13.4±5.5 years before health-related quality of life assessment; 7 of them had undergone PEBD before liver transplant. Ten patients had undergone PEBD (PEBD group) at a mean of	Children with PFIC. Patients with liver transplants, surgically disrupted enterohepatic circulation or decompensated cirrhosis were excluded.

			11.6±4.2 years before assessment of health-related quality of life and still lived with their native liver.	
Results with confidence intervals. Uncertainty around values.	5D itch scale pruritus score: Pre-PIBD mean, median (range): 21.7, 22 (18–24) Post-PIBD mean, median (range): 5.8, 5 (5–12)	PedsQL physical score: 79	PedsQL scale, mean (SD) Liver transplant child Total score: 77 (16) Liver transplant parent proxy Total score: 84 (13) PEBD child Total score: 80 (14) PEBD parent proxy Total score: 81 (17)	ItchRO score Baseline mean (range): 2.27 (0.14–3.79) Change from baseline to week 48 mean (95% CI): -1.01 (-1.40, -0.63) PedsQL total score Baseline mean (range): 61.49 (18.1–85.9) Change from baseline to week 48 mean (95% CI): +8.17 (+0.71, +15.64)
Consistency with reference case.	Low – quality of life score not utility data. Health state details are available, but the population is not from the UK	Low – quality of life score not utility data and health state details are very limited, and the population is not from the UK	Low – quality of life score not utility data and health state details are available, but the population is not from the UK	Low – quality of life not utility data, health state details are limited, and unclear where the population is from

Abbreviations: AE; adverse event, Itch-RO; Itch Reported Outcomes Scale, PEDB; partial external biliary diversion, PedsQL; Pediatric Quality of Life Inventory, PFIC; progressive familial intrahepatic cholestasis, PIBD; partial internal biliary diversion, NR; not reported, SD; standard deviation, SE; standard error, TEAE; treatment-emergent adverse event, UDCA; ursodeoxycholic acid, UK; United kingdom, ULN; upper limit of normal, US; United States, VAS; visual analogue scale

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The values derived from PEDFIC1 could not be compared to values derived from the literature.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

As detailed in section 9.7, the majority of TEAEs were mild to moderate and assessed as unrelated to study treatment. No serious adverse events were observed in PEDFIC1 and therefore disutilities resulting from adverse events were not modelled.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

As described in section 12.1.3, the cost-effectiveness model includes eight health states encompassing the most significant events in PFIC. The HRQL data used in the economic evaluation include health state utility values, caregiver disutility, stoma bag disutility and short stature disutility. Health state utility values used in the model base-case were taken from the literature. Due to the lack of HRQL data in PFIC that could be used in the cost-effectiveness analysis, values identified from closely related diseases have been used.

10.1.9.1 Without PEBD

A study by Kamath et al[43] reported HRQL in children with Alagille syndrome compared with healthy and other liver disease cohorts (including a cohort of children with chronic intrahepatic cholestasis [CIC], approximately half of which had a confirmed PFIC diagnosis) using the PedsQL. These estimates are used in the base case given the large patient numbers included in the analysis, and availability of a mapping algorithm to the EQ-5D, in line with the NICE Reference Case.[88]

While this study has not differentiated between patients with and without response to treatment, no data had been identified in the literature that can be used to inform utilities for these two patient groups. While utility values for patients with a response may be expected to be slightly below those of a healthy child, due to potential continuing mild pruritus and other residual symptoms, in lieu of this data, the utility values for responders have been assumed to be equal to those for healthy patients and the utility values for non-responders to patients with CIC.

The group of patients with CIC in the study is noted as being heterogeneous, containing patients with PFIC1, 2 and 3, and with and without a surgical diversion. 20% of these patients were listed for liver transplant at the time of the study. As such, this group likely contains a combination of patients at varying stages of disease, both with and without a pruritus or SBA response and therefore is likely an overestimate of the HRQL in patients with no response to treatment.

The PedsQL scores were mapped to the EQ-5D using the algorithm by Khan et al[89,90] (see Appendix 17.8). Patient-reported scores are used in the base case.

A disutility associated with short stature is applied to 'loss of response' states from an HRQL study in children with chronic kidney disease.[86] A multiplier of 0.977 was obtained for quality of life in patients with short stature versus those with normal growth.[86]

10.1.9.2 With PEBD

A disutility of stoma bag is applied to the 'After PEBD' scores to obtain utilities in post-PEBD states.[91] In the base case, a 2006 study in ulcerative colitis is used to estimate the ratio of time-trade-off utility weights in the 'remission' and 'ileostomy' populations resulting in a multiplier of 0.72 (0.57/0.79 = 0.72).[91]

10.1.9.3 With LTx

LTx and post-LTx utilities were also informed by the literature.[44] Patients undergoing a liver transplant are assumed to have the most severe disease, with either very severe pruritus or significant liver damage. Thus in the year of transplant it is assumed that patients have the utility associated with severe pruritus (0.71) from Kini et al. (2011).[92]

The PedsQL scores reported in a systematic review of children undergoing LTx are mapped to the EQ-5D to obtain the post-LTx utility score al[89,90] (see Appendix 17.8).[87]

As children with PFIC1 may experience recurrence of disease post-liver transplant, an option to include an additional disutility for the whole population for PFIC1 is included in the model, however this is not applied in the base-case.

10.1.9.4 Caregiver disutility

Caregiver disutilities are applied in the base case and current estimates from the literature. Given the absence of robust estimates collected in a burden of disease study for PFIC, previous NICE Technology Appraisals were examined to estimate caregiver disutilities. NICE TA588 and TA534 reported estimates for caregiver burden in spinal muscular atrophy (SMA) and in moderate to severe atopic dermatitis, respectively.[93,94] These conditions were considered to represent a comparable impact for caregivers in PFIC. A disutility of -0.1 was obtained using the study used in TA588 (referencing a study by Lopez-Bastida et al[95]) and was applied to the model in the first instance. The study reports quality of life in patients with rare diseases in Europe, including caregiver utilities (using the EQ-5D) in Fragile X syndrome, mucopolysaccharidosis, haemophilia and Duchenne muscular dystrophy. A summary of how the decrement was derived is presented in Table C2. In the base-case, a disutility of -0.1 is applied to patients in the most severe health state of the model (PEBD non-response). The midpoint disutility (0.1 – 0.01 = 0.05) is

applied to non-responders to oral therapy/odevixibat, PEBD responders and patients undergoing LT. Furthermore, the 0.05 midpoint disutility is consistent with the scenario value considered for TA534 for dupilumab, which modelled a range of caregiver disutilities between 0.01 and 0.1 and was also reflective of pruritus.

A further study was identified in a targeted literature review to identify caregiver disutilities in rare paediatric diseases.[96] The utilities reported in a study by Wu et al, 2020[97] suggest a similar disutility in caregivers of children with rare conditions as what we currently model. Assuming an SF-6D of 0.788 in age-matched Australian adults, this represents a ~0.08 disutility (0.788 – 0.71 = 0.078), consistent with the values used in the model (0.05–0.1).

Caregiver utility for caregivers of healthy patients (i.e. sBA/pruritus responders) is assumed equivalent to the QoL of healthy patients (see Table 35).

Table 35. Summary of quality-of-life values for cost-effectiveness analysis

Health state	Utility value	Source	Justification
Without PEBD			
sBA & pruritus response	0.91	Kamath et al., 2015[43]	Utility in "Healthy" children (See section 10.1.9.1)
Loss of response	0.830	Al-Uzri et al., 2013[86] Kamath et al., 2015[43]	Utility in children with chronic intrahepatic cholestasis and short stature multiplier (See section 10.1.9.1)
After PEBD			
sBA & pruritus response	0.659	Hornbrook et al., 2011[98], Kamath et al., 2015[43]	Utility in "healthy" children and stoma bag utility (See section 10.1.9.1 and 10.1.9.2)
Loss of response	0.599	Kamath et al., 2015[43], Hornbrook et al., 2011[98] and Al-Uzri et al., 2013[86]	Utility in "healthy" children, stoma bag multiplier, short stature multiplier (See section 10.1.9.1 and 10.1.9.2)
LT	0.710	Kini et al., 2011[92]	See section 10.1.9.3
Post LT	0.850	Parmar et al., 2017[87]	See section 10.1.9.3
Caregiver disutility			

sBA/pruritus response	0	Assumption	See section 10.1.9.4
Loss of sBA/pruritus response	-0.05	NICE TA534[93]	See section 10.1.9.4
PEBD, sBA/pruritus response	-0.05	NICE TA534[93]	See section 10.1.9.4
PEBD, loss of response	-0.10	NICE TA588[94]	See section 10.1.9.4
Post-LTx	-0.05	NICE TA534[93]	See section 10.1.9.4

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts have not validated the utility values used in the economic model. However, on advice received from NICE/the evidence review group (ERG) during the decision problem meeting, Albireo is currently undertaking a valuation survey to elicit utilities for health states in PFIC. The study includes qualitative semi-structured interviews conducted

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

with clinicians who currently treat patients with PFIC, to obtain feedback on different health state vignettes in PFIC which have been developed for this study. The final health state vignettes (refined as needed based on feedback from these interviews) will then be used in time-trade-off (TTO) interviews with the general public to estimate health state utilities in PFIC. The study protocol is provided as a reference.[22]

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The QALY value of a health state is constant, in the context that as long as the patient is in the same health state, they experience the same QALY. Relevant health states have not been previously characterised for PFIC patients.

As a heterogenous condition, it is likely that the simplification of health states does not capture the variability of the patient experience at each severity. For instance, there could be expected to variability in the itch experienced in non-responders, the severity of which is expected to increase over time with progressive liver disease.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

In PFIC, fat malabsorption results in low weight, growth retardation and vitamin deficiencies that can result in life-threatening complications.[5] Although improved growth with odevixibat has been accounted for in the analysis, there are no data available on other complications related to malnutrition. Further extrahepatic manifestations that can occur in PFIC1, i.e, diarrhoea, pancreatitis, and hearing deficits[6], are not accounted for in the analysis, again due to lack of data.

Hepatocellular carcinoma is a health effect that has been identified in the literature and excluded from the economic analysis due to the model structure. Patients with PFIC can progress to hepatocellular carcinoma.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable – quality of life values were determined by health state only.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

A patient's HRQL is reflective of the natural history of the disease. As PFIC is a progressive disease, HRQL is not assumed to be constant over time.

Treatment with odevixibat has shown to be effective in reducing sBA levels and therefore improving pruritus symptoms in patients. Therefore, HRQL in responders (without PEBD) is assumed to be equivalent to healthy children. Once a patient experiences a loss of response, sBA levels begin to rise and consequently so does pruritus severity. Patients who do not have a sBA response may also experience growth impairment.

If patients do not respond adequately to oral therapies or lose the response, they may then go on to receive either PEBD or LTx. PEBD can result in improvements in pruritus; however, the requirement of a stoma and the occurrence of post-surgery complications (see section 8.2.5) may impact negatively on a patient's quality of life, resulting in a lower utility value and potentially a PEBD reversal.

As the disease progresses, patients will eventually require a LTx, indicating they have the most severe disease, with intractable pruritus and/or significant liver damage. Thus, HRQL is assumed to be the lowest before receiving a LTx. Post-LTx patients may experience complications including diarrhoea and liver steatosis.[47,63]

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

Utility values are derived from the literature and therefore the majority of values were mapped to EQ-5D data.

10.1.15.1 Short stature disutility multiplier

A multiplier for short stature was obtained using PedsQL scores reported by Al-Uzri et al., in children with chronic kidney disease[86], and mapped to the EQ-5D as described in the section 10.1.15.2. A weighted average difference was obtained for scores reported for children with short stature vs. children with normal height. The difference between the two was used as a multiplier for non-responders in PFIC, as these patients are assumed not to benefit from a resolution of their pruritus/elevated sBA, resulting in growth impairment.[27] The resulting weighted average EQ-5D scores are 0.852 for children with short stature and 0.871 for children with normal height using the mapping algorithm by Khan et al.[89] This is equivalent to a multiplier of 0.977.

10.1.15.2 Mapping algorithm – PedsQL to EQ-5D

The mapping algorithm used to obtain EQ-5D utilities form the PedsQL scores is from Khan et al.[89] The summary of coefficients and resulting scores from regression used can be found in Appendix 17.8.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The summary of product characteristics for odevixibat states that:[15]

The recommended dose of odevixibat is 40 µg/kg administered orally once daily in the morning.

Improvement in pruritus and reduction of serum bile acid levels can occur gradually in some patients after initiating odevixibat therapy. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased from 40 µg/kg/day to 120 µg/kg/day.

Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat. Prior to changing to alternative treatment, concomitant UDCA and/or rifampicin can be considered.

In the clinical development programme, patients completing PEDFIC1 were allowed to enrol directly into PEDFIC2 in which all patients receive 120 µg/kg/day. This allows for an evaluation of the responses in patients as they transition from 40 µg/kg/day during PEDFIC1 to 120 µg/kg/day in PEDFIC2. For reductions of both pruritus and sBA, there were patients who did not meet the responder definitions while receiving odevixibat 40 µg/kg/day but who did meet the responder definitions during the first 24 weeks of treatment with 120 µg/kg/day:[99]

- Data are available at Week 24 of PEDFIC2 for 8 patients who did not meet the pruritus responder definition during PEDFIC1; [redacted] met the pruritus responder definition, based on a decrease of > 1 point from the PEDFIC1 baseline
- Data are available at Week 24 of PEDFIC2 for 4 patients who did not meet the sBA responder definition during PEDFIC; [redacted] met the sBA responder definition.

This is reflected in the economic model. In the base case, response to odevixibat is assumed equivalent to the primary trial endpoint observed in the PEDFIC1 trial, i.e, ≥ 70% reduction in fasting sBA concentration from baseline to end of treatment or reaching a level ≤70 µmol/L. In a scenario analysis pruritus is used as the response criteria.

There are no additional costs incurred as a result of the continuation rule – patients are expected to be monitored as per usual clinical practice. In clinical practice sBA and pruritus are expected to be used as response criteria. In the UK, sBA is routinely measured in PFIC patients and pruritus is continuously monitored and followed up by clinicians.[8,100] However, the sBA response threshold and the criteria for a pruritus response that will be used in clinical practice may differ to that used in the clinical study and the economic model.

The sBA endpoint was the primary endpoint in the randomised clinical trial and is robust, plausible and can be reasonably achieved.

In the clinical trial PEDFIC1 the sBA response was observed by 8 weeks of treatment (Figure 18), therefore it is reasonable to assess for an initial response at 3 months and increase the dose to 120 µg/kg/day if necessary.

In general, clinicians that attended the UK Advisory Board agreed that an initial response would be expected to be seen within three months, and that a dose increase may be considered at this point if an adequate response is not seen. The clinicians also indicated that another review would occur at six months following treatment initiation.[8]

sBA and pruritus are regularly assessed in clinical practice, however it is unlikely that the exact criteria for pruritus response used in the clinical trial would be used in practice.

Patients whose treatment with odevixibat is withdrawn due to non-response will continue to be monitored for disease progression and supported with other clinical measures and would then be eligible to receive a liver transplant.

Section D — Value for money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

An SLR was conducted to identify economic analyses conducted in patients with PFIC and data on costs and resource use associated with the management of patients with PFIC. Details are provided in Appendix 17.3.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

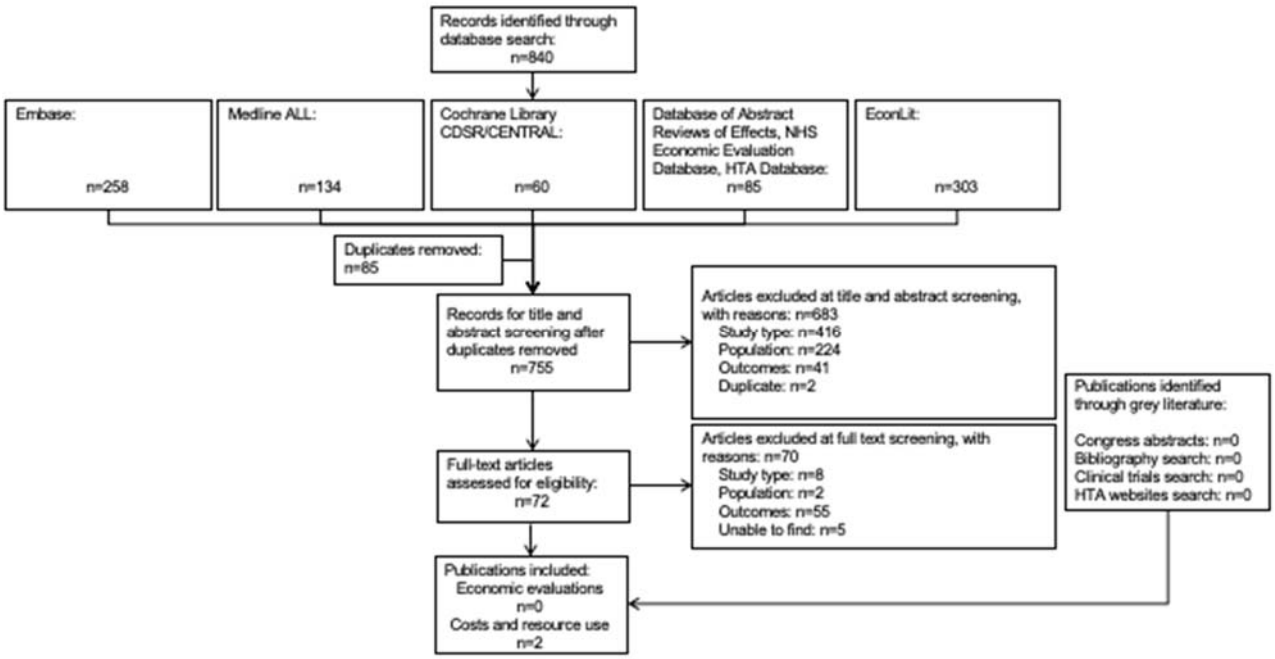
Table 36: Selection criteria used for health economic studies

Inclusion criteria	
Population	People with progressive familial intrahepatic cholestasis (PFIC) Note: All PFIC subtypes will be eligible for inclusion, extracted as defined in the study, including, but not limited to: • PFIC1 (Byler disease, FIC1 deficiency) • PFIC2 (bile salt export pump [BSEP] deficiency, Byler Syndrome) • PFIC3 (multidrug-resistant 3 protein [MDR3] deficiency) • PFIC4 (Tight junction protein two [TJP 2] gene (chromosome 9) subtype) • PFIC5 (farnesoid X receptor [FXR] mutations) • PFIC6 • Benign recurrent intrahepatic cholestasis (BRIC) 1 • BRIC2 Unspecified types of PFIC or BRIC
Interventions	No restriction
Outcomes	**Economic evaluation outcomes, including:** • QALY • DALY • ICER • ICUR • LYG **Costs and resource use**

	• Cost of illness including average annual costs per person, cost of health care and social care, cost of the disease, costs associated with anxiety and depression due to the disease, out of pocket costs and average annual indirect cost per patient/caregiver and cost to the patient/caregiver Rate of use of resources (e.g. hospitalisations, office visits, A&E visits),
Study design	• Economic evaluations, including economic models (cost effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimization analyses) • HTAs • Any primary studies containing resource use or cost data
Language restrictions	No restriction
Search dates	No restriction
Exclusion criteria	
Population	Any other population
Interventions	No restriction
Outcomes	Any other outcomes
Study design	• Animal studies • In-vitro studies • Editorials • Reviews • Letters • Comments • Notes • Erratum SLRs were included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.
Language restrictions	No restriction
Search dates	No restriction

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 38: Economic and resource identification, measurement and valuation SLR PRISMA



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in Table D2.

No economic evaluations or costs studies were identified.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Not applicable.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

Odevixibat is expected to be indicated for the treatment of PFIC in people aged 6 months and older.

The population considered in the cost-effectiveness analysis is individuals with PFIC1 and PFIC2 as this is the population included in the clinical trial. Despite the clinical differences in PFIC1 and 2, a joint population approach has been used. Patient numbers in PEDFIC1 were insufficient to justify modelling separate populations.

In clinical practice the population to be treated with odevixibat will include all subtypes of PFIC, including PFIC3 and episodic PFIC forms (BRIC) (see section 9.9). However due to

the limited clinical data available in these patients they could not be included in the economic analysis.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

Currently there are no licensed treatments for PFIC and the comparator in the economic analysis is partial external biliary diversion (PEBD).

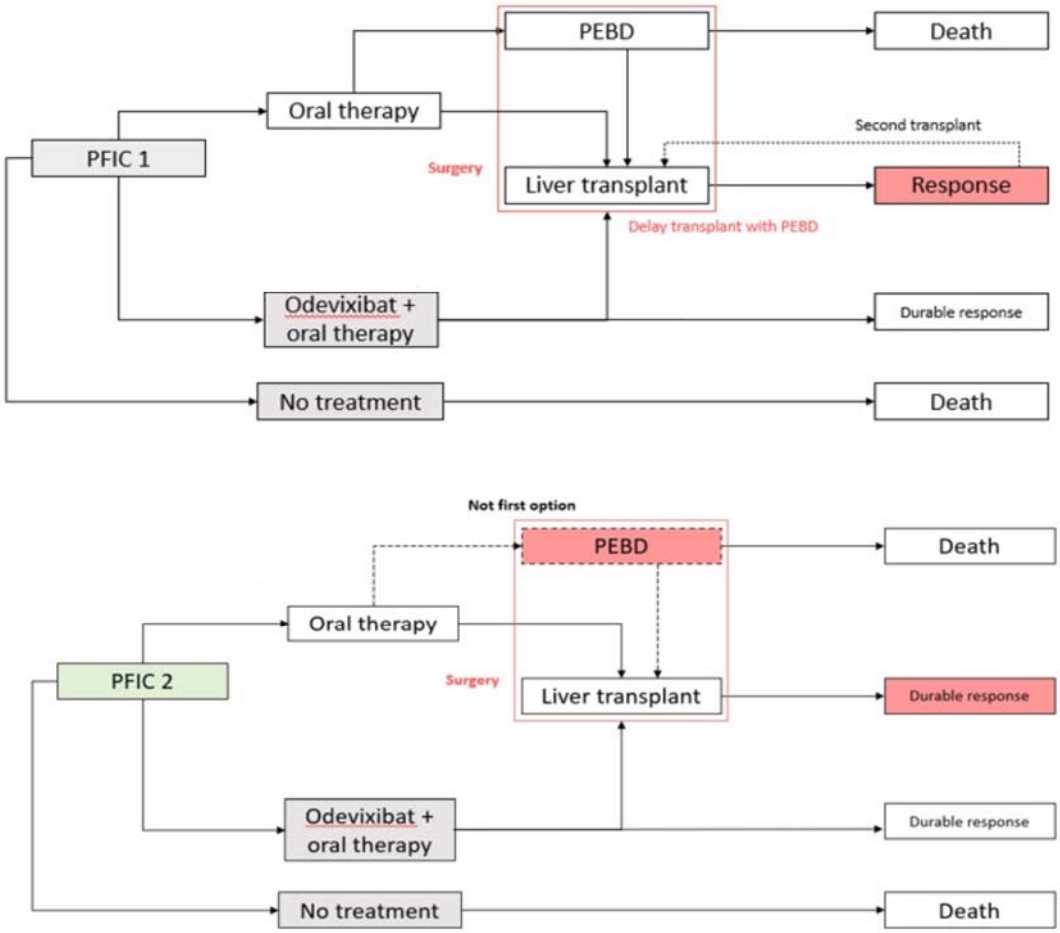
Whilst off-label oral drug treatments are included in the model, such as UDCA and rifampicin, these have very limited symptomatic efficacy and do not alter the underlying disease or change the course of disease. In clinical practice, odevixibat may be used in addition to off-label oral therapies (as was the case in the Phase 3 clinical trial). The odevixibat SmPC states that prior to changing to alternative treatment, concomitant UDCA and/or rifampicin can be considered.[15] Hence, off-label drug treatments will be an addition to odevixbat and cannot be considered an active comparator.

In the economic model off-label oral therapies are assumed to have no treatment effect and costs for off-label therapies are included both for patients receiving odevixibat and the comparator arm. This is reflective of the PEDFIC1 study, where no sBA response was observed in the placebo arm when patients continued on off-label oral therapies alone.

Odevixibat is the pharmacological equivalent of PEBD and therefore it is considered as the relevant comparator for this submission. Odevixibat is expected to replace PEBD in the treatment pathway but not all patients receiving standard of care undergo PEBD. However, without PEBD, all patients eventually progress to end-stage liver disease and need a LTx.

Clinical experts agreed that the treatment pathway models for PFIC1 and PFIC2 shown in Figure 39 are representative of their practices.[8]

Figure 39. Treatment pathway for patients with PFIC1 and PFIC2



Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

An eight-state Markov model was developed in Microsoft Excel to capture the differences in costs and health outcomes associated with the reduced need for LTx between odevixibat and standard of care arms. A more detailed model capturing progression to liver disease was not possible given the absence of data reporting these outcomes (e.g., progression to liver disease). Therefore, disease progression is driven by patients' pruritus, which is consistent with both the natural history and treatment pathway of PFIC.

An sBA response is associated with a corresponding pruritus response and a reduction in progression to PEBD and/or LTx. According to results from PEDFIC1, patients can have a pruritus response in the absence of an sBA response. The precise mechanism of cholestatic pruritus remains unclear but elevated bile acids are most commonly considered

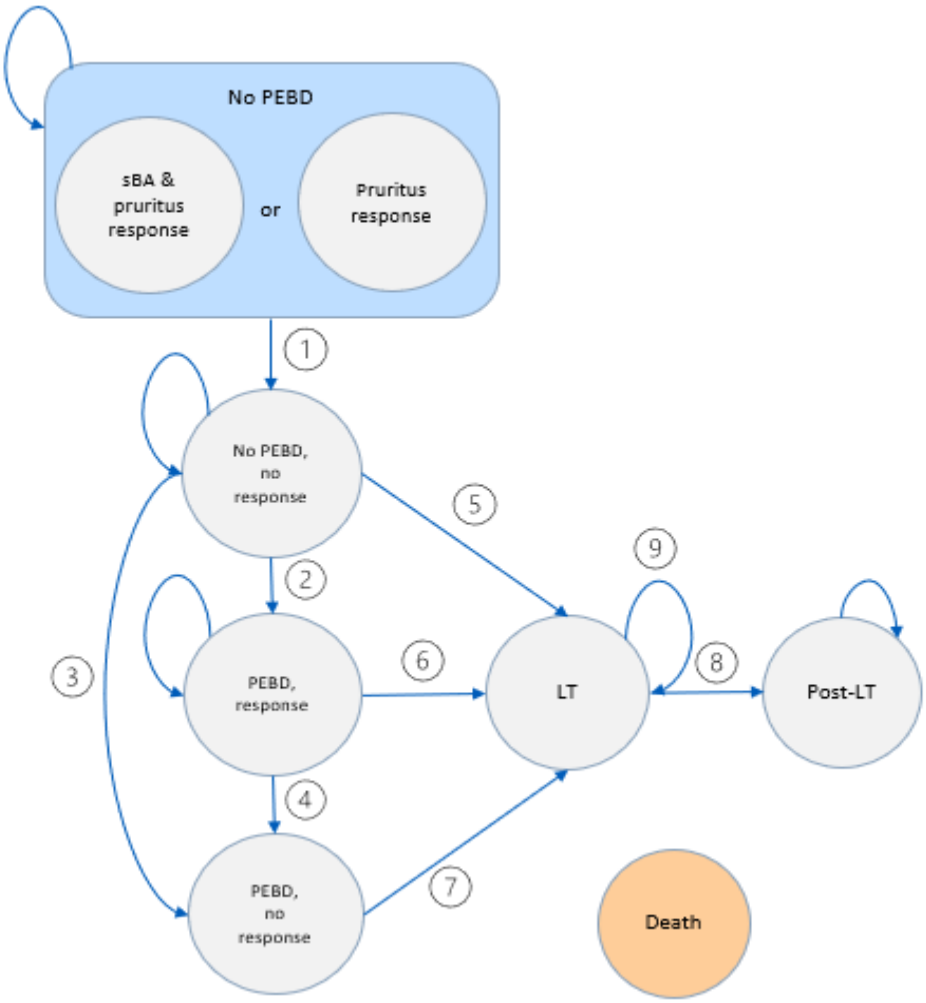
as direct or indirect pruritic mediators.[26] Elevated levels of autotaxin, the serum enzyme that converts lysophosphatidylcholine to lysophosphatidic acid, have also been correlated with cholestatic pruritus.[101] Given the role of pruritus in both disease progression and clinical decision-making, pruritus with or without an sBA response were considered clinically important health states (in consultation with paediatric hepatology consultant).

In the base case, disease progression is determined by an sBA and pruritus response. As a result, the model was structured around the following health states:

- Pruritus response, with or without sBA response
- Loss of pruritus response, with or without loss of sBA response
- Post-PEBD, pruritus response with or without sBA response
- Post-PEBD, loss of pruritus response, with or without loss of sBA response
- LTx
- Post-LTx
- Death

The model schematic is illustrated in Figure 40.The arrows represent the possible transitions between health states in any given cycle.

Figure 40. Model Schematic



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

When entering the model, patients are distributed across the response (pruritus with/without sBA response) and non-response states depending on whether they receive odevixibat or standard of care, respectively. Progression to PEBD and LTx is driven by the exacerbation of pruritus resulting from elevated bile acids. Patients can progress to LTx before or after PEBD. A proportion of patients require a secondary LTx, which occurs in the same year as the first LTx, as described in the literature.[59] The primary benefit of odevixibat is captured in the delayed time to LTx and PEBD. The increased mortality in PFIC in the standard of care arm is captured by acute and long-term LTx mortality as well as increased pre-LTx mortality. Patients in the odevixibat arm do not progress to PEBD, as the mode of action is similar; if a patient has not responded to odevixibat it is considered unlikely that they will respond to PEBD.

Differences between PFIC1 and 2 are captured in the progression to PEBD, LTx and outcomes post-LTx (including re-transplant), given the differences in clinical management and outcomes across these populations (see section 8.2).

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The model structure has been developed around Markov models with similar health-states submitted to NICE in related conditions; obeticholic acid for treating primary biliary cholangitis (TA443[102]) and inotersen for treating hereditary transthyretin amyloidosis (HST9[103]).

Modelled health states were also determined based on the clinical relevance of events throughout the course of a patient's disease (in consultation with paediatric hepatology consultant). The model is driven by patients' pruritus symptoms, which clinical experts described as being the primary indication for surgery and symptom on progress liver damage due to the accumulation of bile acids.

The aim of treatment with odevixibat is delaying or avoiding PEBD surgery and/or LTx, and long-term improvements in quality of life by reducing or eliminating pruritus.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table 37. Key Assumptions

Key assumptions	Justification
Outcomes for responders to odevixibat are comparable to outcomes for responders to PEBD	Data from the NAPPED database has demonstrated the relationship between reduced sBA and increased liver survival. The PEDFIC1 trial and interim results from PEDFIC2 has demonstrated the efficacy of odevixibat in reducing sBA, with the on-going PEDFIC2 and the planned [redacted] studies seeking to demonstrate the comparability of long-term outcomes
Patients with an sBA response do not go on to require liver transplant while they maintain their response	Data from the NAPPED database indicates that patients with an sBA response to PEBD do not go on to require liver transplants, with patients followed for up to 15 years.
Patients with an sBA response will also experience a pruritus response	Data from PEDFIC1 shows generally good concurrence between sBA and pruritus response, with 79% of patients with a sBA response at six months also having a pruritus response . Patients without a pruritus response at week 24 are assumed to achieve a pruritus response by month 12.

Patients that do not respond to odevixibat progress as per the natural history excluding PEBD	As odevixibat and PEBD are considered to be medically equivalent, it is assumed that patients who do not respond to odevixibat will also not response to PEBD.
Patients do not respond to current oral SoC	Current oral SoC is limited to symptom management, with limited efficacy and any response being transient. This assumption has been validated with clinical experts.[8]
Patients with a pruritus response have the QoL of a healthy child reported in Kamath et al.[43]	Pruritus is the main symptom of PFIC and the key driver of QoL in the early stages of the disease. While patients with a pruritus response may still experience some pruritus and additional symptoms, given the paucity of data available on QoL in PFIC, especially data differentiating between responders and non-responders, this has been applied as a simplifying assumption.
Patients without a response have the QoL of a patient with CIC reported by Kamath et al.[43]	No data has been identified reporting QoL in PFIC patients by response status, using either sBA or pruritus response. While the Kamath paper does not report QoL by response status, by comparing the difference in QoL between healthy children and those with CIC we can gain an insight on the impact the response to treatment may have. This assumption is considered conservative, as the population contain patients with and without a biliary diversion and likely contains a mixture of patients with and without a response.
Costs for caregivers and caregiver disutilities are relevant until age 18	This is a simplifying assumption applied in the model.

12.1.6 Define what the model's health states are intended to capture.

The modelled health states are listed in section 12.1.3 and capture the most significant events in the progression of PFIC. Health states were selected based on extensive clinical expert opinion input and previous models in other liver diseases (NICE TA443 and HST9). Progression of pruritus symptoms is reflective of patients' advancing liver disease, determined by patient's loss of response to treatment and the rate at which they progress to surgery.

Clinical opinion suggests pruritus is the primary indication for surgical intervention, given the severity of this symptom (particularly in small children), and that patients often progress to surgery prior to end-stage liver disease. Indeed, confidential data from the [redacted] show that [redacted] (see section 6.1.3).[29] PEBD and/or LTx are the most significant events in PFIC patients in terms of cost, quality of life impact and mortality risk.

In the base case, response is assumed to correspond with the primary endpoint reported in PEDFIC1, a ≥70% reduction in sBA concentration from baseline to end of treatment or reaching a level ≤70μmol/L after 24 weeks of treatment. Given the strong correlation between sBA and pruritus outcomes in PEDFIC1 (Table 39), these patients are assumed to have a pruritus response following their sBA response.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in Table D4.

Table 38: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime time horizon (maximum age of 100 years)	A lifetime time horizon captures differential outcomes over the lifetime of the individual. This approach is in line with NICE guidance, which states the time horizon should be long enough to reflect all important differences in costs or outcomes between technologies being compared	NICE 2013[88]
Discount of 3.5% for costs	1.5%	Costs and outcomes are discounted at a rate of 1.5% in the base case. Discount rates of 1.5% are consistent with those that may be considered by the NICE Appraisal Committee if it is highly likely that, on the basis of the evidence presented, long-term health benefits (normally at least 30 years) are likely to be achieved. The rate used now is too high, relative to the Treasury Green Book (on which the value was calculated), due to the fall in interest rates. NICE's interpretation, and that the discount rate should be 1.5% from 30/40 years, regardless of the intervention.	NICE 2017[104]
Perspective (NHS/PSS)	NHS and PSS in England and Wales	The perspective of costs and outcomes is that of the NHS and PSS in England and Wales, in line with NICE guidance. The perspective for outcomes and costs includes direct and indirect costs and health effects on patients and their caregivers. Scenarios without societal costs and effects are considered.	NICE 2013[88]
Cycle length	1 year (365.25 days)	This is considered sufficiently long to adequately capture the progression of PFIC. Half-cycle correction is implemented using the life table method.[a]	PEDFIC1 trial
NHS, National Health Service; PSS, Personal Social Services			

[a] The time in a given cycle is estimated by taking the average of the number of people at the start and end of the cycle.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

The clinical data used in the economic evaluation include:

- Response to treatment (Sections 12.2.1.1 - 12.2.1.3)
- Transition probabilities to PEBD and/or to LTx (Section 12.2.1.4)
- LTx mortality (acute and long-term) (Section 12.2.1.8)

The probability of and response to LTx and PEBD are primarily informed by publicly available data from NAPPED.

12.2.1.1 Response to odevixibat

The response to odevixibat is assumed equivalent to the primary trial endpoint observed in the PEDFIC1 trial - sBA reduction - for all doses. According to expert consultation, these patients are assumed to have an improvement in pruritus following their positive sBA response. In the base case, patients who do not respond after 3 months on the 40 µg/kg dose are titrated up to 120 µg/kg as per the SmPC recommendation (see Table 39). Following titration, patients who have no response after 6 months are discontinued. Data on response rates among patients up-titrating from 40 µg/kg to 120 µg/kg is taken from patients who did not respond to the 40 µg/kg dose in PEDFIC1 that switched to the 120 µg/kg dose in PEDFIC2.[99]

When using pruritus as the definition of response, results for the secondary efficacy endpoint of the proportion of patients achieving a positive pruritus assessment for >50% of the 24-week treatment period, as requested by the EMA during protocol advice, are used to inform response rates. This is deemed more suitable than the primary pruritus endpoint, which considers the proportion of positive pruritus assessments at the patient level across the 24 weeks; this will be explored in a scenario analysis. This data was not available for patients up-titrating from 40 µg/kg to 120 µg/kg, however response rates for the 120 µg/kg are comparable across the pruritus endpoints and it was assumed that the proportion of responders amongst patients up-titrating would be the same across endpoints.

The rate of discontinuation for odevixibat is taken from patients enrolled in PEDFIC2 after receiving odevixibat in PEDFIC1, as this data was judged to be most representative of patients continuing treatment after the initial 6-month period used to assess response. There was 1 discontinuation event among 34 patients, with a mean exposure time of [redacted] weeks, giving a discontinuation rate of [redacted] per patient year, which results in an annual probability of discontinuing odevixibat of [redacted].

Table 39: Range of response rates collected in PEDFIC1

Response endpoint	40 µg/kg dose	120 µg/kg dose	Combined doses	Response rate with 120 µg/kg in those not responding to 40 µg/kg
sBA response†	43.50%	21.10%	33.30%	[redacted]
Pruitius response at least 50% of the time¥	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus response‡	[redacted]	[redacted]	53.51%	[redacted]

†Defined as the proportion of patients with at least a 70% reduction in sBA concentration from baseline or reaching a level ≤70µmol/L in PEDFIC 1; ‡Defined as the proportion of positive pruritus assessments for morning and evening scores at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument; ; ¥ Defined as the proportion of patients achieving a positive pruritus assessment for >50% of the 24-week treatment period.
Abbreviations: sBA, serum bile acid.

12.2.1.2 Response to standard of care

Response to off-label standard of care (excluding surgical interventions) is assumed to be 0%. This was confirmed by clinicians and the literature on management of PFIC,[27] as currently used symptomatic oral therapy is not considered sufficient to control patients' pruritus or the progression of liver disease.

12.2.1.3 Response to PEBD

Response to PEBD is informed by NAPPED. Clinician input suggested a 50% response rate to PEBD, across PFIC1 and 2. This was consistent with the response rates observed in NAPPED, where 24 out of 38 patients had an sBA response in PFIC2 (63%)[10] and 12 out 23 had an sBA response in PFIC1 (52%).[12] These values use a different definition of response (at least a 75% reduction in sBA, sBA < 65µmol/L respectively), however these correspond to the measures of response used to assess time to liver transplant post-PEBD in the model.[12] The NAPPED estimate is therefore used in the base case. PEBD

can be effective long-term in reducing pruritus and improving native liver survival but is associated with ongoing stoma-related problems and may require reoperation; clinical input (consultation with paediatric hepatology consultant) indicated that some patients seek to have the operation reversed. Long-term data on the durability of PEBD in responders are not available and in the base case, loss of response is assumed to be 5% per year, giving a median response duration of 13.5 years.[59,105]

12.2.1.4 Transition probabilities

To inform the transition between health states, transition probabilities were derived from available data sources in PFIC for the odevixibat and standard of care arms. Survival curves from NAPPED were used to estimate the transition to PEBD and LTx, by PFIC subtype where possible. A summary of the transition probabilities is shown in Table 40.

Table 40. Summary of transition probabilities and their sources

Number on schematic	Transition	Reference
1	Loss of sBA/pruritus response	Assumption
2	PEBD, response	NAPPED study[10,12]
3	PEBD, no response	NAPPED study[10,12]
4	Loss of response to PEBD	Assumption
5	LTx without PEBD	NAPPED study[10,12]
6	LTx after PEBD response	Assumed 0%
7	LTx after PEBD non-response	NAPPED study
8	LTx to post-LTx	General population
9	Re-transplant	Meta-analysed/pooled LY mortality sourced[9,36,41,47]
-	Mortality	Bull et al [59]

Abbreviations: LT, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid; TP, transition probabilities.

Where transitions are based on survival data, exponential models have been used to estimate a constant transition rate. Other candidate distributions were considered; however, these would introduce time dependency into the model that would necessitate the use of tunnel states. For simplicity it was decided to exclude this option. In addition, in some cases the timescale used is age, for example in the data on native liver survival with and without surgical diversion. As a proportion of patients treated with odevixibat will not be at risk of LTx until they discontinue treatment, using age-dependent transition probabilities may not accurately reflect a patient's risk.

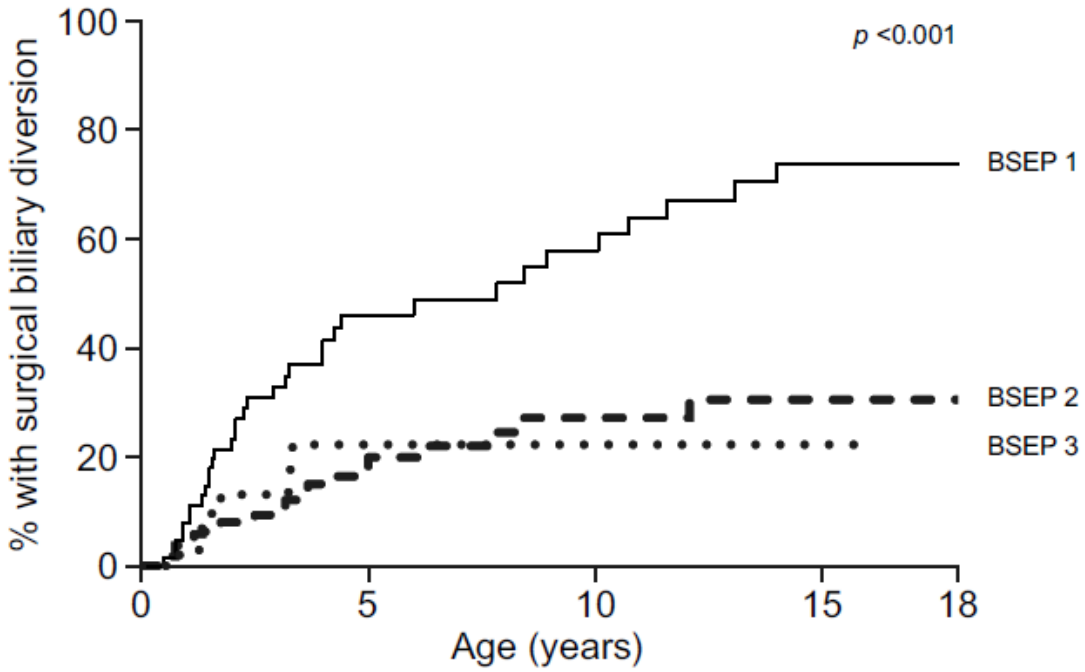
12.2.1.5 Probability of PEBD

Patients who lose response (pruritus with/without sBA response) can progress to PEBD in the standard of care arm. This transition is assumed zero in the treatment arm.

Given the improved prognosis of LTx in PFIC2, these patients are more likely to proceed directly to LTx (Figure 39). This is reflected in the data presented in NAPPED and used in the model. An annual probability of PEBD was obtained from NAPPED for PFIC1 and PFIC2 (Table 43) which reported that 43% and 34% of patients underwent a PEBD by age 10. Published data from NAPPED present the proportion of patients with SBD by age for PFIC2 (Figure 41) and PFIC1 (Figure 42) and this has been used to inform the model.[10,12]

Figure 41 presents the rate of PEBD across 3 subtypes; for the economic model these three have been merged.

Figure 41: SBD rates by age in PFIC2



N° at risk					
BSEP 1	72	20	14	8	5
BSEP 2	136	43	22	16	11
BSEP 3	56	12	9	3	0

Figure 42 shows a clear time trend for the rates of SBD in PFIC1, with the majority of the surgeries occurring by the age of 3.[12] While the majority of transitions do not incorporate time dependence, for the rate of PEBD in PFIC1, a piecewise exponential model has been fit to provide separate rates for patients older or younger than 3 to avoid the over-estimation of the rate of PEBD in PFIC1. Table 41 and Table 42 present the results of the models for PFIC2 and PFIC1 respectively.

Figure 42: SBD rates by age in PFIC1

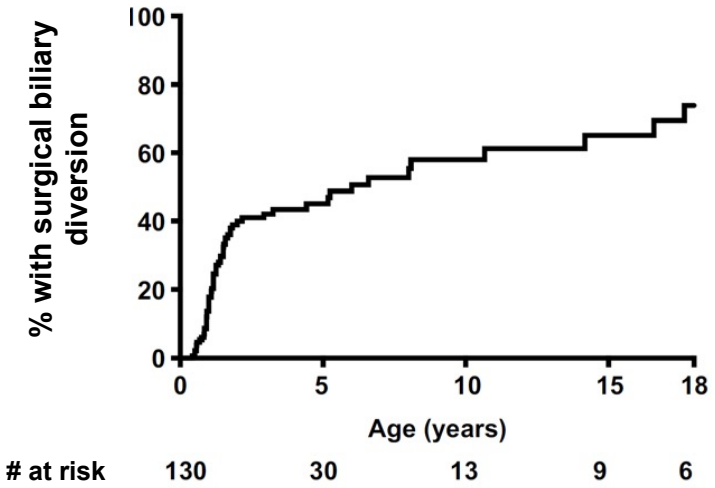


Table 41: Exponential model for the rate of PEBD in PFIC2

	Constant term	Standard error	95% CI
Coefficient	0.0487	0.0052	0.0395-0.0599

Table 42: Piecewise exponential model for the rate of PEBD in PFIC1

	Constant termł	Standard error	95% CI
Constant term	-1.6061	0.1414	-1.8833 - -1.3289
Coefficient for age >3	-1.4167	0.3113	-2.0269 - -0.8065

Ł Terms in the model for PFIC1 are presented on the log scale

An annual probability of PEBD was obtained using these sources for PFIC1 and PFIC2 and weighted by the proportion of PFIC1 observed in PEDFIC1 (27% of PFIC1 patients) to obtain a joint annual probability of 8.43% in patients under 3 and 4.75% in patients aged 3 and up in the base case (see Table 43) .

Table 43 : Probability of PEBD based on NAPPED curve in PFIC1 and PFIC2

Age	PFIC1	PFIC2	Joint*
Up to age 3	18.18%	4.75%	8.43%
3 and older	4.75%	4.75%	4.75%

*Joint population probability is calculated as a weighted average of PFIC 1 and 2 as observed in PEDFIC 1.
Abbreviations: PEBD, partial external biliary diversion.

12.2.1.6 Probability of LTx

The annual probability of LTx with and without PEBD is derived from NAPPED. Estimates are modelled for PFIC1 and 2 separately where possible, given the differences in clinical presentation and outcomes following LTx. See section 8.2.6.

Probability of LTx without prior PEBD

Separate estimates were available for the probability of LTx without prior PEBD in PFIC1 and 2. A summary of the transitions used is provided in Table 44.

Table 44. Probability of LTx before PEBD

PFIC1	PFIC2	Joint*
5.07%	7.52%	6.58%

*Joint population probability is calculated as a weighted average of PFIC 1 and 2 as observed in PEDFIC 1.
Abbreviations: PEBD, partial external biliary diversion.

The probability of LTx without PEBD in PFIC2 patients is derived from the 'no surgical biliary diversion' curve in Figure 32. An annual probability of 7.52% was obtained by digitising the 'no surgical biliary diversion' curve and assuming an exponential distribution (see Table 45).

Table 45, Exponential model results for LTx without PEBD in PFIC2 [106]

	Constant term	Standard error	95% CI
Coefficient	0.0782	0.0069	0.0657 - 0.0931

Abbreviations: CI, confidence interval; LT, liver transplant; PEBD, partial external biliary diversion.

The probability of LTx without PEBD in PFIC1 patients is derived from the "no surgical biliary diversion' curve in Figure 34.[12] An annual probability of 5.07% was obtained by digitising the "no surgical biliary diversion" curve and assuming an exponential distribution (Table 46).

Table 46. Exponential model results for LTx without PEBD in PFIC1

Age, years	Constant term	Standard error	95% CI
Coefficient	0.0519	0.0103	0.0351; 0.0769

Abbreviations: CI, confidence interval; LT, liver transplant; PEBD, partial external biliary diversion.

A rate ratio (Table 47) is applied to patients with a pruritus response only (no sBA response) and is calculated based on the proportion of PFIC1 and 2 patients receiving LTx due to intractable pruritus in the NAPPED study.[29] This is to accurately capture the proportion of patients who are indicated for LTx due to their pruritus rather than liver disease, cirrhosis or other causes. This rate ratio is applied in scenario analysis only, when response in the model is defined as pruritus response.

Table 47. Rate ratio for pruritus responders

Subgroup	Proportion indicated for LTx	Rate ratio
PFIC1	51/91	0.32
PFIC2	19/28	0.44
Joint population*	-	0.41

*Joint rate ratio is calculated as a weighted average using the proportion of PFIC 1 and 2 in the PEDIC trial.
Abbreviations: LT, liver transplant.

12.2.1.7 Probability of LTx after PEBD

The probability of LTx in PEBD responders is assumed to be 0%. A summary of the data used in the model for non-responders is provided in Table 48.

Table 48. Probability of LTx in PEBD non-responders

PFIC1	PFIC2	Joint*
6.34%	11.24%	9.90%

*Joint population probability is calculated as a weighted average of PFIC 1 and 2 as observed in PEDFIC 1.
Abbreviations: LTx, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid.

The probability of LTx after PEBD is available from NAPPED using a 75% reduction in sBA as the response endpoint in PFIC2 and sBA below 65µmol/L in PFIC1.[10] The relevant NAPPED curves used to obtain the transition probabilities to LTx in PEBD non-responders are reproduced in Figure 33 and Figure 35.

An exponential distribution was fitted to the non-responder curves (i.e. ≤70% reduction in sBA and sBA below 65µmol/L) to obtain the annual probability of LTx in PEBD non-responders for PFIC2 and PFIC1 (11.24% and 6.34%, respectively) using Stata. A summary of the exponential models is provided in Table 49 and Table 50.

Table 49: Exponential model results for LTx in PEBD non-responders, PFIC2

Definition of response	Constant term		Standard error	95% CI
≤75% sBA reduction	0.0993		0.0441	0.041;0.237

Abbreviations: CI, confidence interval; LTx, liver transplant; PEBD, partial external biliary diversion.

Table 50: Exponential model results for LTx in PEBD non-responders, PFIC1

Definition of response	Constant term	Standard error	95% CI
sBA below 65µmol/L	0.0655	0.0327	0.0246; 0.1744

12.2.1.8 Mortality

Background mortality is modelled using general population life tables for England and Wales,[107] with a health state-specific mortality effect applied to the non-response, LTx and post-LTx health states using data derived from the literature. Data from NAPPED shows that mortality prior to surgery is higher than the general population, with 4% of PFIC2 patients and 9% of PFIC1 patients dying prior to LTx.[34,35] Data on mortality by health state was not available, so to incorporate this excess mortality into the model it was assumed that there was only excess mortality in the health states with no response (no PEBD, no response and PEBD, no response), then the model was calibrated using the 'Goal Seek' function in Excel to find the annual probability of death that gave the appropriate pre-transplant mortality for PFIC1 and PFIC2 respectively. Table 51 summarises the mortality rates for these states.

Table 51: Annual probability of death prior to surgery

Event	PFIC1	PFIC2	Joint*
Mortality	0.35%	0.24%	0.27%

*Joint population probability is calculated as a weighted average of PFIC 1 and 2 as observed in PEDFIC 1.
Abbreviations: PFIC, progressive familial intrahepatic cholestasis.

Mortality post-liver transplant is split into the acute mortality (within 1 year of transplant) and long-term mortality. An increased mortality rate is applied to the year of transplant to reflect the increased mortality risk from complications and organ rejection.[64] A summary of the data used is presented in Table 52 and Table 53. Additional detail on each of these data sources is provided in Appendix 17.9.

Acute mortality rates from the literature varied (between 0% and 37%). Given these variations, a meta-analysis (see Appendix 17.9) was performed on the following three sources and the resulting rate applied:

- LTx for progressive familial intrahepatic cholestasis: clinical and histopathological findings, outcome and impact on growth, Aydogdu et al., 2007[47]
- Outcomes of LTx for paediatric recipients with progressive familial intrahepatic cholestasis (abstract), Valamparampil et al., 2019[36]
- Fifteen years single centre experience in the management of progressive familial intrahepatic cholestasis of infancy, Wanty et al., 2004[41]

An alternative estimate of acute post-LTx mortality from NHS transplant data[64] was included for scenario analysis, and reflects year-one mortality in children with LTx for any indication in the UK.

Table 52: Summary of data used for LTx mortality (acute – in year of LT)

Annual probability			Reference
PFIC1	PFIC2	Joint*	
1.02%	1.02%	1.02%	Wanty et al., 2004[41]
37%	15.4%	21.32%	Valamparampi et al., 2019[36]
25%	25%	25%	Ayodgdu et al., 2007[47]
13%	13%	13%	Meta-analysed rate (annual)
2.7%	2.7%	2.7%	NHS transplant report, 2020[64]

*Joint population probability is calculated as a weighted average of PFIC 1 and 2 as observed in PEDFIC 1.
Abbreviations: LTx, liver transplant; PFIC, progressive familial intrahepatic cholestasis.

Post-LTx mortality in PFIC was available from a smaller number of sources, and a meta-analysis was not considered methodologically accurate (Appendix 17.9). A pooled estimate was used instead using the following two sources:

- Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy, Wanty et al., 2004[41]
- Progressive familial intrahepatic cholestasis: a single-centre experience of living-LTx during two decades in Japan, Hori et al., 2011[108]

These rates were calculated by digitising Kaplan-Meier curves from the papers and generating pseudo-patient-level data for each curve. These were combined and an exponential curve was fit to survival conditional on being alive at 12 months post-LTx. As

for acute mortality, an estimate from NHS transplant for all paediatric LTx is included in a scenario analysis.[64]

Table 53: Summary of data used for post-LTx mortality (long-term)

Annual probability			Reference
PFIC1	PFIC2	Joint*	
1.02%	1.02%	1.02%	Wanty et al., 2004
3.57%	3.57%	3.57%	Hori et al., 2011[108]
1.45%	1.45%	1.45%	Weighted average (base-case)
1.29%	1.29%	1.29%	NHS transplant report [64]

*Joint population probability is calculated as a weighted average of PFIC 1 and 2 as observed in PEDFIC 1.
Abbreviations: LTx, liver transplant; PFIC, progressive familial intrahepatic cholestasis.

12.2.1.9 Re-transplantation

Secondary LTx occurs in a significant proportion of children with PFIC, according to clinicians. Estimates from Bull et al., 2019, are used in the model base-case.[59] Re-transplant is assumed to occur in the same year as the first transplant (Table 54).

Table 54: Rate of re-transplantation in PFIC1 and 2

Population	Re-transplant rate
PFIC1	4%
PFIC2	12%
Joint*	9.81%

*Joint population probability is calculated as a weighted average of PFIC 1 and 2 as observed in PEDFIC 1.
Abbreviations: PFIC, progressive familial intrahepatic cholestasis.
Source: Bull et al. 2018 [59]

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Costs and clinical outcomes have not been extrapolated beyond the study follow-up period.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

In the model changes in sBA were used to predict long-term outcomes in PFIC1 and PFIC2 patients. As described in section 8.2.5 and 9.8, sBA levels after biliary diversion

surgery are associated with native liver survival. In those with PFIC2, reduction of bile acid levels below 102 µmol/L, or a 75% reduction from pre-diversion values significantly increased native liver survival (Figure 33).[10] Recent analysis of patients with PFIC1 in NAPPED showed that post-SBD sBA level <65 µmol/L tended to be associated with prolonged NLS after SBD (P = 0.05; Figure 35).[12]

These outcomes have been used to inform the long-term clinical outcomes for patients with an sBA response to odevixibat or PEBD. It has been assumed that patients with an sBA response do not require a liver transplant while their response is maintained.

Survival curves from NAPPED were used to estimate the transition to PEBD and LTx, by PFIC subtype where possible, as described in section 12.2.1.4.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

12.2.4.1 Post-LTx complications

No serious adverse events were observed in PEDFIC1. Costs associated with common-treatment emergent adverse events occurring in greater than 5% of patients were included in a scenario analysis.

Table 55: Incidence of common treatment-emergent adverse events in PEDFIC1

Event	Incidence with standard of care alone (placebo arm)	Incidence with odevixibat (all doses)
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Upper respiratory infection	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Alanine aminotransferase	[redacted]	[redacted]
Blood bilirubin	[redacted]	[redacted]
Asapartate aminotransferase	[redacted]	[redacted]
Blood alkaline phosphatase	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]

Given the clinical consensus on the presence of extrahepatic complications following LTx in PFIC1 and 2, event rates from Davit-Spraul (stunted growth, deafness) and Bull (diarrhoea, liver steatosis, pancreatitis) are applied. Few data were available on post-LTx

complications, and the event rates presented in Table 56 were identified in a systematic literature review.[109] Costs were allocated to each event and are reported in Table 56.

Table 56: Post-LTx complications in PFIC1 and 2

Event	Post-LTx complications		
	PFIC1	PFIC2	Joint*
Diarrhoea	81%	7%	27.28%
Liver steatosis	90%	6%	29.02%
Stunted growth	67%	0%	18.36%
Deafness	33%	0%	9.04%
Pancreatitis	40%	0%	10.96%

*Joint population estimates were calculated as a weighted average of PFIC 1 and 2 in PEDFIC 1.
Abbreviations: LT, liver transplant; PFIC, progressive familial intrahepatic cholestasis.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

A meeting was held with the [redacted] on 22nd November 2019. This meeting provided various assumptions applied in the cost-effectiveness model.

An advisory board was held March 3rd 2021, comprising 9 attendees with the following backgrounds:[8]

- [redacted]
- [redacted]
- [redacted]

The topics that were covered across the advisory boards included understanding the proportion of patients with PFIC, determining drivers to treat PFIC, understanding the current treatment pathway for patients, the impact of introducing odevixibat based on clinical trial data, cost-effectiveness modelling approach, various parameters and validating assumptions made in previous interview.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in below.

All model parameters were systematically and independently varied over a plausible range determined by either the 95% confidence interval, or ±15% where no estimates of precision were available. Table 57 provides a summary of all variables applied in the cost-effectiveness model.

Table 57: Summary of variables applied in the cost-effectiveness model

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Age at baseline	4.25	Normal	3.61	4.89	PEDFIC 1 CSR. Baseline characteristics.
% female	50%	Beta	43%	58%	PEDFIC 1 CSR. Baseline characteristics.
% PFIC1	27%	Beta	23%	32%	See section 12.2.1.5
Response to odevixibat - sBA & pruritus response – up-titrators	[redacted]	Beta	[redacted]	[redacted]	See section 12.2.1.1
Annual loss of response (odevixibat)	[redacted]	Beta	[redacted]	[redacted]	See section 12.2.1.1
Response to SoC, any therapy	0	Not varied	0	0	See section 12.2.1.2
Annual loss of response (SoC)	0	Not varied	0	0	See section 12.2.1.2
PEBD hazard, PFIC2	0.05	Normal	0.04	0.06	See section 12.2.1.5
PEBD hazard, age <3, PFIC1	-1.61	Normal	-1.88	-1.33	See section 12.2.1.5
PEBD hazard, age >=3, PFIC1	0.08	Normal	-2.03	-0.81	See section 12.2.1.5
Response to PEBD - PFIC1	0.52	Beta	0.33	0.71	See section 12.2.1.3
Response to PEBD - PFIC2	0.63	Beta	0.47	0.78	See section 12.2.1.3
Annual loss of response to PEBD	0.05	Beta	0.04	0.06	See section 12.2.1.3
% LTx, without PEBD, PFIC2	0.08	Normal	0.07	0.09	See section 12.2.1.6
% LTx, without PEBD, PFIC1	0.05	Normal	0.04	0.08	See section 12.2.1.6
% LTx, with PEBD, no response, PFIC2	0.12	Normal	0.06	0.23	See section 12.2.1.8
% LTx, with PEBD, no response, PFIC1	0.07	Normal	0.02	0.17	Section 12.2.1.7
LTx mortality, post-LTx - pooled rate	1.45%	Beta	1%	2%	See section 12.2.1.8
LTx mortality, in year of transplant -	37%	Beta	31%	43%	See section 12.2.1.8

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Valamparampil, FIC 1 deficiency					
LTx mortality, in year of transplant - Valamparampil, BSEP-deficiency	15%	Beta	13%	18%	See section 12.2.1.8
LTx mortality, in year of transplant - meta-analysis	13%	Beta	4%	38%	See section 12.2.1.8
LTx mortality, post-LTx - Wanty	1.02%	Beta	1%	2%	See section 12.2.1.8
Re-transplant rate - PFIC1	4%	Beta	3%	5%	Section 12.2.1.9
Re-transplant rate - PFIC2	12%	Beta	10%	14%	Section 12.2.1.9
Pre-transplant mortality - PFIC1	0.00%	Beta	0.00%	0.00%	Section 12.2.1.8
Pre-transplant mortality - PFIC2	0.00%	Beta	0.00%	0.00%	Section 12.2.1.8
Diarrhoea - Post-LTx complications PFIC1	81%	Beta	69%	100%	Section 12.2.4.1
Liver steatosis - Post-LTx complications PFIC1	90%	Beta	77%	100%	Section 12.2.4.1
Stunted growth - Post-LTx complications PFIC1	67%	Beta	57%	77%	Section 12.2.4.1
Deafness - Post-LTx complications PFIC1	33%	Beta	28%	38%	Section 12.2.4.1
Pancreatitis - Post-LTx complications PFIC1	40%	Beta	34%	46%	Section 12.2.4.1
Diarrhoea - Post-LTx complications PFIC2	7%	Beta	6%	8%	Section 12.2.4.1
Liver steatosis - Post-LTx complications PFIC2	6%	Beta	5%	7%	Section 12.2.4.1.
Stunted growth - Post-LTx complications PFIC2	0%	Not varied	0%	0%	Section 12.2.4.1.
Deafness - Post-LTx complications PFIC2	0%	Not varied	0%	0%	Section 12.2.4.1.
Pancreatitis - Post-LTx complications PFIC2	0%	Not varied	0%	0%	Section 12.2.4.1.
Utility value - LTx	0.71	Beta	0	1	Section 10.1.9.4
Disutility of LTx - PFIC1 only	0	Not varied	0	0	Assumption.
Disutility of LTx - all patients	0	Not varied	0	0	Assumption.
Disutility of stoma bag - ulcerative colitis	0.72	Beta	0.61	1	Section 10.1.10.2
Age-based multiplier - constant	0.95	Not varied	0.95	0.95	Cost-effectiveness model
Age-based multiplier - male	0.02	Not varied	0.02	0.02	Cost-effectiveness model
Age-based multiplier - age	0	Not varied	0	0	Cost-effectiveness model
Age-based multiplier - age^2	0	Not varied	0	0	Cost-effectiveness model
PedsQL to EQ-5D mapping - Physical Health	0.01	Normal	0.00409	0.01416	Section 17.8

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
PedsQL to EQ-5D mapping - Emotional Health	0.01	Normal	0.00165	0.01157	Section 17.8
PedsQL to EQ-5D mapping - Social Functioning	0.01	Normal	0.00016	0.01125	Section 17.8
PedsQL to EQ-5D mapping - School Functioning	0.01	Normal	0.00137	0.01065	Section 17.8
PedsQL to EQ-5D mapping - Physical Health squared	0	Normal	-0.00003	0.00007	Section 17.8
PedsQL to EQ-5D mapping - Emotional Health squared	0	Normal	-0.00008	-0.00001	Section 17.8
PedsQL to EQ-5D mapping - Social Functioning squared	0	Normal	-0.00002	0.00004	Section 17.8
PedsQL to EQ-5D mapping - School Functioning squared	0	Normal	-0.00005	0.00001	Section 17.8
PedsQL to EQ-5D mapping - Physical x Emotional Health	0	Normal	-0.00006	0.00005	Section 17.8
PedsQL to EQ-5D mapping - Physical x Social Functioning	0	Normal	-0.00011	0	Section 17.8
PedsQL to EQ-5D mapping - Physical x School Functioning	0	Normal	-0.00012	-0.00001	Section 17.8
PedsQL to EQ-5D mapping - Emotional x Social Health	0	Normal	-0.00005	0.00004	Section 17.8
PedsQL to EQ-5D mapping - Emotional x School Functioning	0	Normal	0.00002	0.0001	Section 17.8
PedsQL to EQ-5D mapping - Social x School Functioning	0	Normal	-0.00007	0.00002	Section 17.8
PedsQL to EQ-5D mapping - Constant	-0.43	Normal	-0.61315	-0.24384	Section 17.8
Post-LTx PedsQL - total score	77.29	Not varied	65.7	88.88	Section 17.8
Post-LTx PedsQL - physical score	68.46	Not varied	58.19	78.73	Section 17.8
Post-LTx PedsQL - emotional score	74.97	Not varied	63.72	86.21	Section 17.8
Post-LTx PedsQL - social score	81.11	Not varied	68.95	93.28	Section 17.8
Post-LTx PedsQL - school score	71.47	Not varied	60.75	82.19	Section 17.8
Healthy PedsQL - total score (Kamath 2015)	83.91	Normal	59.47	108.35	Section 17.8
Healthy PedsQL - physical score (Kamath 2015)	87.77	Normal	62.05	113.49	Section 17.8

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Healthy PedsQL - emotional score (Kamath 2015)	79.21	Normal	43.89	114.53	Section 17.8
Healthy PedsQL - social score (Kamath 2015)	84.97	Normal	52.22	117.72	Section 17.8
Healthy PedsQL - school score (Kamath 2015)	81.31	Normal	49.77	112.85	Section 17.8
sBA≥118 PedsQL - total score (Kamath 2015)	73.04	Normal	42.07	104.01	Section 17.8
sBA≥118 PedsQL - physical score (Kamath 2015)	78.91	Normal	47.43	110.39	Section 17.8
sBA≥118 PedsQL - emotional score (Kamath 2015)	67.35	Normal	25.09	109.61	Section 17.8
sBA≥118 PedsQL - social score (Kamath 2015)	76.26	Normal	35.47	117.05	Section 17.8
sBA≥118 PedsQL - school score (Kamath 2015)	65.94	Normal	27.23	104.65	Section 17.8
Short stature multiplier	0.97719	Gamma	0.83	1	Section 10.1.10.1
UDCA - % patients treated	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.6.1.2
Cholestyramine - % patients treated	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.6.1.2
Rifampicin - % patients treated	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.6.1.2
Naltrexone - % patients treated	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.6.1.2
UDCA - Days/cycle	365.25	Gamma	310.46	420.04	Section 12.1.7
Cholestyramine - Days/cycle	365.25	Gamma	310.46	420.04	Section 12.1.7
Rifampicin - Days/cycle	365.25	Gamma	310.46	420.04	Section 12.1.7
Naltrexone - Days/cycle	365.25	Gamma	310.46	420.04	Section 12.1.7
Cholestyramine - Dose/day (mg)	4000	Gamma	3400	4600	Section 12.3.6.1.2
Rifampicin - Dose/day (mg)	10	Gamma	8.5	11.5	Section 12.3.6.1.2
UDCA - Mg/kg	12	Not varied	10.2	13.8	Section 12.3.6.1.2
Naltrexone - Mg/kg	2	Not varied	1.7	2.3	Section 12.3.6.1.2.
UDCA - Mg/unit	150	Not varied	127.5	172.5	Section 12.3.6.1.2
Cholestyramine - Mg/unit	4,000.00	Not varied	3400	4600	Section 12.3.6.1.2
Rifampicin - Mg/unit	150	Not varied	127.5	172.5	Section 12.3.6.1.2
Naltrexone - Mg/unit	50	Not varied	42.5	57.5	Section 12.3.6.1.2
UDCA - Cost/pack	£14.49	Not varied	£12.32	£16.66	Section 12.3.6.1.2
Cholestyramine - Cost/pack	£10.76	Not varied	£9.15	£12.37	Section 12.3.6.1.2
Rifampicin - Cost/pack	£18.32	Not varied	£15.57	£21.07	Section 12.3.6.1.2.
Naltrexone - Cost/pack	£23.00	Not varied	£19.55	£26.45	Section 12.3.6.1.2
UDCA - Units/pack	60	Not varied	51	69	Section 12.3.6.1.2

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Cholestyramine - Units/pack	50	Not varied	42.5	57.5	Section 12.3.6.1.2
Rifampicin - Units/pack	100	Not varied	85	115	Section 12.3.6.1.2
Naltrexone - Units/pack	28	Not varied	23.8	32.2	Section 12.3.6.1.2
Odevixibat, number of days	365.25	Gamma	310.46	420.04	Section 12.1.7
Odevixibat, capsules per pack	30	Gamma	25.5	34.5	Section 12.3.6.1.1.
Odevixibat, cost of low dose	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.6.1.1
Proportion of patients - Pediatrician - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Hepatologist - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Gastroenterologist - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Dietitian - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Emergency medicine - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Orthopedist - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Physiotherapist - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Psychologist - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Speech and language therapist - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Endocrinologist - Pre-surgery	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - GP visit - Pre-surgery	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Nurse visit - Pre-surgery	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Stoma care - Pre-surgery	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Pediatrician - Post-PEBD	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Hepatologist - Post-PEBD	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Gastroenterologist - Post-PEBD	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Dietitian - Post-PEBD	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Emergency medicine - Post-PEBD	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Proportion of patients - Orthopedist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Physiotherapist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Psychologist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Speech and language therapist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Endocrinologist - Post-PEBD	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - GP visit - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Nurse visit - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Stoma care - Post-PEBD	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Pediatrician - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Hepatologist - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Gastroenterologist - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Dietitian - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Emergency medicine - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Orthopedist - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Physiotherapist - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Psychologist - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Speech and language therapist - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Endocrinologist - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - GP visit - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Nurse visit - Post-LTx	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Stoma care - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Pediatrician - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Hepatologist - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Mean number of visits - Gastroenterologist - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Dietitian - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Emergency medicine - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Orthopedist - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Physiotherapist - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Psychologist - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Speech and language therapist - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Endocrinologist - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - GP visit - Pre-surgery	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Nurse visit - Pre-surgery	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Stoma care - Pre-surgery	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Pediatrician - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Hepatologist - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Gastroenterologist - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Dietitian - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Emergency medicine - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Orthopedist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Physiotherapist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Psychologist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Speech and language therapist - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Endocrinologist - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - GP visit - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Mean number of visits - Nurse visit - Post-PEBD	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Stoma care - Post-PEBD	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Pediatrician - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Hepatologist - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Gastroenterologist - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Dietitian - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Emergency medicine - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Orthopedist - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Physiotherapist - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Psychologist - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Speech and language therapist - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Endocrinologist - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - GP visit - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Nurse visit - Post-LTx	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.3
Mean number of visits - Stoma care - Post-LTx	[redacted]	Not varied	[redacted]	[redacted]	Section 12.3.3
Unit cost - Pediatrician	£119.00	Gamma	£101.15	£136.85	Section 12.3.7
Unit cost - Hepatologist	£119.00	Gamma	£101.15	£136.85	Section 12.3.7
Unit cost - Gastroenterologist	£119.00	Gamma	£101.15	£136.85	Section 12.3.7
Unit cost - Dietitian	£84.67	Gamma	£71.97	£97.37	Section 12.3.7
Unit cost - Emergency medicine	£181.00	Gamma	£153.85	£208.15	Section 12.3.7
Unit cost - Orthopedist	£71.00	Gamma	£60.35	£81.65	Section 12.3.7
Unit cost - Physiotherapist	£71.00	Gamma	£60.35	£81.65	Section 12.3.7
Unit cost - Psychologist	£288.00	Gamma	£244.80	£331.20	Section 12.3.7
Unit cost - Speech and language therapist	£84.67	Gamma	£71.97	97.37	Section 12.3.7
Unit cost - Endocrinologist	£119.00	Gamma	£101.15	136.85	Section 12.3.7
Unit cost - GP visit	£39.00	Gamma	£33.15	£44.85	Section 12.3.7
Unit cost - Nurse visit	£39.00	Gamma	£33.15	£44.85	Section 12.3.7
Unit cost - Stoma care	£788.43	Gamma	£670.16	£906.69	Section 12.3.7

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Proportion of patients - Serum bilirubin	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Serum bile acid	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Complete blood count	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - ALT	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - AFP	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - GGT	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - AST	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - PT	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Glucose	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Albumin	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Proportion of patients - Vitamin A, E, D, K status	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.3
Unit cost - Serum bilirubin	£22.88	Gamma	£19.45	£26.32	Section 12.3.7
Unit cost - Serum bile acid	£2.85	Gamma	£2.42	£3.28	Section 12.3.7
Unit cost - Complete blood count	£6.78	Gamma	£5.76	£7.80	Section 12.3.7
Unit cost - ALT	£3.06	Gamma	£2.60	£3.52	Section 12.3.7
Unit cost - AFP	£2.85	Gamma	£2.42	£3.28	Section 12.3.7
Unit cost - GGT	£2.85	Gamma	£2.42	£3.28	Section 12.3.7
Unit cost - AST	£3.06	Gamma	£2.60	£3.52	Section 12.3.7
Unit cost - PT	£28.86	Gamma	£24.53	£33.19	Section 12.3.7
Unit cost - Glucose	£6.79	Gamma	£5.77	£7.81	Section 12.3.7
Unit cost - Albumin	£3.06	Gamma	£2.60	£3.52	Section 12.3.7
Unit cost - Vitamin A, E, D, K status	£18.70	Gamma	£15.90	£21.51	Section 12.3.7
Immunosuppression - azathioprine, daily dose month 0-3	1	Gamma	0.85	1	Section 12.3.6.5
Immunosuppression - azathioprine, daily dose month 3-6	1	Gamma	0.85	1	Section 12.3.6.5
Immunosuppression - azathioprine, daily dose month 6-9	1	Gamma	0.85	1	Section 12.3.6.5
Immunosuppression - azathioprine, daily dose month 9-12	1	Gamma	0.85	1	Section 12.3.6.5

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
Immunosuppression - azathioprine, daily dose month 12	1	Gamma	0.85	1	Section 12.3.6.5
Azathioprine, cost per pack	£2.05	Not varied	2.05	2.05	Section 12.3.6.5
Azathioprine, pack size	28	Not varied	28	28	Section 12.3.6.5
Azathioprine, mg per pack	25	Not varied	25	25	Section 12.3.6.5
Immunosuppression - tacrolimus, daily dose month 0-3	0.12	Gamma	0.1	0.14	Section 12.3.6.5
Immunosuppression - tacrolimus, daily dose month 3-6	0.09	Gamma	0.08	0.1	Section 12.3.6.5
Immunosuppression - tacrolimus, daily dose month 6-9	0.08	Gamma	0.07	0.09	Section 12.3.6.5
Immunosuppression - tacrolimus, daily dose month 9-12	0.07	Gamma	0.06	0.08	Section 12.3.6.5
Immunosuppression - tacrolimus, daily dose month 12	0.07	Gamma	0.06	0.08	Section 12.3.6.5
Tacrolimus, cost per pack	£55.69	Not varied	£55.69	£55.69	Section 12.3.6.5
Tacrolimus, pack size	50	Not varied	50	50	Section 12.3.6.5
Tacrolimus, mg per pack	1	Not varied	1	1	Section 12.3.6.5
Immunosuppression - prednisolone, daily dose month 0-3	15	Gamma	12.75	17.25	Section 12.3.6.5
Immunosuppression - prednisolone, daily dose month 3-6	7.5	Gamma	6.38	8.63	Section 12.3.6.5
Immunosuppression - prednisolone, daily dose month 6-9	0	Not varied	0	0	Section 12.3.6.5
Immunosuppression - prednisolone, daily dose month 9-12	0	Not varied	0	0	Section 12.3.6.5
Immunosuppression - prednisolone, daily dose month 12	0	Not varied	0	0	Section 12.3.6.5
prednisolone, cost per pack	£0.85	Not varied	£0.85	£0.85	Section 12.3.6.5
prednisolone, pack size	28	Not varied	28	28	Section 12.3.6.5
prednisolone, mg per pack	5	Not varied	5	5	Section 12.3.6.5
PEBD - cost of procedure	£12,643	Gamma	£10,746.55	£14,539.45	Section 12.3.6.4
PEBD - cost of reoperation	£12,643	Gamma	£10,746.55	£14,539.45	Section 12.3.6.4
PEBD - cost of treating infections	£1,846.95	Gamma	£1,569.91	£2,123.99	Section 12.3.6.4
PEBD - cost of treating bowel prolapse	£2,986.33	Gamma	£2,538.38	£3,434.28	Section 12.3.6.4
PEBD - % patients - procedure	100%	Not varied	100%	100%	Section 12.3.6.4

Parameter name	Current value	Parameter distribution	Lower value of parameter	Upper value of parameter	Reference
PEBD - % patients - reoperation	67%	Beta	57%	77%	Section 12.3.6.4
PEBD - % patients - infections	43%	Beta	36%	49%	Section 12.3.6.4
PEBD - % patients - bowel prolapse	7%	Beta	6%	8%	Section 12.3.6.4
Liver transplant - pre-transplant cost	£19,698.82	Gamma	£16,743.99	£22,653.64	Section 12.3.6.5
Liver transplant - transplant phase cost (Singh et al)	£70,320	Gamma	£59,772.02	£80,868.03	Section 12.3.6.5
Liver transplant - 2-years post-transplant cost	£39,287.44	Gamma	£33,394.32	£45,180.55	Section 12.3.6.5
Cost of liver	£1,786	Gamma	£15,181.85	£20,540.15	Section 12.3.6.5
Cost of liver retrieval	£24,614	Gamma	£20,922.22	£28,306.54	Section 12.3.6.5
LTx complications - cost of diarrhoea	£592	Gamma	£502.80	£680.26	Section 12.3.8.1
LTx complications - cost of liver steatosis	£2,917	Gamma	£2,479.75	£3,354.96	Section 12.3.8.1
LTx complications - cost of stunted growth	£0.00	Not varied	£0.00	£0.00	Section 12.3.8.1
LTx complications - cost of deafness	£198	Gamma	£68.00	£227.29	Section 12.3.8.1
LTx complications - cost of pancreatitis	£1,066	Gamma	£905.85	£1,225.56	Section 12.3.8.1
Average weekly wage	£537	Gamma	£456.45	£617.55	Section 12.3.9
Work impairment - loss of response	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.9
Work impairment - response	[redacted]	Beta	[redacted]	[redacted]	Section 12.3.9
Number of caregivers per household	1.78	Gamma	1.51	2.05	Section 12.3.9
Cost of travel to treatment centre	£24	Gamma	£20.40	£27.60	Section 12.3.9
Number of visits per year	[redacted]	Gamma	[redacted]	[redacted]	Section 12.3.9

12.3 Resource identification, measurement and valuation

NHS costs

All costs were valued in 2020 UK pounds. Where necessary, costs were inflated to 2019/20[2] prices using the hospital and community health services (HCHS) pay and prices

[2] The most recent edition of the Unit Costs of Health and Social Care includes inflation indices up to 2019/20.

index from the Unit Costs of Health and Social Care, as issued by the Personal Social Services Research Unit (PSSRU). [110]

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There is no specific Healthcare Resource Group (HRG) for the clinical management of PFIC, however costs associated with PEBD are assumed equivalent to small intestine procedure (Section 12.3.6.4). The economic model is structured to align the clinical pathway of care (Figure 39), with costs based on health states associated with the severity of pruritus. NHS reference costs and PSSRU cost for the clinical management of PFIC are listed in section 12.3.6.4-12.3.8.1

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria and consider published and unpublished studies.

See section 11.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[3].

Clinical advisers did not assess the resource use in the model; instead this was informed by the burden of illness (PICTURE) study:[100]

A burden of illness study was performed to evaluate resource use frequencies and caregiver burden of PFIC [redacted]. Clinician consultation visits (average number of visits and proportion of patients) is reported in Table 58. Rates for patients without surgery were applied to the odevixibat and SoC non-response states. Rates for post-PEBD patients were applied in the PEBD states regardless of response. The frequency of tests administered is reported in Table 59 and was applied to all pre-LTx states.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 58. Resource use in PFIC, clinical consultations in the last 12 months

	% patients			Mean number of visits (annual)		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pediatrician	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenterologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dietitian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emergency medicine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthopaedist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physiotherapist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Speech and language therapist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endocrinologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nurse visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stoma care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GP, general practitioner; LT, liver transplant; PEBD, partial external biliary diversion.

Table 59: Proportion of PFIC patients administered tests in the last 12 months, UK patients only

	% patients
Serum bilirubin	[redacted]
Serum bile acid	[redacted]
Complete blood count	[redacted]
Alanine aminotransferase (ALT)	[redacted]
Alpha fetoprotein (AFP)	[redacted]
Gamma glutamyl transpeptidase (GGT)	[redacted]
Aspartate aminotransferase (AST)	[redacted]
Prothrombin (PT)	[redacted]
Glucose	[redacted]
Albumin	[redacted]
Vitamin A, E, D, K status	[redacted]

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

Odevixibat is an oral therapy provided as capsules containing 200 µg, 400 µg, 600 µg or 1,200 µg; which have a list price of [redacted] respectively per pack of 30 capsules.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

A patient access scheme has been proposed at simple discount. Both list price and PAS price have been modelled in the cost-effectiveness analysis.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in Tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

12.3.6.1 Acquisition

12.3.6.1.1 Intervention costs

Odevixibat is dosed based on weight at either 40 mcg/kg or 120 mcg/kg and is available in 200, 400, 600 and 1200 mcg capsules, resulting in nine potential weight bands that patients may fall into for dosing purposes. Table 60 summarises the cost per pack of odevixibat and Table 61 summarises the daily and annual cost for each weight band.

Table 62 summarises the mean weight by age group in the model.

Table 60: Cost per pack of odevixibat

Odevixibat dose	Capsule	Capsule strength (mcg)	Cost per pack	Tablets per pack	Cost per tablet
Low dose (40 mcg/kg)	Sprinkle	200	[redacted]	30	[redacted]
	Swallow	400	[redacted]	30	[redacted]
High dose (120 mcg/kg)	Sprinkle	600	[redacted]	30	[redacted]
	Swallow	1200	[redacted]	30	[redacted]

Table 61: Daily and annual cost by weight band

Weight	Daily dose		Capsules/day		Daily cost		Annual cost	
	Low dose	High dose	Sprinkle	Swallow	Low dose	High dose	Low dose	High dose
4	200	600	1		[redacted]	[redacted]	[redacted]	[redacted]
7.5	400	1200	2		[redacted]	[redacted]	[redacted]	[redacted]
12.5	600	1800	3		[redacted]	[redacted]	[redacted]	[redacted]
17.5	800	2400	4		[redacted]	[redacted]	[redacted]	[redacted]
19.5	800	2400		2	[redacted]	[redacted]	[redacted]	[redacted]
25.5	1200	3600		3	[redacted]	[redacted]	[redacted]	[redacted]
35.5	1600	4800		4	[redacted]	[redacted]	[redacted]	[redacted]
45.5	2000	6000		5	[redacted]	[redacted]	[redacted]	[redacted]
55.5	2400	7200		6	[redacted]	[redacted]	[redacted]	[redacted]

Patients are assumed to be in the 25th percentile of weight in the year that they start treatment, moving to the 33rd percentile in year 2 and then the 50th percentile each year after that. Weights for children have been taken from growth charts and weights for adults have been taken from HSCIC Health Survey data.

Table 62: Mean weight by age

Age	Weight				Modelled weight	
	25th percentile		50th percentile			
	Male (kg)	Female (kg)	Male (kg)	Female (kg)	Male (kg)	Female (kg)
4	15.25	15.00	16.50	16.25	[redacted]	[redacted]
5	17.25	16.75	18.50	18.50	[redacted]	[redacted]
6	19.25	18.75	20.75	20.50	[redacted]	[redacted]
7	21.25	21.00	23.00	23.00	[redacted]	[redacted]
8	23.50	23.50	25.50	26.00	[redacted]	[redacted]
9	25.75	26.00	28.50	28.75	[redacted]	[redacted]
10	28.50	27.75	31.50	32.25	[redacted]	[redacted]
11	31.25	32.00	34.75	36.00	[redacted]	[redacted]
12	34.25	35.50	38.25	40.25	[redacted]	[redacted]
13	38.50	40.25	43.00	45.25	[redacted]	[redacted]
14	43.75	45.00	49.25	50.00	[redacted]	[redacted]
15	49.50	47.25	55.50	53.50	[redacted]	[redacted]
16	54.75	50.50	60.75	55.50	[redacted]	[redacted]
17	58.50	51.75	64.50	56.75	[redacted]	[redacted]
18	61.00	52.50	67.00	57.50	[redacted]	[redacted]
25	83.98	69.49	83.98	69.49	[redacted]	[redacted]
35	87.26	72.38	87.26	72.38	[redacted]	[redacted]
45	88.67	75.25	88.67	75.25	[redacted]	[redacted]
55	88.01	73.94	88.01	73.94	[redacted]	[redacted]
65	85.75	72.01	85.75	72.01	[redacted]	[redacted]
75	79.68	67.98	79.68	67.98	[redacted]	[redacted]

Patients are assumed to receive odevixibat as long as they have an sBA and pruritus response. Response was assessed at 24 weeks in PEDFIC 1, non-responders in the model are therefore assumed to receive a maximum of 24 weeks (6 months) of treatment before treatment is discontinued. A scenario is included where patients are treated until LTx.

12.3.6.1.2 Standard of care costs

Patients receiving standard of care are administered a combination of oral drugs to control their pruritus symptoms. A summary of the therapies administered is provided in Table 63 and costs are referenced from the BNF.[111] The proportion of patients receiving each oral therapy was taken from PEDFIC1 for UDCA and rifampicin. Clinical opinion suggested a proportion of patients would also receive naltrexone and cholestyramine. These proportions were derived from clinical input in TA443 for treating primary biliary cholangitis[102] and the burden of illness study (cholestyramine).[100]

Table 63: Acquisition costs, standard of care

Therapy	% patients	Dose per day	Mg/unit	Units/pack	Cost/pack	Cost/cycle
UDCA	95%	12mg/kg	150	60	£14.49	£7.05/kg
Cholestyramine	37.5%	4,000mg	4,000	50	£10.76	£78.60
Rifampicin	66%	10mg	150	100	£18.32	£4.46
Naltrexone	10%	2mg/kg	50	28	£23.00	£12.00/kg

Abbreviations: UDCA, ursodeoxycholic acid

12.3.6.4 PEBD costs

The cost of PEBD surgery is assumed equivalent to a major small intestine procedure, with Casemix Companion (CC) score 2+ from NHS reference costs 2018/19, see

Table 64. This cost was validated by a clinical expert. The proportion of patients with complications (re-operations, infection or bowel prolapse) was informed by Bjornland et al., 2020.[105] The weighted average cost of PEBD and associated complications is £22,119.

Table 64: Costs associated with PEBD surgery and complications

Description	Unit cost	Proportion of patients*	Source
PEBD surgery Very complex hepatobiliary or pancreatic procedure, CC score 2-3	£12,643	100%	National schedule of reference costs 2018/2019[112] (code GA03D0)

Re-operations Very complex hepatobiliary or pancreatic procedure, CC score 2-3	£12,643	67%	National schedule of reference costs 2018/2019[112] (code GA03D0)
Treatment for infection Paediatric intermediate infection, CC score 2-4	£1,846.95	43%	National schedule of reference costs 2018/2019[112] (code PW17F)
Surgery for bowel prolapse Paediatric other gastrointestinal disorders	£2,986.95	7%	National schedule of reference costs 2018/2019[112] (code PF26B)
Total weighted average cost of PEBD and associated complications	£22,118.67		

Abbreviations: CC, Casemix companion; PEBD, partial external biliary diversion
*Of those receiving PEBDs

12.3.6.5 Liver transplant cost

Cost of procedure

The cost of LTx surgery is assumed equivalent to the cost reported in TA443[113] for patients diagnosed with chronic hepatitis C and B in the UK, and inflated from 2014 to 2019/20 costs. This cost captures pre-transplant costs and transplant phase costs. Costs for the organ and its retrieval were taken from NHS Blood and Transplant (NHSBT)[64] and data from the National Organ Retrieval Service (NORS)[114] in the UK. The cost per organ was based on NHSBT's total annual expenditure divided by the number of organs transplanted. The cost of retrieval was based on NORS' total annual expenditure divided by the number of livers retrieved in 2019/20.

All of these are applied to patients in the year of LTx (Table 65)

Table 65: Costs incurred in year of LTx

Type of cost	Cost (inflated to 2019/20)
Pre-transplant phase (waiting list)	£19,699
Transplant phase	£70,320
Organ	£17,861
Retrieval of organ	£24,614

Monitoring

Post-LTx costs include the post-transplant cost reported in TA443 in the 2 years following LTx (Table 66) and immunosuppression informed by the regimen reported in TA348 (azathioprine, tacrolimus, and prednisolone) (Table 67).[113,115] Immunosuppression costs were referenced from the latest BNF.[111]

Table 66: Costs incurred in 2 years following LTx

Type of cost	Cost (inflated to 2019/20)	Cost per cycle, years 1 and 2
Post-LTx cost	£39,287	£19,644

Abbreviations: LTx, liver transplant.

Table 67: Costs of immunosuppression

Therapy	Dose per day (mg/kg)	Mg/unit	Units/pack	Cost/pack	Year 1	Cost/cycle
						Subsequent years
Azathioprine	1	25	28	£2.05	£1.34	£1.07
Tacrolimus	Month 0-3: 0.12	1	50	£55.69	£43.73	£28.48
	Month 3-6: 0.09					
	Month 6-9: 0.08					
	Month 9-12+: 0.07					
Prednisolone	Month 0-3: 15	5	28	£0.85	£12.47	£0
	Month 3-6: 7.5					

Table 68: Costs per treatment/patient associated with the odevixibat in the cost-effectiveness model

Items	Value	Source
Intervention cost of odevixibat per 30 200mcg capsules*	[redacted]	Section 12.3.4
Administration cost	None	Self-administered
Pre-surgery resource use per annual cycle	[redacted]	Weighted average of resource use (see section 12.3.7)
Pre-LTx resource use	£71	Weighted average cost (see section 12.3.7)

*price per mcg of odevixibat is equal across pack strengths

Table 69: Costs per treatment/patient associated PEBD in the cost- effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	£22,118.67	Section 12.3.6.4
Cost of procedure	£12,643	Weighted average included in price of treatment
Reoperations	£12,643	Weighted average included in price of treatment
Treatment for infection	£1,846.95	Weighted average included in price of treatment
Surgery for bowel prolapse	£2,986.33	Weighted average included in price of treatment
Pre-surgery resource use per annual cycle	[redacted]	Weighted average of resource use
Pre-LTx resource use	£71	Weighted average of tests
Post-PEBD resource use per annual cycle	[redacted]	Weighted average of resource use

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in Section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Costs for clinical consultation considered in the model are presented in Table 70. Costs of tests administered to patients are presented in Table 71. The frequency of resource use and tests were taken from the burden of illness study.[100]

Table 70: Healthcare resource use categories

Type of consultation	Unit cost	Source of cost
Paediatrician	£119.00	PSSRU 2020, cost per working hour for a medical consultant.[110]
Hepatologist	£119.00	PSSRU 2020, cost per working hour for a medical consultant. [110]
Gastroenterologist	£119.00	PSSRU 2020, cost per working hour for a medical consultant. [110]
Dietitian	£84.67	PSSRU 2020, consultant dietitians/speech and language therapists, average of cost per working hour for a band 8a-c. [110]
Emergency medicine	£181.00	PSSRU 2020 Average of all emergency medicine costs.[110]
Orthopaedist	£71.00	PSSRU 2020, cost per working hour of a physiotherapist.[110]
Physiotherapist	£71.00	PSSRU 2020, cost per working hour of a physiotherapist.[110]
Psychologist	£288.00	PSSRU 2020, child and adolescent mental health services, average cost per patient contact, Outpatient attendance .[110]
Speech and language therapist	£84.67	PSSRU 2020, consultant dietitians/speech and language therapists, average of cost per working hour for a band 8a-c.[110]
Endocrinologist	£119.00	PSSRU 2020, cost per working hour for a medical consultant.[110]
GP visit	£39.00	PSSRU 2020, direct care staff costs with qualifications per 9.22-minute consultation.[110]
Nurse visit	£39.00	PSSRU 2020, cost per working hour of a band 5 nurse.[110]
Stoma care	£788.43	Average of the cost of stoma care for ulcerative colitis and Crohn's disease, inflated to 2019/20 in Buchanan et al.[116]

Abbreviations: GP, general practitioner;

Table 71: Unit costs of test

Type of test	Unit cost	Source of cost
Serum bilirubin	£22.88	Cost of total serum bilirubin test[117]
Serum bile acid	£2.85	NHS reference costs 2018/19, directly accessed pathology services, haematology (DAPSS05)[112]
Complete blood count	£6.78	NICE preoperative tests[118]
Alanine aminotransferase (ALT)	£3.06	Akhtar et al.[119]

Alpha fetoprotein (AFP)	£2.85	NHS reference costs 2018/19, directly accessed pathology services, haematology (DAPSS05)
Gamma glutamyl transpeptidase (GGT)	£2.85	NHS reference costs 2018/19, directly accessed pathology services, haematology (DAPSS05)
Aspartate aminotransferase (AST)	£3.06	Akhtar et al.[119]
Prothrombin (PT)	£28.86	NICE preoperative tests[118]
Glucose	£6.79	NHS reference costs 2018/19, directly accessed pathology services, haematology (DAPSS05), phlebotomy (DAPSS08)
Albumin	£3.06	Akhtar et al.[119]
Vitamin A, E, D, K status	£18.70	Cost of a vitamin D test, NICE [120]

Adverse-event costs

12.3.8 Complete Table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

12.3.8.1 Cost of LTx complications

LTx complications are commonly reported in PFIC1, including diarrhoea and liver steatosis, resulting in poorer post-LTx outcomes in this population. The complications reported in Table 56 were allocated the costs shown in Table 72.

Table 72: List of adverse events and summary of costs included in the cost- effectiveness model

Adverse events	Cost per event	Total cost			Reference
		PFIC1	PFIC2	Joint	
Diarrhoea	£592	£479	£41	£161	NHS reference costs 2018/19 (code ED05B)[112]
Liver steatosis	£2,917	£2,626	£175	£847	Crossan et al., 2015[121]
Stunted growth	£0	£0	£0	£0	Assumption
Deafness	£198	£65	£0	£18	NICE Guideline 98[117]
Pancreatitis	£1,066	£426	£0	£117	NHS reference costs 2018/19 (code GC17K)[112]
Total		**£3,596**	**£216**	**£1,143**	

The cost of diarrhoea and pancreatitis were taken from NHS reference costs 2018/19 (codes ED05B and GC17K, respectively). Stunted growth is not assumed to incur any cost. The cost of liver steatosis is calculated as the total cost of treating liver steatosis in patients with non-alcoholic steatohepatitis (excluding surgical procedures) by Crossan, inflated to 2019/20.[121] The cost of hearing loss was taken from NICE Guideline 98, which reported the annual cost of treatment for hearing loss (inflated to 2019/20).[118]

12.3.8.2 Adverse event costs

Adverse events were not applied in the base-case. However, the costs in Table 73 were explored in scenario analysis. An option is included to apply an additional consultation with a clinician.

Table 73: Adverse events costs included in scenario analysis

Event	Cost per event	Source
Diarrhoea	£2.21	Average cost of a paediatric course of loperamide, BNF[111]
Vomiting	£30.80	Average cost of a course of ondansetron, BNF
Abdominal pain	£0	No cost assumed.

Upper respiratory infection	£0.98	Average cost of a paediatric course of amoxicillin for respiratory infections, BNF
Nasopharyngitis	£3.04	Average cost of a paediatric course of amoxicillin for nasopharyngitis, BNF
Increased alanine aminotransferase	£2.79	Haematology cost, NHS reference costs (2018/29)[112]
Increased blood bilirubin	£2.79	
Increased aspartate aminotransferase	£2.79	
Increased blood alkaline phosphatase	£2.79	
Pyrexia	£8.82	Average cost of a course of paracetamol for fever, BNF

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Societal costs are included in the model base case to capture the financial burden for parents and caregivers of children with PFIC, and annual costs are reported in Table 75. At the time of model completion, insufficient information was available on the burden of disease in PFIC specifically. The estimates applied in the model are therefore assumptions.

Lost productivity is based on the proportion of work impairment recorded in the burden of illness study[100] in the no response states (30.3%) and assumed half in response states (30.3% ÷ 2 = 15.2%). An hourly wage of £537 was taken from the Office for National Statistics (ONS) and assumed for 75% of the average number of caregivers per household (1.78, from the ONS)[122]. This cost is applied until the age of 18 in the model.

Table 74: Productivity loss

	No response states (sBA/pruritus, PEBD)	**Response (sBA/pruritus, PEBD, LT)**
Work impairment	30.3%	15.2%
Annual productivity loss	£11,404	£5,702

The number of specialist visits per year was informed by a clinical expert, who confirmed that the annual number of specialist visits for individuals with PFIC was [redacted]

[redacted]. The cost per trip was borrowed and inflated from NHS data on haemodialysis transport, which suggested an annual cost of £3,750 for 156 return journeys.[123]

Table 75: List of societal costs

Type of cost	Frequency per cycle	Annual cost	Reference
Travel to specialist centre	[redacted]	[redacted]	Clinical expert

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Deterministic (one-way) and probabilistic sensitivity analyses were conducted on the model base-case parameters. Scenario analyses were conducted in order to further test the uncertainty around specific model inputs and assumptions.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% confidence interval, or ±15% where no estimates of precision were available.

Probabilistic sensitivity analysis

Joint parameter uncertainty is explored through probabilistic sensitivity analysis (PSA), in which all appropriate parameters[4] are assigned distributions and varied jointly. A total of 1,000 Monte Carlo simulations were recorded. Results were plotted on the cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

Scenario analyses

A number of variations were considered in the structural assumptions and several exploratory analyses (both optimistic and pessimistic), Table 76 provides a summary of the different scenarios explored. Results are presented in section 12.5.1.2.

Table 76. Summary of scenarios

Scenario	Parameter	Base-case	Scenario	Justification
1	Perspective	Societal	NHS	NICE reference case
2	Discount rate	1.5%	3.5%	NICE reference case
3	LTx mortality	Meta analyses and pooled estimates from literature	NHS data	Included as an exploratory analysis
4	Quality of life	Patient reported estimates from the literature	PEDFIC1 patient reported	Included as an exploratory analysis, outcomes reported in PEDIFC1 were investigated
5			PEDIFC1 parent-proxy	
6	Source of stoma bad disutility	Ulcerative colitis study	Colorectal cancer study	Included as an exploratory analysis

[4] Model parameters that are not varied include those that are considered to be structural assumptions (e.g. cell links for model options, time horizon) and those considered to be certain (e.g. drug costs).

7	Time on treatment with odevixibat	Until loss of response	Until surgery	Clinicians are likely to keep patients on the lower dose for a longer duration
8	PEBD in odevixibat arm	Excluded	Include	Included as an exploratory analysis
9	Response assessment	sBA and pruritus	Pruritus only	Based on pruritus endpoint from PEDFIC1
10	Annual loss of response to odevixibat	[redacted]	5%	Odevixibat is expected to replace PEBD within treatment pathway, therefore the same PEBD withdrawal rate is assumed
11	Annual loss of response to PEBD	5%	[redacted]	Same as above and 10% included as an exploratory analysis
12			10%	
13	Proportion of PFIC1	27%	50%	Proportion of PFIC1 patients maybe higher than those seen in PEDFIC1
14	Adverse event costs	Not applied	Include	Common treatment-emergent adverse events occurring in greater than 5% of patients were included
15	Growth curve used for weight-based dosing	25th percentile until year 1, 33rd percentile until year 2, 50th percentile thereafter, UK growth curved	25th percentile	Assuming patients are underweight for age - Patients are expected to start on odevixibat at 4.25 years, therefore categorising them in the lower weight band

12.4.3 Summarise the variables used in the sensitivity analysis.

Deterministic, scenario and probabilistic sensitivity analyses were undertaken, as described above. Distributions and their sources are stated in Table 57.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

No parameters or variables listed in Table 57 were omitted from the sensitivity analyses.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme.

In the model base case, discounted model results are presented in Table 77 for list price and Table 78 for PAS price. Using a lifetime time horizon, the incremental total LYs gain of odevixibat versus standard of care was [redacted] years. The discounted incremental costs of [redacted] and incremental QALYs of [redacted] resulted in an ICER of [redacted] versus standard of care. When the PAS discount is applied the incremental cost is [redacted] which results in an ICER of [redacted].

Table 77: Base-case results – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	33	[redacted]				
Odevixibat	[redacted]	36.33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 78: Base-case results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	33	[redacted]				
Odevixibat	[redacted]	36.33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The following clinical outcomes were modelled:

- Years with response
- Years with loss of response
- Years in PEBD
- Years in LTx
- Years in post-LTx

Modelled results could not be compared to those reported in the clinical trials, as long-term outcomes data are not available from the clinical studies.

Table 79: Summary of model results

Outcome	Standard of care	Odevixibat
Years with response	0.00	14.88
Years with loss of response	7.93	12.84
Years in PEBD	8.38	0.00
Years in LTx	1.05	0.99
Years in Post-LTx	34.64	29.48

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The proportion of patients in response, loss of response, PEBD, LTx, post LTx and mortality for both odevixibat and SoC are presented in Figure 43 and Figure 44 for the full lifetime time horizon.

Figure 43: Health states - standard of care

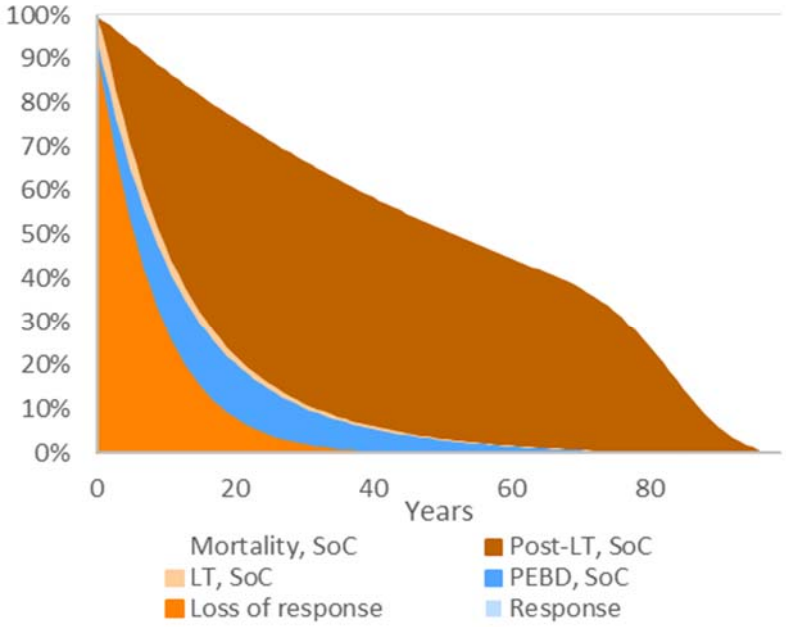
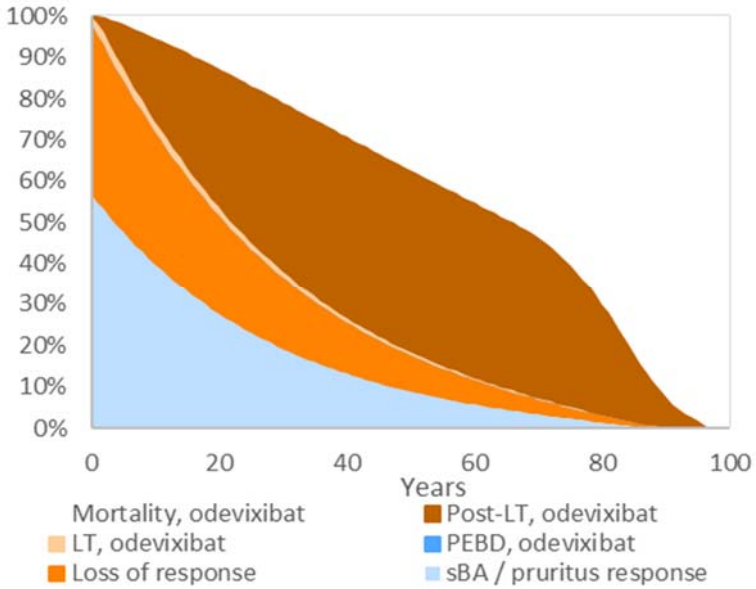


Figure 44: Health states - odevixibat arm



12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The QALYs accrued over time for the first 20 years for both odevixibat and SoC are presented in Table 80. Graphical representations are presented in Figure 45 for the full-time horizon.

Table 80: Accrued QALYs (first twenty years only)

Year	Odevixibat	SoC
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]

13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]
19	[redacted]	[redacted]
20	[redacted]	[redacted]

Figure 45: Accrued QALYs

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 79 and Table 81 show life year gains and QALY gains disaggregated by health state.

Table 81: Model outputs by clinical outcomes - QALY

	Standard of care	Odevixibat
QALYs with response	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]
QALYs LTx	[redacted]	[redacted]
QALYs Post-LTx	[redacted]	[redacted]

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table 82 shows a summary of QALY gains by health state. Just over half of the QALY gains ([redacted]) were due to patients responding to treatment; post-liver transplant accounted for [redacted] of the QALY gains.

Table 82: Summary of QALY gain by health state

Health state	QALY Odevixibat	QALY Standard of care	Increment	Absolute increment	% absolute increment
QALYs with response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrements	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

Total undiscounted QALYs for treatment with odevixibat was [redacted] compared to [redacted] for standard of care over a lifetime time horizon, resulting in an incremental benefit of [redacted].

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table D12.

A summary of costs by category per patient provided in Table 83 and Table 84 for both odevixibat and SoC.

Table 83: Summary of costs by category of cost per patient – list price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 84: Summary of costs by category of cost per patient – PAS price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Table D13.

Costs for technology and comparator by health state are summarised in Table 83 and Table 84.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Table D14.

Not applicable.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Results for the ten most influential parameters identified by univariate sensitivity analysis are presented in Table 85 and Figure 46 at list price; and Table 86 and Figure 47 at PAS price.

Table 85: One-way sensitivity analysis results – list price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
Response to odevixibat - sBA & pruritus response – up-titrators	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - emotional score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx PedsQL - social score	[redacted]	[redacted]	[redacted]	[redacted]
Response to PEBD - PFIC1	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - social score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
% PFIC1	[redacted]	[redacted]	[redacted]	[redacted]
Re-transplant rate - PFIC2	[redacted]	[redacted]	[redacted]	[redacted]
Pre-transplant mortality - PFIC2	[redacted]	[redacted]	[redacted]	[redacted]
Average weekly wage	[redacted]	[redacted]	[redacted]	[redacted]

Table 86: One-way sensitivity analysis results – PAS

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
PAS discount	[redacted]	[redacted]	[redacted]	[redacted]
Response to odevixibat - sBA & pruritus response - uptitrators	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
Response to PEBD - PFIC1	[redacted]	[redacted]	[redacted]	[redacted]
PEBD hazard, PFIC2	[redacted]	[redacted]	[redacted]	[redacted]
% LTx, without PEBD, PFIC1	[redacted]	[redacted]	[redacted]	[redacted]
sBA≥118 PedsQL - emotional score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
sBA≥118 PedsQL - physical score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
% PFIC1	[redacted]	[redacted]	[redacted]	[redacted]
Short stature multiplier	[redacted]	[redacted]	[redacted]	[redacted]

Figure 46: Change in ICER - list price

Figure 47: Change in ICER – PAS price

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis

Table 87: Scenario analysis

Parameter	Scenarios	ICER - List	ICER - PAS
Base case			
Perspective	NHS		
Discount rate	3.5%		
LTx mortality	NHS data		
Quality of life	PEDFIC 1 parent-proxy		
Quality of life	PEDFIC 1 patient reported		
Source of stoma bag disutility	Colorectal cancer study		
Time on treatment with odevixibat	Until surgery		
PEBD in odevixibat arm	Include		

Response assessment	Pruritus only	[redacted]	[redacted]
Annual loss of response to odevixibat	5%	[redacted]	[redacted]
Annual loss of response to PEBD	[redacted]	[redacted]	[redacted]
Annual loss of response to PEBD	[redacted]	[redacted]	[redacted]
Proportion of PFC 1	50%	[redacted]	[redacted]
Adverse event costs	Include	[redacted]	[redacted]
Growth curve used for weight-based dosing	25th percentile	[redacted]	[redacted]

12.5.13 Present results of the probabilistic sensitivity analysis

PSA – List price

PSA simulations were plotted on the cost-effectiveness plane (

Figure 48) and a CEAC was generated (Figure 49). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted]

Figure 48: Cost effectiveness plane – List price

Figure 49: Cost-effectiveness acceptability curve – List price

PSA – PAS price

PSA simulations were plotted on the cost-effectiveness plane (Figure 50) and a CEAC was generated (Figure 51). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs.

The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted] and [redacted] respectively.

Figure 50: Cost effectiveness plane – PAS price

Figure 51: Cost-effectiveness acceptability curve – PAS price

12.5.14 What were the main findings of each of the sensitivity analyses?

The most influential parameter for the list price is the response to odevixibat - sBA & pruritus response – up-titrators. Other influential parameters relate to the quality-of-life

impact of PEBD (stoma bag) and mapping of PedsQL to the EQ-5D in the responder states.

Scenario analyses demonstrated that the ICER is sensitive to treatment duration with odevixibat and as anticipated, PEDFIC1 patient reported quality of life. PEDFIC1 patient reported outcomes results were counterintuitive due to the small patient numbers and poor results reporting. Moreover, responders reported lower QoL at baseline, consequently, resulting in non-responders having a higher QoL than responders. The ICER remained below £300,000, in all scenarios modelled for PAS price.

The mean PSA results for PAS price lie very close to the deterministic base-case results (Table 78). Odevixibat accrued [redacted] at cost of [redacted] compared to SoC. The corresponding ICER was [redacted] per QALY gained.

12.5.15 What are the key drivers of the cost results?

The key driver of cost results is the price of odevixibat, time spent on odevixibat, parameters relating to quality of life and the impact of a stoma bag.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

In line with final scope, no subgroup analyses were undertaken.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

In line with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) taskforce report on model transparency and validation[5] [124], the following types of validation were conducted:

1) Face validation
2) Internal validation
3) Cross validation
4) External validation

Face validity

Interviews with clinical experts (including a [redacted]) and an academic health economist were conducted to review the model decision problem, structure, and data use. Following the availability of

[5] Note that no attempt was made to conduct a predictive validation (the fifth validation type specified in the ISPOR taskforce report)

results from PEDFIC 1, additional interviews with experts and an advisory board were conducted to evaluate the data used in the model.

External validity

Outputs of the model were compared against the outcomes observed in the clinical trial to evaluate the internal consistency of the model.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The economic model represents the most valid characterisation of PFIC modelling. Modelling decisions are based on the primary endpoint reported in PEDFIC1 and clinician input.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The cost-effectiveness analysis does not include patients with subtypes of PFIC other than PFIC1 and PFIC2, however odevixibat will be used to treat all subtypes (see section 9.9.4). In addition, clinicians may wish to treat some patients with the episodic forms of PFIC1 and PFIC2 (BRIC1 and BRIC2).

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A key strength of this analysis is the use of trial endpoints in the model for a number of inputs, and their consistency with endpoints from the NAPPED study, which enabled modelling disease progression based on clinically meaningful sBA/pruritus thresholds.

An additional strength is that a wide range of scenarios have been considered, to test model sensitivity to parameters for which multiple sources were available (e.g. rate of LTx, mortality, and quality of life).

A key limitation of the analysis is the paucity of data. Where possible, data specific to PFIC were used (e.g. NAPPED, PEDFIC 1), but small patient numbers and the limited number

of studies available on outcomes in PFIC1 and PFIC2 result in a significant level of uncertainty in the model's outcomes. In addition, a number of assumptions were made where data were not available (e.g. annual loss of response to PEBD).

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Albireo is currently undertaking a vignette study to accurately estimate the QoL of patients with PFIC. Results from the utility elicitation study are intended to reduce uncertainty around QoL parameters and produce robust results. The full results will be incorporated at technical engagement step.

The planned [redacted] and Prospective, registry-based studies to investigate the long-term safety and efficacy of odevixibat in patients with PFIC will provide further data that can be included in the economic analysis in the longer term.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

As discussed in Section 6.2, accurate prevalence estimates are not available for PFIC in England or the UK. At a UK advisory board, clinical experts attending (see section 12.2.5) were asked to provide information on the number of patients they treat with PFIC. Eight paediatric consultants from the three specialised treatment centres in England completed the questionnaire. All diagnosed paediatric cases are therefore expected to be accounted for. The numbers provided were analysed according to the centre to avoid double-counting, and the final numbers were further validated by one clinical expert.[8]

As PFIC presents in childhood, with most patients undergoing LTx before 18 years of age[35], patients in clinical practice are expected to start treatment with odevixibat at a very early age (from 6 months). According to the questionnaire results, there are an estimated

[redacted] paediatric patients in England currently diagnosed with PFIC, excluding patients with episodic PFIC forms (BRIC). Of these PFIC patients, 16% were estimated to have PFIC1, 38% PFIC2, 20% PFIC3, and 26% other types or not genetically confirmed.

At the UK advisory board [redacted] of clinicians stated they would use odevixibat in patients with PFIC1 and PFIC2; [redacted] would use odevixibat in patients with PFIC3; and [redacted] would use it in patients with other PFIC subtypes and in episodic patients.

Based on the total number of estimated PFIC cases in England, there is an estimated [redacted] prevalent patients eligible for treatment in England in the first year following introduction. This assumes that patients with the BSEP3 mutation and those that have had LTx or SBD will not be treated with odevixibat (Table 88).

A [redacted] advised that there are [redacted] new PFIC patients diagnosed per year at their centre. As this is based on data from the genetic laboratory that covers two-thirds of the patients in England this means there are estimated to be [redacted] new cases of PFIC diagnosed across England each year. Therefore, on average there is an estimated [redacted] newly diagnosed patients each year, [redacted] of which (i.e., excluding those with BSEP3 mutations) would be eligible for treatment with odevixibat in Year 1.

Therefore, in Year 1 there are an estimated [redacted] patients eligible for treatment.

The budget impact calculations include patients with all PFIC subtypes but do not include patients with episodic PFIC (BRIC). A proportion of patients with episodic PFIC evolve into permanent, progressive cholestasis; these patients would be eligible for odevixibat and would be accounted for in the cohort of prevalent PFIC patients. A [redacted] estimated that they see [redacted] paediatric cases of episodic PFIC per year. The majority of BRIC cases are in adults, who are not expected to be treated with odevixibat.

Table 88. Derivation of number of children on treatment in their first year

Parameter	Value	Reference
Prevalent cohort		
Patients with PFIC in England	[redacted]	Clinical expert estimate[20]
Prevalent eligible population	[redacted]	[redacted] excluded due to BSEP mutation (NAPPED[10]), [redacted] have had LTx and [redacted] of the remaining patients have had SBD (Clinical expert estimate)[20]
Incident cohort		
Number of new patients diagnosed with PFIC	[redacted]	Clinical expert estimate[20]
Incident eligible population	[redacted]	8% excluded due to BSEP mutation NAPPED[10]
Total eligible in Year 1	[redacted]	

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

The expected uptake of odevixibat is presented in Table 89 below. For the eligible patient population, odevixibat is expected to be used in the majority of patients. Cumulative market share for odevixibat following a positive NICE recommendation is estimated at [redacted] of eligible prevalent patients in year 1, and [redacted] of eligible patients in Years 2, 3, 4 and 5. Clinicians attending the advisory board stated that until there is more widespread use of odevixibat they would still try off-label therapies first. Therefore, in clinical practice, uptake may be slower in the incident population. In addition, there is some variation in clinical opinion regarding which PFIC subtypes would be treated.[8]

Table 89. Market uptake of odevixibat over 5 years in England

Year	Treated with standard of care	Treated with odevixibat
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

There are no other costs associated with odevixibat treatment.

13.4 Describe any estimates of resource savings associated with the use of the technology.

Odevixibat is expected to replace PEBD in the treatment pathway, therefore avoiding the cost of surgery. By delaying disease progression, odevixibat maintains patients in earlier health states (i.e., prior to LTx) than the standard of care (see section 12.5.3). Odevixibat has the potential to delay LTx, therefore the cost of LTx and the use of associated costs including immunosuppressive therapy are reduced from Year 2 onwards.

In addition odevixibat is associated with reductions in other medical resource use, such as visits to consultants, nurses, dieticians and other healthcare professionals.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It is not anticipated that any additional resource savings or redirection of resources would occur, and no other resource savings have been identified.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

In terms of additional savings, the earlier health states of the disease are associated with a lower requirement of care. By delaying progression into the later health states, and increasing the time spent in the earlier health states, the level of care required for patients is lower, and lower productivity losses can be expected as a result.

Although it has not yet been possible to quantify, it is highly likely that there will be significant long-term savings to patients, since patients may lead normal lives and be less impacted by their symptoms. For example, patients may be able to work more, or obtain further career progression through improved education not inhibited by PFIC. In the short term, parents might not have to take time off from work to care for their child suffering with PFIC, or pay for specialised childcare.

Due to the rarity of the disease, there are limited treatment centres able to initiate the treatment. As a result, there can be substantial journey and transportation costs for the family of the patient.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Estimates of the budget impact associated with the introduction of odevixibat, factoring in cost savings, are shown in Table 90, assuming each of the proposed list price and the proposed PAS price, respectively. The number of patients remaining on treatment in each year takes into account patients discontinuing treatment due to a lack of response. The distribution of weights for the eligible patient population in the budget impact model was based on clinical input.[20]

Table 90. Net budget impact of odevixibat in England over 5 years (proposed list price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient numbers					
Prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patient group (new patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients (total cumulative)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients remaining on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact - List price					
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact - PAS price					
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The patient numbers are based on clinical estimations. Although this may not be completely accurate these are the most reliable estimates available.

The patient numbers take into account patients discontinuing due to lack of treatment effect, based on data from the Phase 3 studies. In clinical practice response to treatment may be measured differently and therefore patients may remain on treatment for longer.

However, to address this uncertainty, Albireo is engaging with clinical experts to define the response to treatment, as part of a proposed eligibility, start/stop criteria as discussed with NICE Managed Access Team on the 29th April 2021.

Section E — Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

The relevant costs and health outcomes associated to the decision problem are explored within the economic evaluation presented in Section D, with costs of treatment and management of PFIC endured by the NHS and PSS. However, the societal care costs associated with PFIC can be considerable.

The intractable pruritus and lack of sleep experienced by children with PFIC means that they may struggle at school.[7] Some parents are therefore unable to work or have to reduce working hours and lose income in order to care for their child.[7,100]

Because of the progressive liver damage and intractable pruritus, many patients with PFIC require biliary diversion surgery or liver transplantation at an early age.[10,12] Having surgery requires time off school for the patient as well as time off work for the caregiver. Recovering from a liver transplant can be a long process, and it can take three months or longer to return to school or work, and up to a year to fully recover.[21] Furthermore, complications such as rejection or infections may require further hospitalisation.

Although it is not possible to quantify at this stage in development, it is likely that there will be significant savings to patients and their families through reduction or elimination of

symptoms, avoidance of biliary diversion surgery and possible delay or avoidance of liver transplantation.

Children treated with odevixibat are expected to be less impacted by their symptoms, sleep better and therefore be more able to engage fully at school. With their children attending school more and experiencing fewer sleep disturbances, caregivers may also be able to work more.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It has not been possible to identify and quantify at this stage costs to other government bodies.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

The main cost for the families of children with PFIC is the loss of education and income as described above.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

The number of hours spent by family members providing care has not yet been estimated; however considering what is known about the symptoms and management of the condition, it is expected to be considerable. In addition to time spent throughout the day and night trying to soothe their child's itching, caregivers must also take their child to attend multiple hospital appointments which may involve travelling a distance to the specialised centre. In interim results from the PICTURE study, UK physicians [redacted] reported that on average in a year a child would have [redacted] visits to a paediatrician, [redacted] to a hepatologist, [redacted] visits to a gastroenterologist, [redacted] visits to a dietician, [redacted] emergency visits and [redacted] visits to a GP.[100]

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The clinical trial programme for odevixibat, comprising the randomised placebo-controlled study PEDFIC1 and its open label extension study PEDFIC2, represents the first such large programme designed for registration in PFIC and is pioneering in this field.

In designing the studies, Albireo has contributed a significant amount in terms of establishing outcome measures for clinical trials of PFIC, in particular the development and validation of patient-reported outcome measures.

In addition, to raise awareness with policymakers and healthcare professionals, and provide support for the patient/caregiver community, Albireo has invested in the PICTURE Study that is examining the substantial burden and unmet medical need of patients with PFIC and is overseen by PFIC medical experts, academics and patient advocates.

Albireo has also provided sponsorship for the last 4 years to the NAPPED registry which is the largest PFIC registry currently involving >50 sites around the world collecting data on the natural history of PFIC.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

In England there are three highly specialised centres that manage patients with PFIC, and these are study sites for the odevixibat clinical trials. To date 17 patients (including patients from Ireland) have been treated in the UK as part of the clinical trial programme.

King's College, London and Birmingham Women's and Children's Hospital are recognised internationally as two of the leading centres in expanding the scientific knowledge on PFIC natural history, genetics, types of PFIC, diagnosis and management. Indeed, some of the UK experts are highly respected and sought after by their peers and colleagues for their opinion and expertise in the management of PFIC.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

The PFIC Network Self Report Registry (https://www.pfic.org/pfic-patient-registry/) is an international registry that collects information about diagnosis, family history, quality of life, medications, surgeries, other diseases, and patient demographics.

Following request by the EMA, Albireo will, in [redacted] collect long-term safety and efficacy data for odevixibat in patients with PFIC. Data from patients with [redacted] will be collected. The data collected in the registry will be used for a [redacted] As currently designed, the registry collects most of the information required for the [redacted]

Albireo has developed the following outline for the disease registry to be established [redacted]

[redacted]

Title of Study [redacted]
Study Centres: [redacted]
Planned Study Period: [redacted]
[redacted]
Methodology: [redacted]
Number of Patients: [redacted]
Diagnosis and Main Criteria for Inclusion: [redacted]
Variables to be entered **Baseline:** [redacted] **Periodic Data Collection (odevixibat and concomitant medications):** [redacted] **Periodic Data Collection (Safety):** [redacted]

[redacted]

Periodic Data Collection (Efficacy):

[redacted]

[redacted]

are provided in Appendix 17.10. Detailed study protocols including a statistical analysis plan will be [redacted]

The statistical analysis plan will include [redacted] patients selected from those participating in the [redacted]

The efficacy study will continue until a minimum of [redacted] patients with each of the [redacted] have been treated with [redacted] Data from the safety section will be collated when [redacted] patients with [redacted] treated with [redacted] have been treated for a minimum of [redacted]

Albireo is engaging with the [redacted] identified during the NICE assessment.

The NAPPED study is ongoing with an estimated completion date in 2027 (https://clinicaltrials.gov/ct2/show/NCT03930810).

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

The ongoing PEDFIC2 study aims to generate long-term efficacy and safety data; Cohort 2 in the study is still recruiting patients and therefore the data will become available after the submission to NICE, likely in [redacted].

Albireo is also planning to perform the Odevixibat vs External Control [redacted] study aiming to compare clinical outcomes in odevixibat to comparable external controls.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The draft Summary of Product Characteristics for odevixibat states that treatment must be initiated and supervised by physicians, including paediatricians, experienced in the management of PFIC.[15] In England, odevixibat treatment will be initiated and monitored in three highly specialised centres:

- King's College Hospital, London
- Birmingham Women's and Children's Hospital
- Leeds Teaching Hospital

Other than monitoring for an adequate response, there are no additional monitoring requirements with odevixibat, and no special warnings or precautions for use.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No additional infrastructure requirements have been identified. Albireo is currently exploring options for provision of odevixibat via a homecare service.

Section F — Managed Access Arrangements

(please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

Whilst odevixibat has been assessed in a phase 3 randomised study, there remain gaps in the evidence base:

- Longer-term follow up of patients (expected from the open-label extension study)
- Comparison of long-term outcomes to those seen with SBD (expected from the [redacted]
- Limited data are available on patients with subtypes of PFIC other than PFIC1 and PFIC2
- No data are available on patients with the intermittent forms of PFIC1 and PFIC2, i.e., BRIC1 and BRIC2

The need for a [redacted] is being explored – meetings were held with the [redacted] Further meetings will be scheduled with the [redacted]

Albireo is also engaging with [redacted]

15.2 Describe the specifics of the MAA proposal, including:

- The duration of the arrangement, with a rationale
- What evidence will be collected to reduce uncertainty
- How this evidence will be collected and analysed
- The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA
- Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)

- Funding arrangement, including any commercial proposals or financial risk management plans
- The roles and responsibilities of clinical and patient groups during the MAA
- What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed

[redacted] Albireo is also engaging with [redacted]

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

[redacted]

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17 Appendices

All appendices are provided in a separate document.

17.1 Appendix 1: Search strategy for clinical evidence

17.2 Appendix 2: Search strategy for adverse events

17.3 Appendix 3: Search strategy for economic evidence

17.4 Appendix 4: Systematic literature review - resource identification, measurement and valuation

17.5 Appendix 5: Systematic literature review - Utility and quality of life appendix

17.6 Appendix 6: Comparator studies identified in the SLR

17.7 Appendix 7: Methodology for Study A4250-003 (Odevixibat Phase 2 study)

17.8 Appendix 8: HRQL and Mapping of PedsQL

17.9 Appendix 9: Data used for LTx mortality

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- a PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Patient Access Scheme submission template

May 2019

1 Introduction

In acknowledgment of the introduction of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (2019 VS) the transition arrangements as set out in paragraph 3.28 state that commercial flexibilities analogous to simple confidential and complex published Patient Access Schemes will continue to operate and be available for new products using existing processes and in accordance with existing criteria and terms as set out originally in the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and guidance on the National Institute for Health and Care Excellence (NICE) website. Once NHS England establishes the approach in the commercial framework as referred to in paragraph 3.26 of the 2019 VS, any new commercial flexibilities analogous to simple confidential and complex published PAS will operate in accordance with the commercial framework.

The PPRS (2014) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for Patient Access Schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for companies and sponsors

This document is the Patient Access Scheme submission template for highly specialised technologies. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a highly specialised technologies evaluation, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a Patient Access Scheme on the clinical and cost effectiveness of a technology, in the context of a highly specialised technologies evaluation, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Highly Specialised Technologies Interim Evidence Submission Template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the highly specialised technologies evaluation process, please see NICE's 'Interim methods and process statement for highly specialised technologies'. The 'Highly Specialised Technologies Interim Evidence Submission Template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the highly specialised technologies evaluation, including details of the proposed Patient Access Scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a Patient Access Scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the Patient Access Scheme incorporated.

If you are submitting the Patient Access Scheme at the end of the evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the highly specialised technology and the disease area to which the Patient Access Scheme applies.

Odevixibat (Bylvay®▼) 200 micrograms hard capsule, 400 micrograms hard capsule, 600 micrograms hard capsules, 1200 micrograms hard capsules. Odevixibat is anticipated to be indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

3.2 Please outline the rationale for developing the Patient Access Scheme.

This patient access scheme (PAS) is for the provision of odevixibat at a simple PAS discount. This scheme is being provided to improve the cost effectiveness of odevixibat with the expectation that it will allow for a positive recommendation from NICE.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price

The PAS is a simple percentage discount.

Current proposed UK list prices (ex-VAT) for the brand name and preparations of the product:
Bylvay 200mcg, pack 30 capsules: [redacted]
Bylvay 400mcg, pack 30 capsules: [redacted]
Bylvay 600mcg, pack 30 capsules: [redacted]
Bylvay 1200mcg, pack 30 capsules: [redacted]
Subject to Department of Health approval.

Proposed percentage discount prices (ex-VAT) for the brand name and preparations based on a percentage discount of [redacted] from the above proposed list prices are:
Bylvay 200mcg, pack 30 capsules: [redacted]
Bylvay 400mcg, pack 30 capsules: [redacted]
Bylvay 600mcg, pack 30 capsules: [redacted]
Bylvay 1200mcg, pack 30 capsules: [redacted]
Subject to NHS England approval.

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup? If so:

- **How is the subgroup defined?**
- **If certain criteria have been used to select patients, why have these have been chosen?**
- **How are the criteria measured and why have the measures been chosen?**

The scheme applies to the whole licensed population. The license indication for odevixibat is for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- **Why have the criteria been chosen?**
- **How are the criteria measured and why have the measures been chosen.**

Not applicable. The scheme is not dependent on any criteria, i.e., as long as a patient remains on treatment, the PAS will be applied. All patients will be eligible to enter the scheme in line with the marketing authorisation for odevixibat.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The simple PAS discount will be applied from the list price and applied to all original invoices for odevixibat.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

As the scheme is a simple discount, there are no administration requirements. NHS organisations will be provided with a single simple letter regarding the details at the start of the scheme for reference.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable. The simple PAS discount will be applied from the list price and applied to all original invoices for odevixibat.

3.10 Please provide details of the duration of the scheme.

As this is a simple discount scheme, it would be in place from the date of guidance publication until NICE next reviews the guidance on odevixibat and a final decision has been published on the NICE website.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the evaluation? If so, how have these been addressed?

No equity or equality issues have been identified.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

Not applicable. The patient access scheme is a simple discount.

3.13 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the highly specialised technologies evaluation (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Highly Specialised Technologies Interim Evidence Submission Template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The PAS applies to all eligible patients taking odevixibat.

3.14 If you are submitting the Patient Access Scheme at the end of the highly specialised technologies evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

Not applicable as this PAS submission is at the beginning of the NICE appraisal process [ID1570]. It should be noted though that the updated economic model base case submitted by the company adopts the ERG's clarification requests for this appraisal. Final resource use and societal perspective results from the PICTURE study have also been incorporated into the model (please see Addendum A and B).

3.15 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the HST Evaluation Committee considered most plausible.

Albireo AB has submitted two updated models, one at list price and one with PAS. The PAS price has been incorporated into the economic model by amending cell C44 on the "*key results*" page to [redacted] and amending the cell D30 and C30 on the "*control page*" to [redacted].

3.16 **Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme**.

No changes to the clinical effectiveness data are made between the 'List Price' and 'PAS Price' versions of the revised model. Please see Section 12.2 of the NICE HST submission.

The updated economic model base case submitted by the company on the 15th June 2021 adopts the ERG's clarification requests. These changes are described in full in the company supplementary Addendum A (June 2021), and the company's ERG clarification responses (June 2021), but briefly these include:

ERG clarification requests:

1. ERG question **A8 & B25:** Post-Liver Transplant (LTx) mortality meta-analysis updated to include an additional 6 studies and pooled analysis of long-term mortality updated
2. ERG question **B30**: Weight-based dosing updated using assumed standard deviation & age groups
3. ERG question **B8**: All costs and outcomes have been discounted at 3.5%
4. ERG question **B31**: Cholestryamine + rifampicin doses corrected

3.17 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs.

The PAS price will be shown on the Trust's original invoice for odevixibat from the nominated wholesaler to the purchasing organisation. There are no costs associated with operating the PAS.

3.18 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be

provided for the intervention both with and without the Patient Access Scheme. Please give the reference source of these costs.

The PAS price will be shown on the Trust's original invoice for odevixibat from the nominated wholesaler to the purchasing organisation. There are no additional treatment-related costs associated with operating this PAS.

Summary results

Base-case analysis

3.19 Please present in separate tables the economic results as follows.[1]

- **the results for the intervention without the Patient Access Scheme**
- **the results for the intervention with the Patient Access Scheme.**

Table 1: Base-case value for money results – List price

	Odevixibat	Standard of care
Intervention cost (£) per 30 pack, 200 mcg capsules* (SmPC)	[redacted]	
Other costs (£)		
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG (or other outcome)	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
QALYs (undiscounted)	[redacted]	[redacted]
QALY difference (undiscounted)	[redacted]	[redacted]
ICER (£)	[redacted]	

[1] For outcome-based schemes, please see section 5.7 in appendix A.

Table 2: Base-case value for money results – PAS price

	Odevixibat	Standard of care
Intervention cost (£) per 30 pack, 200 mcg capsules* (SmPC)	[redacted]	
Other costs (£)		
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG (or other outcome)	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
QALYs (undiscounted)	[redacted]	[redacted]
QALY difference (undiscounted)	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

3.20 Please present in separate tables the incremental results as follows. [2]

- **the results for the intervention without the Patient Access Scheme**
- **the results for the intervention with the Patient Access Scheme.**

Results are shown below in Error! Reference source not found. and Error! Reference source not found..

[2] For outcome-based schemes, please see section 5.8 in appendix A

Table 3: Base-case results – List price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.54	[redacted]				
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 4: Base-case results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.54	[redacted]				
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity analyses

3.21 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of

evidence for the highly specialised technologies evaluation. Consider using tornado diagrams.

One-way sensitivity analysis was conducted. The results shown below use the confidential PAS price.

4 Figure 1 shows the impact on the ICER from the one-way sensitivity analysis for odevixibat versus standard of care (SoC). Results are shown in

5

6

Table 5. Confidence intervals were used where available, and parameters were varied by +/- 15%.

Figure 1: One-way sensitivity analysis tornado diagram – top 10 results

Table 5: One-way sensitivity analysis results – top 10 results

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
PAS discount	[redacted]	[redacted]	[redacted]	[redacted]
Response to odevixibat - sBA & pruritus response – up-titrators	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
PEBD hazard, PFIC 2	[redacted]	[redacted]	[redacted]	[redacted]
Work impairment - loss of response	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - school score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
% LT, without PEBD, PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
sBA≥118 PedsQL - school score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant - transplant phase cost (Singh et al)	[redacted]	[redacted]	[redacted]	[redacted]
% LT, with PEBD, no response, PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]

6.1 Please present scenario analysis results as described for the main company/sponsor submission of evidence for the highly specialised technologies evaluation.

Table 6 presents further scenario analyses; all results use the confidential PAS price. Results show the impact of changing various assumptions on

discount rates, utility values, natural history sources and exploratory scenarios.

Table 6: Scenario analyses results

Parameter	Scenarios	ICER – PAS
Base case		[redacted]
Perspective	NHS	[redacted]
LTx mortality	NHS data	[redacted]
Quality of life	Vignette – EQ-5D	[redacted]
Quality of life	Vignette – TTO	[redacted]
Quality of life	PEDFIC1 characteristics from baseline (CFB) analysis	[redacted]
Quality of life	Vignette EQ-5D + stoma bag disutility multiplier	[redacted]
Quality of life	Vignetter TTO + stoma bag disutility multiplier	[redacted]
Source of stoma bag disutility	Colorectal cancer study	[redacted]
Time on treatment with odevixibat	Until surgery	[redacted]
PEBD in odevixibat arm	Include	[redacted]
Response assessment	Pruritus only	[redacted]
Annual loss of response to odevixibat	5%	[redacted]
Annual loss of response to PEBD	[redacted]	[redacted]
Annual loss of response to PEBD	10%	[redacted]
Proportion of PFC 1	50%	[redacted]
Adverse event costs	Include	[redacted]
Growth curve used for weight-based dosing	25th percentile	[redacted]

6.2 Please present any probabilistic sensitivity analysis results and include scatter plots and cost-effectiveness acceptability curves.

7 A thousand PSA simulations were plotted on the cost-effectiveness plane (Figure 2) and a CEAC was generated (

8

Figure 3). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted]

Figure 2: Cost effectiveness plane – PAS price

Figure 3: Cost-effectiveness acceptability curve – PAS price

9.1 **If any of the criteria on which the Patient Access Scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.**

Clinical variables (e.g., response measure/level of response) do not influence the type or level of PAS discount offered, i.e., all patients remaining on treatment with odevixibat will receive the PAS discount. It is noted, however that start/stop criteria at 6 months of treatment will inform treatment discontinuation/continuation. Therefore, the level of patient discontinuation/continuation will impact the total treatment costs incurred, which in turn effects the impact that the PAS price has on the budget impact.

Impact of Patient Access Scheme on ICERs

9.2 For financially based schemes, please present the results of the value for money analyses showing the impact of the Patient Access Scheme on the base-case and any scenario analyses. A suggested format is shown below (see table 4). If you are submitting the Patient Access Scheme at the end of the evaluation process, you must include the scenario with the

assumptions that the HST Evaluation Committee considered to be most plausible.

See Table 7 below.

Table 7: Scenario analysis

#		ICER (£/QALY) versus Soc	
		Without PAS	**PAS**
Base case		[redacted]	[redacted]
1	NHS perspective	[redacted]	[redacted]
2	Liver transplant mortality sourced from NHS	[redacted]	[redacted]
3	Vignette EQ-5D utility data	[redacted]	[redacted]
4	Vignette TTO utility data	[redacted]	[redacted]
5	PEDFIC1 CFB analysis	[redacted]	[redacted]
	Vignette EQ-5D + stoma bag disutility multiplier utility data	[redacted]	[redacted]
	Vignette TTO + stoma bag disutility multiplier utility data	[redacted]	[redacted]
6	Source of stoma bag disutility – colorectal cancer	[redacted]	[redacted]
7	Time on treatment with odevixibat, until surgery	[redacted]	[redacted]
8	Patients undergoing PEBD in odevixibat arm	[redacted]	[redacted]
9	Response assessment – pruritus only	[redacted]	[redacted]
10	Annual loss of response to odevixibat – 5%	[redacted]	[redacted]
11	Annual loss of response to PEBD – [redacted]	[redacted]	[redacted]
12	Annual loss of response to PEBD – 10%	[redacted]	[redacted]
13	Proportion of PFIC1 – 50%	[redacted]	[redacted]
14	Adverse event costs – included	[redacted]	[redacted]
15	Growth curve used for weight-based dosing – 25th percentile	[redacted]	[redacted]

10 Appendix A: Details for outcome-based schemes only

10.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- **the current price of the intervention**
- **the proposed higher price of the intervention, which will be supported by the collection of new evidence**
- **a suggested date for when NICE should consider the additional evidence.**

Not applicable. The PAS is a simple discount.

10.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- **the current price of the intervention (the price that will be supported by the collection of new evidence)**
- **the planned lower price of the intervention in the event that the additional evidence does not support the current price**
- **a suggested date for when NICE should consider the additional evidence.**

Not applicable.

10.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- **design of the new study**
- **patient population of the new study**
- **outcomes of the new study**
- **expected duration of data collection**

- **planned statistical analysis, definition of study groups and reporting (including uncertainty)**
- **expected results of the new study**
- **planned evidence synthesis/pooling of data (if applicable)**
- **expected results of the evidence synthesis/pooling of data (if applicable).**

Not applicable.

10.4 Please specify the period between the time points when the additional evidence will be considered.

Not applicable.

10.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Not applicable.

10.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

10.7 Please present the cost-effectiveness results as follows.

- **For a scheme that is expected to result in a price increase, please summarise in separate tables:**
  - **the results based on current evidence and current price**
  - **the anticipated results based on the expected new evidence and the proposed higher price.**
- **For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:**

- **the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)**
- **the results based on the current evidence and the lower price (if the new evidence is not forthcoming).**

A suggested format is shown in table 3, section 4.7.

Not applicable.

10.8 **Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.**

Not applicable.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies (HST)

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Clarification question response

15 June 2021

File name	Version	Contains confidential information	Date
		Yes	

List of tables and figures

Section A: Clarification on effectiveness data

Literature searching and systematic literature review

A1. CS Table 9, page 66, and CS Appendix 1, Table 97, page 9. Please clarify why surgery, liver transplant, ursodeoxycholic acid and rifampicin/rifampin are listed in the 'intervention' category of the inclusion criteria for the SLR of clinical evidence.

A1. Company Response

The literature review had a broad scope as we wanted to identify clinical studies that could be used to inform other aspects of reimbursement submissions or the economic modelling. In addition, we wanted to demonstrate the lack of evidence for off-label oral treatments. They should perhaps have been listed in the comparators row of the table instead of the intervention row as they were comparators when considering the literature review as a whole, however we wanted to make it clear to the reviewers that during the abstract and full text reviews we were looking for all suitable studies using these treatments; they did not have to have an odevixibat arm to be included.

A2. CS Appendix 1, section 17.1.7, page 10. "*Data was extracted by one reviewer and checked by a second*" - please clarify the procedure for dealing with any disagreements.

A2. Company Response

Changes by the second reviewer were made using the "Track Changes" Word function, which were then accepted by the first reviewer if agreed with or discussed if not. If there was still doubt, a third reviewer discussed the disagreement until consensus was reached.

A3. CS Section 9.3.2, page 73. The sub-heading says "*9.3.2 State the rationale behind excluding any of the published studies listed in Tables C3 and C4*" and the text says "*No studies were excluded*." Please clarify which tables this text relates to (as the tables are numbered differently to the subheading), as Figure 9 (page 67) lists 167 studies excluded at full text. Please also provide a list of, and PDFs, for the 167 studies excluded at full text in the SLR.

A3. Company Response

The text relates to CS Table 10 (List of relevant unpublished studies).

The 176 publications excluded at the full text review stage of the clinical review with reasons for exclusion are now listed in Appendix 1.

The PDFs of these publications have also been provided. Please note, four papers were available online, therefore not downloaded into the reference pack. The links for these publications are available in the excluded studies reference list table.

A4. Priority question. CS Table 15, page 92. Please clarify which critical appraisal checklist was used to assess the quality of the PEDIFIC1 and PEDIFIC2 studies.

A4. Company Response

Table 15 was taken from the HST template Table C7 Critical appraisal of randomised control trials. It is adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

Please note that throughout the clarification questions there are typographical errors in the spelling of the phase 3 study names (these should be PEDFIC1 and PEDFIC2).

A5. CS Section 9.5.1, page 92. Please clarify how the risk of bias assessment was performed, for instance by how many reviewers, and how disagreements were

resolved. Please clarify whether risk of bias assessment was performed using the same procedure for all studies.

A5. Company Response

The risk of bias assessments were performed by one reviewer, then checked by a second. Disagreements were discussed and resolved with a third reviewer when required. The risk of bias assessment was performed using the same procedure for all studies.

A6. CS Appendix 6, Table 111, page 21. Please clarify why items 6(b), 9, 10, 11 and 12 from the CASP checklist for cohort studies (see https://casp-uk.net/wp-content/uploads/2018/03/CASP-Cohort-Study-Checklist-Download.pdf) were omitted from Table 111.

A6. Company Response

Table 111 was taken from the HST template Table C8 Critical appraisal of observational studies. We feel the answers to the remaining questions have been answered in other parts of the submission where relevant.

A7. CS Appendix 7, Table 115, page 37. Please clarify which checklist was used to assess the quality of the odevixibat Phase 2 study. If this one was also adapted from the CASP checklist for cohort studies, please clarify why items 6(b), 9, 10, 11 and 12 were omitted from Table 115.

A7. Company Response

Table 115 was also taken from the HST template Table C8 Critical appraisal of observational studies. We feel the answers to the remaining questions have been answered in other parts of the submission where relevant.

A8. Priority question. CS Appendix 9. Please clarify which systematic literature review the studies used to assess LTx mortality are from, including whether or

not these are among the "*36 additional studies investigating outcomes in patients receiving LTx*" (CS Section 9.3.1.2, page 72) identified from the SLR of clinical evidence. If this is the case, please also clarify how the four studies and two NHS datasets in Tables 122 and 123 were selected.

A8. Company Response

An epidemiology and burden of disease SLR was performed in 2019 to identify relevant data on the epidemiology and natural history of PFIC and on the human and economic burden of PFIC (referenced in section 12.2.4.1 of the submission: *Few data were available on post-LTx complications, and the event rates presented in Table 56 were identified in a systematic literature review*.[1]) 18 studies were identified that reported prevalence or mortality data for PFIC, and the studies included in the meta-analysis were those among these that reported 1-year survival post-LTx.

The additional 36 studies identified in the clinical SLR have subsequently been reviewed and used to update the post-LTx mortality estimates. An additional 6 studies reporting 1-year survival were identified and included in the meta-analysis of 1-year survival rates. Two of these papers included Kaplan-Meier analysis of long-term survival and have been incorporated into the estimates of year 2+ survival. See response to question B25 for further details.

The NHS data sets were identified as a supplementary source of LTx mortality data, unrelated to PFIC. They were identified through non-systematic searches and are presented as an alternative source of mortality data that is directly applicable to a UK population.

Clinical effectiveness evidence and statistical analysis

A9. Priority question. CS Table 2, page 25. Please clarify the definition of [redacted] required for dose escalation of odevixibat, and how clinicians would judge this in practice.

A9. Company Response

Following the issue of positive CHMP opinion on May 20th and the final SmPC, Albireo has conducted a meeting with the [redacted] of the PEDFIC trials on [redacted] to obtain their feedback on the SmPC [redacted]).

Fourteen clinical experts attended the meeting, [redacted].

During this meeting the clinicians were asked to describe how they would decide to escalate or reduce the odevixibat dose; how they would determine meaningful changes in pruritus that would constitute a positive response in a real-world setting; how they would determine a clinically meaningful change in serum bile acid levels, and the specific criteria that would be important for the decision to withdraw odevixibat.

Whilst the clinicians have provided initial feedback (see Appendix 2), it is not possible to provide a clear definition of adequate response in the real-life setting at this stage. Odevixibat represents a paradigm shift in the treatment of PFIC, and whilst clinicians have had experience of odevixibat in the clinical trial setting, there is very limited experience of its use in clinical practice (i.e. [redacted], Albireo would like to further explore this with UK

clinicians to define specific criteria for dose escalation and withdrawal of treatment once the SmPC becomes publicly available.

A10. CS, Section 9.4.1, pages 73-82. Please explain how the patients included in the PEDIFIC1 trial, the PEDIFIC2 study and the Phase 2 study were identified and recruited.

A10. Company Response

PEDFIC 1 and PEDFIC 2 were conducted globally across 15 countries (including the UK) at 45 activated sites (three in UK). The Phase 2 study was conducted at 6 recruiting sites in 4 countries (study was also approved in UK but site did not screen any patients). The patients were identified by the site investigators participating in the studies. The patients were either identified from the investigator's patient pool or by colleagues at other institutions/hospitals who referred their patients to the study sites. Since PFIC is a rare disease no advertising in the media was used to find patients for any of the three studies. Competitive recruitment was applied and there was no cap on how many patients the sites could screen.

A11. CS, Section 9.4.1, pages 73-82. Please explain how many patients were excluded from participation in each of PEDIFIC1 and PEDIFIC2 due to having an SBA concentration of <100 µmol/L but who had a history of pruritis and a caregiver-reported observed scratching or patient-reported itching score of ≥2 at baseline.

A11. Company Response

Five patients were excluded from participation in PEDFIC1 due to having a serum bile acid level below 100 umol/L during screening but who had a history of pruritus and a caregiver reported observed scratching score of ≥2.

Three patients were excluded from participation in PEDFIC2 due to having a serum bile acid level below 100 umol/L during screening but who had a history of pruritus and a caregiver reported observed scratching score of ≥2.

A12. CS, Section 9.4.1.3, page 79. Please explain why patients in the PEDIFIC2 study started on odevixibat at the higher dose of 120 µg/kg/day, when the recommended dose according to the draft SmPC is 40 µg/kg/day, with potential for dose escalation to 120 µg/kg/day if an adequate clinical response has not been achieved after 3 months of continuous therapy. Please clarify the potential impact of this on the results from the PEDIFIC2 study.

A12. Company Response

The trial designs and protocols for PEDFIC1 and PEDFIC2, including the dose regimens, were developed concurrently, prior to the availability of any data from PEDFIC1. During the conduct of the studies, patients completing PEDFIC1 enrolled into PEDFIC2 in an ongoing, staggered manner. Because PEDFIC1 was an ongoing double-blind study, the patients, investigators, and the company remained blinded to the individual patient treatment assignments in PEDFIC1.

Pruritus data were available during the conduct of the studies but were not fully analysed until database lock for PEDFIC1. Because treatment assignment remained blinded at the time of a patient's transition from PEDFIC1 to PEDFIC2, there was no mechanism to know the treatment assignment for patients with an improved pruritus response during PEDFIC1.

In order to prevent potential unblinding of a patient's treatment assignment in PEDFIC1, serum bile acid results for all patients in both PEDFIC1 and PEDFIC2, after the first dose of study drug in PEDFIC1, were blinded. Therefore, there was no available mechanism to assess whether a patient met the serum bile acid responder definition or not at the time of transition from PEDFIC1 into PEDFIC2.

Throughout the duration of the clinical studies, a data safety and monitoring board met frequently to review the accumulating data. There was no indication that there was a safety signal from either odevixibat arm that would necessitate a change to the PEDFIC2 design.

The decision from the CHMP on the dosing of odevixibat in the SmPC was made based on the results of PEDFIC1 and PEDFIC2. In clinical practice, according to the SmPC, patients who have not had an adequate response to the 40 µg/kg/day dose will have their dose increased to 120 µg/kg/day. In the submission, a subgroup

analysis of the trial data was provided to reflect this clinical situation - see CS section 10.1.16, which is reproduced below:

In the clinical development programme, patients completing PEDFIC1 were allowed to enrol directly into PEDFIC2 in which all patients receive 120 µg/kg/day. This allows for an evaluation of the responses in patients as they transition from 40 µg/kg/day during PEDFIC1 to 120 µg/kg/day in PEDFIC2.

In essence, the 40 and 120 ug/kg/day dose are equivalent in terms of efficacy and have a comparable observed safety and tolerability profile. Therefore, application of 120 ug/kg/day in PEDFIC2 is anticipated to allow for the appropriate evaluation of long-term clinical benefits, clinical outcomes and assessment of safety and tolerability. In PEDFIC1, both doses of odevixibat (40 µg/kg/day and 120 µg/kg/day) resulted in reductions in serum bile acids levels and in pruritus severity that were statistically significantly greater than the reduction observed in patients treated with placebo and were [redacted] from each other for either endpoint. Thus, data from PEDFIC2 do not allow for a clear separation of the 2 dose regimens of odevixibat with respect to efficacy in the treatment of patients with PFIC.

Review of the efficacy data from the Pooled Phase 3 studies allows for an investigation of changes in serum bile acids levels in patients who transition from the 40 µg/kg/day to the 120 µg/kg/day dose. The improvements in serum bile acids levels and pruritus severity were maintained after the transition to the higher odevixibat dose. Review of individual patient data shows that for some patients who received 40 µg/kg/day in PEDFIC1, the response to treatment was enhanced following transition to the higher dose, in particular for pruritus. Thus, increasing the dose in patients receiving 40 µg/kg/day to the higher dose for inadequate response has been shown to be effective.

For reductions of both pruritus and sBA, there were patients who did not meet the responder definitions while receiving odevixibat 40 µg/kg/day but who did meet the responder definitions during the first 24 weeks of treatment with 120 µg/kg/day:[2]

- Data are available at Week 24 of PEDFIC2 for 8 patients who did not meet the pruritus responder definition during PEDFIC1; [redacted]

[redacted] met the pruritus responder definition, based on a decrease of > 1 point from the PEDFIC1 baseline

- Data are available at Week 24 of PEDFIC2 for 4 patients who did not meet the sBA responder definition during PEDFIC1; [redacted] met the sBA responder definition.

This is reflected in the economic model.

Importantly, the safety profiles of the 40 and 120 µg/kg/day regimens in Study PEDFIC1 were generally comparable. There were no deaths, drug-related SAEs, or liver decompensation TEAEs reported by patients in either dose group. One patient in the 120 µg/kg/day dose group discontinued treatment due to mild to moderate diarrhoea; the overall rate of diarrhoea was 39% among patients who received the 40 µg/kg/day dose compared with 21% for patients who received the 120 µg/kg/day dose. The incidence of other commonly reported TEAEs was similar between the 2 dose groups or was comparable to the placebo group. Thus, the data from Study A4250-005 do not allow for a clear separation of the 2 dose regimens of odevixibat with respect to safety in the treatment of patients with PFIC. The safety of long-term treatment with the higher 120 µg/kg/day dose was confirmed by review of the pooled safety data. Further, dose reductions to 40 µg/kg/day were uncommon (3 patients, 4%).

A13. Priority question. CS Section 9.4.4, page 87. Please clarify which of the subgroup analyses were pre-planned and which were post-hoc. Were the analyses intended to test any particular hypotheses and how well powered were they to do so? For completeness, please provide the p-values for all subgroup analyses undertaken.

A13. Company Response

The following efficacy and safety subgroup analyses were pre-planned per the statistical analysis plans for PEDFIC2 and for the Summary of Clinical Efficacy (ISE SAP for 2.7.3) and for the Summary of Clinical Safety (ISE SAP 2.7.4):

- Subgroup analyses on the primary efficacy endpoints were performed by age (≤5 years, ≥6 to ≤12 years, ≥13 years), PFIC type (PFIC1 vs PFIC2), region (US, Europe, RoW), sex (male vs female), race (White vs Non-White), ethnicity (Hispanic or Latino vs Not Hispanic or Latino), baseline serum bile acids (≥250 and <250 µmol/L), baseline pruritus severity score (≥3 and <3), BSEP type for PFIC 2, hepatic impairment status based on Child-Pugh (A, B, and C) and NCI ODWG (normal, mild, moderate, severe), baseline ALT (≤3 × ULN, >3 to ≤5 × ULN, >5 × ULN), baseline total bilirubin (≤3 × ULN, >3 to ≤5 × ULN, >5 × ULN), and use of UDCA and rifampicin alone or in combination.

- Statistical analysis was performed only when the sample size was ≥10 in each subgroup. If the sample size was <10 in any subgroup, only summary statistics were provided and the p-values were not reported. Forest plots were also produced.

TEAEs and treatment-emergent SAEs were summarised by SOC and preferred term for the following demographic and Baseline disease subgroups:

- Age (≤ 5 years, ≥ 6 to ≤ 12 years, ≥ 13 years)
- PFIC Type (1, 2, 3)
- Region (European Region, Rest of World (RoW), US)
- Sex (male versus female)
- Race (white versus non-white)
- Ethnicity (Hispanic or Latino versus not Hispanic or Latino)
- Hepatic function at baseline:
    - Hepatic impairment categories based on Child-Pugh classification (A, B, or C) and NCI-ODWG (mild, moderate, severe).
    - ALT ≤ 3 × upper limit of normal (ULN), > 3 and ≤ 5 × ULN, > 5 × ULN
    - Total bilirubin < 3 × ULN, > 3 to ≤ 5 × ULN, > 5 × ULN
- Time from diagnosis (≤ 3 years, > 3 to 6 years, > 6 years),
- BSEP type (PFIC 2 patients),
- Concurrent use of UDCA or rifampicin (alone or either)

- Baseline serum bile acid level (≥ 250 and < 250 µmol/L)

PEDFIC1: Subgroup Efficacy Analyses

Subgroup efficacy analyses on the primary endpoint and selected secondary endpoints (changes from baseline to each visit in serum bile acid, ALT, and growth) were pre-specified in the statistical analysis plan (SA) and performed by age group (6 months to 5 years, 6 to 12 years, and 13 to 18 years), by PFIC type (1 and 2), region (US, Europe and RoW), sex (male and female), race (White and non-White), ethnicity (Hispanic, non-Hispanic, and unknown), baseline serum bile acids level (≥250 and <250 µmol/L), Child-Pugh classification (A, B, C), BSEP type of PFIC2 patients, and the use of UDCA and rifampicin (alone or either). Subgroup analyses may have been conducted for hepatic impairment classification per NCI ODWG (NCI Organ Dysfunction Working Group), if appropriate.

Statistical analysis was performed only when the sample size was ≥10 in each treatment group. If the sample size was <10 in any treatment group, only summary statistics are provided; the p-value is not reported. Forest plots were also produced. Due to the anticipated small sample size in these subgroups, analyses by subgroups did not include the stratification factors.

All subgroup analyses were not intended to test any particular hypotheses and were not powered.

Note that the comparison of subgroups in PEDFIC1 was conducted primarily based on the overall odevixibat group as the sample sizes were small across subgroups for the individual dose groups.

PEDFIC2: Efficacy Analyses Based on Patient Subgroups

Subgroup analyses were pre-specified in the SAP and were performed for each of 5 age groups (< 6 months, 6 months to 5-years-old, 6 to 12-years-old, 13 to 18-years-old, and > 18 years), PFIC type, region (US or Europe and RoW), sex (male and female), race (White and non-White), ethnicity (Hispanic, non-Hispanic, and unknown), baseline serum bile acids level (≥ 250 and < 250 µmol/L), Child-Pugh classification (A, B, C), BSEP type of PFIC2 patients, and the use of UDCA and

rifampicin (alone or either). Subgroup analyses may have been conducted for hepatic impairment classification per NCI ODWG, if appropriate.

No hypotheses testing was performed for any subgroup analysis.

Forest plots showing the subgroup analyses for the primary endpoints are shown in Appendix 3.

A14. CS Figure 15, page 89. Please clarify that the "*Did not complete treatment period*" box for the odevixibat 120 µg/day should include two patients with lack of efficacy/intolerable symptoms in addition to the one with AEs already mentioned.

A14 . Company Response

Yes. This has been omitted in error, The box should include two patients with lack of efficacy/intolerable symptoms.

A15. CS Figure 15, page 89. Please clarify the definitions of the treatment period and follow-up period as labelled in this figure, how they differ from each other, and why patients who completed PEDIFIC1 (Study A4250-005) and rolled over into PEDIFIC2 (Study A4250-008) were not considered to have completed the follow-up period for PEDIFIC1 when follow-up data for these patients are available.

A15 . Company Response

PEDFIC1 included a 24-week treatment period, and a 4-week follow-up period. The follow-up period in this diagram relates to the 4-week follow-up period in PEDFIC1 in which no treatment was received. However, at Week 24, patients had the option to enrol into the open-label extension study PEDFIC2 in which all patients received active treatment (and therefore did not complete the follow-up of PEDFIC1).

Note that prior to Amendment 6 of the PEDFIC1 protocol, patients who completed at least 12 weeks of treatment who were subsequently withdrawn from this study due to patient/caregiver judgment of no improvement/intolerable symptoms could enrol in the open-label extension study (CSR section 9.1.1[3]). This provision was

removed by protocol amendment in order to protect the validity of the final study results by ensuring a sufficient number of patients completed the 24-week study. It was observed that some patients who rolled over early had not experienced documented worsening of symptoms. Patients continued to have the right to withdraw early from the study; however, completion of the study was required for entry into the extension study.

If a patient was continuing into PEDFIC2, Week 24 (Visit 9) (or the last completed visit in this study) was considered the first visit in PEDFIC2. All patients not continuing into PEDFIC2 returned to the study site for a follow-up visit (Week 28/Visit 10) conducted 28 days after end of treatment (EOT).

A16. Priority question. CS Figure 15, page 89. Please clarify the reasons for the four patients who completed the treatment period in PEDIFIC 1 not rolling over into PEDIFIC2. The PEDIFIC1 CSR (page 98) states that it was because [redacted] in the case of [redacted] please clarify the reason for the one remaining patient who completed the treatment period but did not roll over into PEDIFIC2, and state which arm in PEDIFIC1 this patient was in.

A16 . Company Response

Among the 4 patients who did not enter PEDFIC 2, 3 patients from the site in Saudi Arabia could not enrol as the study was not open in that country, and one patient was not deemed eligible per the investigator to roll over to PEDFIC2 due to lack of compliance with study drug.

A17. Priority question. CS Section 9.4.5.2, page 90. Please clarify how many weeks of treatment (odevixibat 120 µg/kg/day) patients in PEDIFIC2 had received since the PEDIFIC2 baseline (up to the data cut-off of 15th July 2020).

Please provide a mean and standard deviation or median and interquartile range, as well as a minimum and maximum duration.

A17. Company Response

Median overall duration of exposure to odevixibat 120 µg/kg/day in PEDFIC2 was 35.9 weeks and ranged from < 1 to 93.9 weeks at the time of the data cut off of 15 July 2020 (see section 11.1 in CSR A4250-008).

Median duration of exposure was approximately 45, 37, and 36 weeks in patients who had received 40 µg/kg/day, 120 µg/kg/day, and placebo in that study, respectively. In Cohort 2, which started enrolment approximately 1 year after the first patient in Cohort 1 was rolled over to PEDFIC2, median exposure was 19 weeks (Table 1).

Table 1. Study Medication Exposure (Full Analysis Set)

	ODEVIXIBAT 120 µg/kg, ONCE DAILY DOSING						
	COHORT 1[a]						
CATEGORY STATISTIC	40 µg/kg N=19	120 µg/kg N=15	ALL DOSES N=34	PLACEBO N=19	COHORT 2 N=16	COHORT 2 + PLACEBO[b] N=35	OVERALLCOHORT 1 + COHORT 2 N=69
Duration of exposure (week), n	19	15	34	19	16	35	69
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 31, CSR A4250-008

A18. CS Section 9.6.1.3 (Baseline demographics and characteristics), page 97. Please clarify how many of the patients with [redacted] had PEBD surgery, and the distribution of both biliary tract surgery overall and PEBD specifically across trial arms.

A18. Company Response

A total of [redacted] patients with prior medical history of biliary diversion surgery enrolled in PEDFIC1; [redacted] in the placebo group, [redacted] in the odevixibat 40 ug/kg/day group and [redacted] in the odevixibat 120 ug/kg/day group. All had received PEBD surgery.

A19. CS Section 9.6.1.3 (Baseline demographics and characteristics), page 97. Please clarify how many of the patients in each trial arm had prior IBAT treatment, the duration of that treatment and the reasons for discontinuing.

A19. Company Response

Three patients from the Phase 2 study A4250-003 were enrolled in the pivotal PEDFIC1 study as permitted by the protocol (one in each treatment cohort). The patient numbers in Study A4250-003 with corresponding patient numbers from PEDFIC1, time between treatments, and treatment received in PEDFIC1 are provided in Table 2. As shown, all 3 patients had a washout of ≥1.8 years between odevixibat treatment in Study A4250-003 and treatment in PEDFIC1. None of the patients were directly enrolled from Study A4250-003 to PEDFIC1. The treatment duration of A4250-003 was 4 weeks and none of the patients discontinued from the study A4250-003 study nor subsequently from the PEDFIC1 study.

Table 2. Listing of Patients who were Enrolled in Both Study A4250-003 and PEDFIC1

PT ID IN STUDY A4250-003	TREATMENT IN STUDY A4250-003	PT ID IN PEDFIC1	TREATMENT IN PEDFIC1	TIME BETWEEN END OF TREATMENT IN STUDY A4250-003 AND START OF TREATMENT IN PEDFIC1
[redacted]	30 µg/kg/day	[redacted]	40 µg/kg/day	2.4 years
[redacted]	60 µg/kg/day/ 30 µg/kg/day	[redacted]	120 µg/kg/day	1.8 years
[redacted]	100 µg/kg/day	[redacted]	Placebo	2.6 years

PT ID: patient identifier

[a] Patient was initially enrolled as Patient [redacted] and was re-enrolled, as allowed by the A4250-003 protocol, as Patient [redacted].

A20. CS Table 20, page 109. Please clarify whether these PEDIFIC2 baseline data for Cohort 1 are from the start of the PEDIFIC2 LTE (i.e. after patients had completed PEDIFIC1) or from the baseline time point of PEDIFIC1.

A20. Company Response

The PEDFIC2 baseline data for Cohort 1 are from the start of the PEDFIC 2 open label extension.[4] It is defined as the last value (or the average of the last 2 values for

serum bile acids) prior to the first dose in PEDFIC2. The pre-dose assessment of PEDFIC2 was allowed to be done in PEDFIC1.

A21. Priority question. CS Section 9.7.2.2, page 120. PEDIFIC1 CSR, Section 9.5.4.1, page 64. Treatment-related adverse events are defined as "*Based on medical judgment there was no reasonable possibility that the study drug caused the event*". What procedure was used to determine whether an adverse event was caused by the study drug?

A21. Company Response

Investigators were provided odevixibat core safety information in the Investigator Brochure and guidance on assessing causal relationship between adverse events and study drug in the PEDFIC1 and PEDFIC2 study protocols. Investigators were instructed to consider whether the adverse event followed a known pattern of response to study drug. In addition, investigators were instructed to apply the following criteria in determining whether there was a reasonable possibility that an adverse event was caused by the study drug:

- Temporal sequence: Investigators were instructed to determine whether the event followed a reasonable temporal sequence from administration of study drug to the onset of the adverse event.
- Patient's clinical state: Investigators were instructed to consider whether the adverse event could reasonably be attributed to the known characteristics of the patient's clinical state, environmental or toxic factors.
- Concomitant medications and other therapies: Investigators were instructed to consider whether the adverse event could reasonably be attributed to concomitant medications or other modes of therapy administered to the patient.
- Study drug dechallenge: Investigators were instructed to determine whether the event decreased or disappeared following study drug discontinuation or interruption.
- Study drug rechallenge: Investigators to instructed to determine whether the event worsened or reappeared following study drug re-administration after interruption.

A22. Priority question. CS Section 9.7.2.3, page 122. PEDIFIC2 CSR, Section 9.5.4.1, page 63. Treatment-related adverse events are defined as "*Based on*

***medical judgment there was no reasonable possibility that the study drug caused the event*". What procedure was used to determine whether an adverse event was caused by the study drug?**

A22. Company Response

As per question A22.

A23. Priority question. CS Section 9.8.2.1, page 126. Please clarify why a matching-adjusted indirect comparison using study data from patients treated with odevixibat and controls from the NAPPED study was not undertaken to compare odevixibat with PEBD.

A23. Company Response

[redacted] from the final PEDFIC2 data will be compared to NAPPED study data in the [redacted] (described in the submission sections 4.1.1.2 and 9.8.2.1). [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

A24. CS Figure 32, page 133. Please clarify if the axis represents different quantities for the two plotted functions: age for patients without SBD and years post SBD for SBD patients. Plotting these two curves together suggests a comparison but please clarify in what sense a comparison is meaningful.

A24. Company Response

The figure is adapted from the PFIC2 NAPPED publication (Van Wessel et al. 2020[5]). The publication states that the clock-reset approach allows visualisation of native liver survival up to SBD (black line, all patients) and after SBD (orange line, only patients that underwent SBD). The estimated HR is achieved by Cox regression with SBD as a time-dependent risk-factor, adjusted for genotype, sex and birth year. Time-dependent Cox regression analysis showed that SBD was associated with significantly higher NLS (HR 0.50; 95% CI 0.27–0.94; p = 0.03) in BSEP1 and BSEP2.

A25. CS Figure 34, page 136. Please clarify what the time origin represents and the nature of the x-axis for each of the two plotted functions.

A25. Company Response

The figure is adapted from the PFIC1 NAPPED publication Van Wessel et al. 2021[6]

As for the PFIC2 analysis described in the response to A24, the publication states that the clock-reset approach allows visualisation of native liver survival up to SBD (solid line, all patients) and after SBD (dotted line, only patients that underwent SBD). The estimated hazard ratio is achieved by Cox-regression with SBD as a time-dependent risk-factor, adjusted for genotype, sex and birth year. dependent Cox regression analysis (corrected for sex, genotype, and birth year) showed that SBD tended to be associated with NLS (overall HR, 0.55; 95% CI, 0.28-1.03; P = 0.06).

Section B: Clarification on cost-effectiveness data

B1. Priority question Please provide an updated base case (deterministic and probabilistic) that incorporates all changes that are made following the clarification process. Provide supplementary analyses as you see fit.

B1. Company response

Please see Addendum A for updated base-case and results.

Comparator

B2. Priority question CS Section 12.1.2, page 169. It is stated that PEBD is the comparator. However, the model seems to suggest that all patients start in the standard care but not all of them go on to receive PEBD. Please clarify the comparator used in the cost-effectiveness analysis.

B2. Company response

The comparator in the cost-effectiveness analysis is current standard of care, which includes PEBD, although not all patients will go on to receive it. There are variations in care, partially due to disease sub-type with PEBD being more common in PFIC1 where liver transplant is less effective.

A direct comparison to PEBD (i.e. a comparison where all patients undergo a PEBD at baseline) is not presented because discussion with clinicians indicated that they are likely to use odevixibat at an earlier point in the treatment pathway and not all patients who receive odevixibat would otherwise go on to receive PEBD. NAPPED data indicates that patients typically present before they reach one year of age, but the median age at surgical diversion was 2.3 years in PFIC2 and 5.9 years in PFIC1.[5,6] This is reflected in the treatment pathway presented and has been validated by clinicians.

Model Structure and assumptions

B3. Priority question Please clarify why a starting age of 4.25 years was used in the model.

B3. Company Response

The reported baseline characteristics of the whole cohort of participants in PEDFIC1 was 4.25 years and 50% were females. The starting age of 4.25 years reflects the participants in the PEDFIC1 clinical trial and is therefore used in the model.

B4. Please clarify why a separate health state was not used for patients who have a re-transplant. In the model, the “Transitions” sheet has a health state re-transplant (column AA) but this does not seem to be used in the “Engine” sheets where the calculations are performed.

B4. Company Response

For ease of interpretation and model simplicity, re-transplants were modelled in the same health state as the LTx health state. Data from the literature indicated that re-transplantations were most common within one year of the initial surgery.[7] Patients entering the post-LTx state in each 12-month cycle (column Y in the ‘Transitions’ sheet) are therefore those patients who have survived LTx and are not indicated for re-transplant (using the estimates from Bull et al). Column AA of the ‘Transitions’ sheet has been removed to reflect this assumption.

B5. CS, Section 10.1.12, page 160. The CS states that patients with PFIC can progress to hepatocellular carcinoma. This was confirmed by the ERG’s clinicians. Please clarify why the model structure was not adapted to account for this.

B5. Company Response

There is a high incidence of hepatocellular carcinoma (HCC) observed in patients with PFIC2, occurring in 6.2% (15/241) of patients followed-up in Van Wessel 2020. However, there is little data available on the rate at which patients progress to HCC or way that it interacts with sBA. HCC is generally related to end-stage liver disease and clinical input indicated that generally clinicians are not waiting for patients to reach end-stage liver disease before transplant. This was confirmed by a UK clinician who stated that he had never performed a liver transplant for HCC. Observations of HCC we limited to early signs found incidentally during a liver transplant. As such, HCC was excluded from the model as a simplifying assumption.

The outcome of HCC will ultimately be liver transplant or death and it is expected that this is implicitly captured within the transition probabilities, though it is not captured in costs or utilities. It is anticipated that reducing sBA will reduce the incidence of HCC, and thus this is expected to be a conservative assumption.

B6. CS Figure 39, page 170. Please describe the figure in more detail, and clarify the meaning of the coloured shading in the figure.

B6. Company Response

Figure 39 highlights the differences in the treatment pathway of PFIC1 and PFIC2, which is described in further detail in Section 8.2.2 of the CS. The original pink shading drew attention to key differences between each pathway.

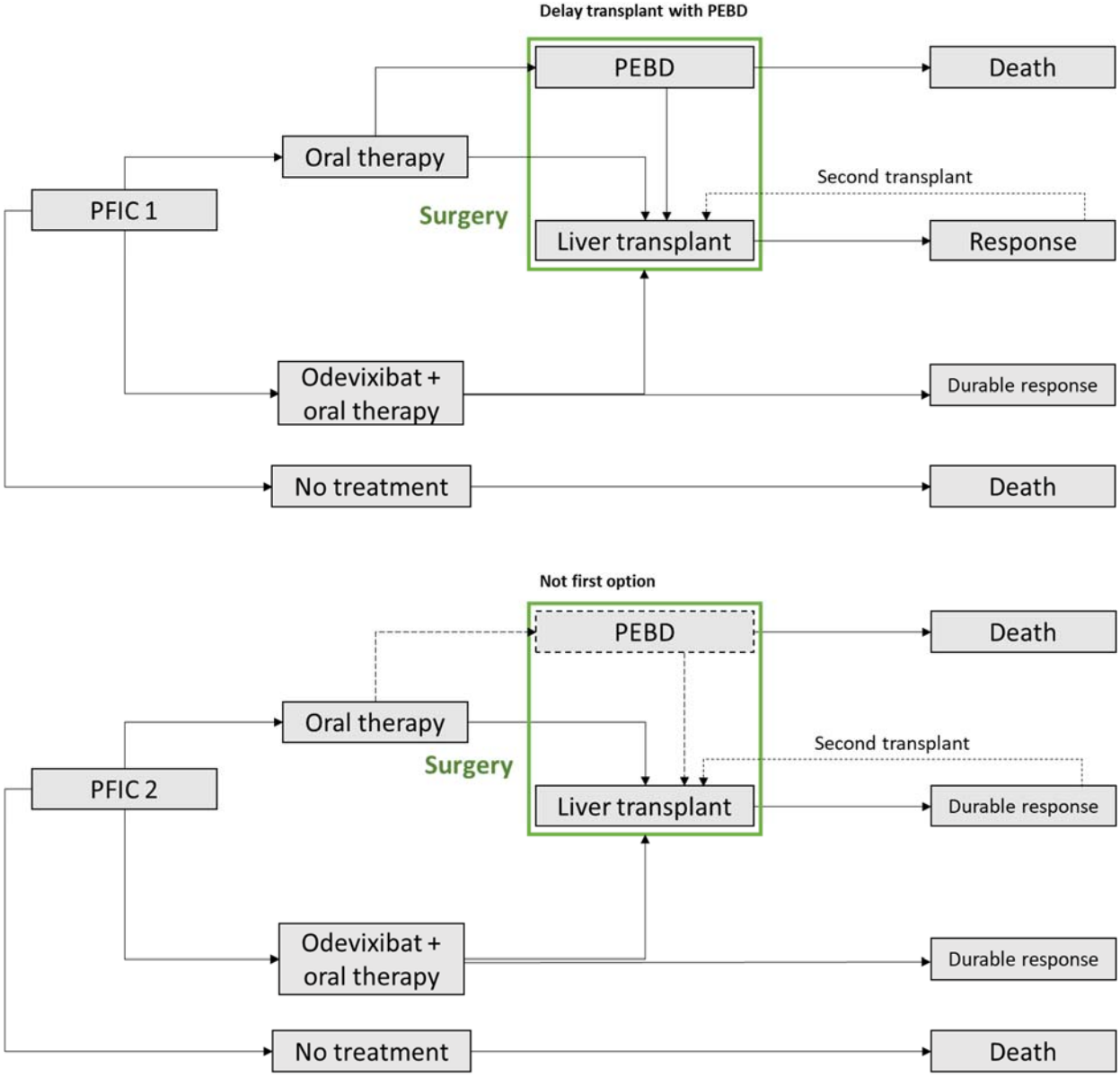
All individuals with PFIC1 or PFIC2 are treated with oral therapy (standard of care), odevixibat in combination with oral therapy or receive no treatment.

As confirmed by a clinical expert, PFIC1 patients are more likely to receive PEBD prior to LTx, as LTx can lead to a number of complications and doesn't result in a durable response (extrahepatic symptoms remain present after LTx). PFIC1 patients generally progress to LTx following PEBD. Re-transplant is more common in PFIC1 than PFIC2. PFIC2 patients are less likely to receive PEBD as a first surgery following oral treatment, as the prognosis with LTx is better and more likely to result in a durable response.

In both populations, LTx is possible after treatment with odevixibat (e.g. non-responders). The absence of treatment results in death. It should be noted that the original figure only included the possibility of re-transplant in PFIC1, but re-transplant (or second LTx) is modelled in both PFIC1 and PFIC2.

A corrected Figure 39 of the CS is presented in Figure 1, without shading and the addition of re-transplant in both PFIC1 and PFIC2, to reflect the treatment pathway in the economic model.

Figure 1: Treatment pathway of PFIC1 and PFIC2



B7. Priority question CS, Section 12.1.5, Table 37 page 173. Please provide more justification for the third key assumption listed. Please provide rationale for assuming sBA response is associated with a corresponding pruritus response when only 79% of patients with a sBA response at six months also have a pruritus response. Also, it is stated that "*patients without a pruritus response at week 24 are assumed to achieve a pruritus response by month 12*". Please clarify the rationale for this assumption.

B7. Company Response

Discussion with the Albireo clinical team indicated that some patients may have a delayed pruritus response, but that everyone whose sBA becomes controlled will eventually have a pruritus response. This was confirmed in a later data review which shows that all patients with an sBA response had a pruritus response. Of the 14 sBA responders in PEDFIC1, [redacted] were also pruritus responders at week 24 in PEDFIC1. The [redacted] pruritus non-responders at week 24 in PEDIFC1 became pruritus responders at Week 25-36 in PEDFIC2 and [redacted] response during PEDFIC2 (note: pruritus response was based on 1 point drop at their last monthly assessment in a particular interval based on available date). These [redacted] patients had received the 40 µg/mg/kg dose in PEDFIC1 and became responders when they transitioned to the 120 µg/mg/kg dose. The analysis presented below shows individual patient pruritus scores for pruritus responders over up to 48 weeks of treatment with odevixibat. From this analysis it can be noted that there are patients who become pruritus responders after the 24 weeks.

Figure 2: Individual patient pruritus scores - Pruritus responders over up to 48 weeks of odevixibat

The assumption that patients with an sBA response will also experience a pruritus response primarily impacts the rate of LTx as patients without a pruritus response will go on to require a LTx, with approximately 50% of LTx in PFIC indicated for intractable pruritus. Therefore, the NAPPED data also suggest that patients with an sBA response will have manageable pruritus, as they do not require a LTx.

B8. Priority question CS, Section 12.1.7, Table 38 page 175. The rationale for using a 1.5% discount rate is not clear. Please provide further justification for this choice of discount rate. For more information about discounting in HST, please refer to section 47 of the HST interim process and methods guide.

B8. Company Response

The HST interim guidance states:

"In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered…"

"A discount rate of 1.5% for costs and benefits may be considered by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved."

Response to odevixibat is expected to be durable, with approximately 1/3 of responders remaining on therapy for at least 30 years and an average treatment duration among responders of 25 years in the model. Those patients who respond see a large increase in QoL, with mapped data in PEDFIC1 showing the utility scores for responders increasing from an average of 0.559 to 0.783, an increase of 0.224.

Therefore, it is the company's opinion that a significant long-term benefit is likely for a proportion of patients and that this is a relevant analysis for the committee to consider. However, it is acknowledged that the full set of criteria are not met and in the updated base-case results a discount rate of 3.5% has been applied, with 1.5% discount rates applied in a scenario analysis.

Clinical parameters and variables

B9. Priority question CS Section 12.2.1.1, page 177. Please clarify why discontinuation rate was used as a proxy to define loss of response in the model. The clinical section suggests that the response rates in PEDIFIC2 are [redacted] which seems to indicate [redacted]

[redacted] **Please provide the loss of response estimated from PEDIFIC2 data.**

B9. Company Response

It is unclear which data from PEDFIC2 is being referred to that indicates patients lose response over time, however we would like to clarify that patients who responded in PEDFIC1 maintained their response in PEDFIC2.

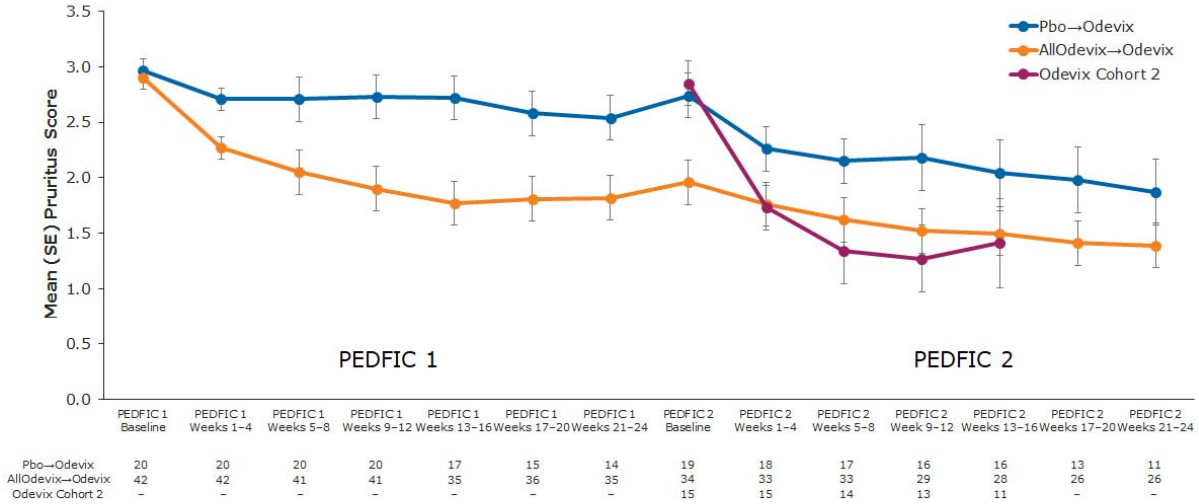
The ERG may be referring to data on the proportion of positive pruritus assessments which may at first appear lower in PEDFIC2 compared to PEDFIC1. However, when patients rolled into PEDFIC2, the PEDFIC1 final pruritus assessment (at 24 weeks or last available) became the new baseline for assessment of response. Therefore, any benefit seen during PEDFIC2 should be considered as an added improvement compared to PEDFIC1, as shown in

Figure **3** below (Figure 26 of the company submission). A positive pruritus assessment was defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the ObsRO instrument; if patients had already achieved at least a 1-point drop during PEDFIC1 then another 1-point drop or a a scratching score of ≤1 would be considered a response.

Among the patients who were pruritus responders on 40 µg/kg/day in PEDFIC1 and went on to receive 120 µg/kg/day in PEDIFC2, all [redacted] with monthly pruritus data available at Week 12 remained responders as did all [redacted] with data available at Week 24. Thus, [redacted] who met the pruritus responder definition on 40 µg/kg/day demonstrated reduced efficacy after transitioning to 120 µg/kg/day. This is illustrated further in Figure 4, that shows that patients who were pruritus responders in PEDFIC1 (pruritus score reduction >1 point) [redacted] in PEDFIC2 (post-hoc analysis).

Therefore, discontinuation of therapy in PEDFIC2 was considered as a best proxy of loss of response over time. In fact, only [redacted] patient who received odevixibat in PEDFIC1 discontinued in PEDFIC2 (due to [redacted] and there were [redacted] who discontinued due to lack of response.

Figure 3. Mean (±SE) of the proportion of positive pruritus assessments by grouped weeks



Source: Thompson et al, 2020[19]

Figure 4. Post Hoc Analysis: Continued Pruritus Response For Patients Receiving Prior Odevixibat, PEDFIC 1 Baseline Through PEDFIC 2 Week 24

[redacted]

B10. Priority question CS Table 39, page 177. Please provide these response rates by dose separately for patients with PFIC1 and PFIC2. Figure 19, which presents the SBA response at 24 weeks in patients according to PFIC type, seems to suggest that the [redacted] **Please provide two tables in the same format as Table 39, one with**

response rates separately for patients with PFIC1 and other with response rates separately for patients with PFIC2.

B10. Company Response

Results for patients with PFIC1 and PFIC2 are shown in Table 3. The results of subgroup analyses based on demographic and baseline disease characteristics indicated no clinically meaningful differences in odevixibat treatment effect for reduction in serum bile acids or improvement in pruritus severity across patient subgroups (see Appendix 3). Note that the results for comparison of subgroups was conducted primarily based on the overall odevixibat group as the sample sizes were small across subgroups for the individual dose groups.

Patients with both PFIC1 and PFIC2 obtained substantial benefit from treatment with odevixibat. The proportions of positive pruritus assessments over the 24-week period were [redacted] and [redacted] for PFIC1 and PFIC2 patients, respectively, on odevixibat. Although the proportion of serum bile acids responders was lower among odevixibat-treated patients with PFIC1 ([redacted]%) compared to patients with PFIC2 ([redacted]%), review of mean changes from baseline in serum bile acid levels for patients with PFIC1 who received odevixibat did show reductions in serum bile acids to Week 22/24 with a decrease of [redacted] compared with a mean increase of [redacted] in the PFIC1 patients who received placebo.[3]

Table 3: Range of response rates collected in PEDFIC1

Response endpoint	Population	Placebo	40 µg/kg dose	120 µg/kg dose	Combined doses	Response rate with 120 µg/kg in those not responding to 40 µg/kg % (n/N1)
sBA response†	Overall	0	43.50%	21.10%	33.30%	[redacted]
	PFIC1	0	NA	NA	[redacted]	[redacted]
	PFIC2	0	NA	NA	[redacted]	[redacted]
Pruritus response at least 50% of the time¥	Overall	[redacted]	[redacted]	[redacted]	[redacted]	NA*
	PFIC1	[redacted]	[redacted]	[redacted]	[redacted]	NA
	PFIC2	[redacted]	[redacted]	[redacted]	[redacted]	NA
Pruritus response‡	Overall	28.74%	[redacted]	[redacted]	53.51%	[redacted]
	PFIC1	[redacted]	NA	NA	[redacted]	[redacted]
	PFIC2	[redacted]	NA	NA	[redacted]	[redacted]

†Defined as the proportion of patients with at least a 70% reduction in sBA concentration from baseline or reaching a level ≤70µmol/L in PEDFIC 1; ‡Defined as the proportion of positive pruritus assessments for morning and evening scores at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument; ¥ Defined as the proportion of patients achieving a positive pruritus assessment for >50% of the 24-week treatment period.
*As this analysis was not available, in the economic model the values for the pruritus response defined as the proportion of positive pruritus assessments for morning and evening scores at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument
N1 is the number of patients who reached the timepoint and had the assessment.
Abbreviations: sBA, serum bile acid, NA, not avaliable

B11. Priority question CS Table 39, page 177. In the CS, an SBA response was defined as ≤70 µmol/L at week 24 or a reduction from baseline to week 24 of ≥70%. However, for PFIC1, the NAPPED study data provided in CS page 136 suggest that, only a post-SBD sBA level <65 µmol/L tended to be associated with prolonged NLS after SBD (Figure 35) and a decrease of at least 76% (based on ROC curve) in sBAs was not associated with improved NLS after SBD. As such, please provide odevixibat SBA response rates for PFIC1 using a definition of ≤70 µmol/L at week 24 (that is, excluding those with a reduction from baseline to week 24 of ≥70%).

B11. Company Response

Table 4 shows the number (%) of patients reaching a level ≤70 umol/l in fasting sBA in PEDFIC1. However, it should be noted that this analysis is only up to 24 weeks and reaching this more stringent threshold may take longer in some patients. In addition, PFIC1 patients also demonstrated significant pruritus improvement (as described in B10) which is important for preserving native liver and avoiding LTx due to intractable pruritus.

Table 4. Number (%) of Patients Reaching a Level ≤70 umol/L in Fasting sBA after 24 Weeks of Treatment – PFIC1 Patients

	Placebo N=5	Odevixibat 40 ug/kg/day N=7	Odevixibat 120 ug/kg/day N=5	Odevixibat All Doses N=12
n (%) of responders	[redacted]	[redacted]	[redacted]	[redacted]

B12. Priority question CS Section 12.2.1.2, page 177. In the scenario analysis using pruritus response, a) please clarify why the response to standard of care is assumed to be 0% when there seems to be a [redacted] according to Table 19, page 103. It is [redacted] see Figure 20, page 101. Additionally, b) please clarify why [redacted] instead of the pruritus outcome measured in the study (that is the proportion of positive pruritus assessments (i.e., a scratching score of ≤1 or at least a 1-point drop from baseline)).

B12 a) Company Response

Pruritus response to SoC oral therapies can occur; however, clinical opinion provided to the company stated that it is expected to be transient. Pruritus response with odevixibat is expected to alter the natural history of PFIC by treating the underlying cause of the disease, as opposed to symptomatic treatment with off-label therapies such as UDCA and rifampicin. Table 5, Table 6 and Table 7 below present

results for the scenario analysis with pruritus response in the SoC arm set to [redacted], with [redacted], [redacted] and [redacted] loss of response per year.

Table 5: Results assuming [redacted] pruritus response in SoC arm with [redacted] loss of response per year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.74	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	2.17	[redacted]	[redacted]

Table 6: Results assuming [redacted] pruritus response in SoC arm with [redacted] loss of response per year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.67	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	2.24	[redacted]	[redacted]

Table 7: Results assuming [redacted] pruritus response in SoC arm with [redacted] loss of response per year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.63	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.91	[redacted]	[redacted]	2.28	[redacted]	[redacted]

B12 b) Company Response

The proportion of positive pruritus assessments at the patient level over the [redacted] treatment period was not considered to be as relevant for the economic modelling as it takes into account all assessments recorded over the study. Pruritus score was measured in both the morning and evening every day, and there were therefore 336 assessments planned over the 24-week treatment period (168 days × 2 assessments/day) for each patient. This endpoint does not therefore account for response rates in individual patients, and is not suitable to inform transitions in the model.

In contrast, the percent of patients achieving positive pruritus assessment for more than [redacted], provides the proportion of patients that could be considered to respond to treatment (and is relevant to clinical practice).

B13. CS, Section 12.2.1.3, page 178. Please clarify the precise source of the assumption that [redacted] of responders to PEBD will lose response per year. Was this value suggested by the company's clinical advisors or by the company? If it was the latter scenario, did the clinical advisors agree with this assumption?

B13. Company Response

This value has been proposed by the company, based on clinical input received which indicated that while PEBD is generally durable among responders, however response can be lost over time. Clinical input suggested that the rate of loss of response to PEBD was likely to be similar to that for odevixibat. The value of 5% was selected as this reflects a similar loss of response as is modelled for odevixibat, but allowing for a slightly higher rate due to on-going complications associated with PEBD[8] that may lead to loss of response or liver transplant. The company submission presents a scenario using identical discontinuation rates for PEBD and odevixibat. A scenario is presented in Table 8 where discontinuation with PEBD is set identical to the rate observed in PEDFIC 1 for odevixibat [redacted]

Table 8: Scenario with alternative discontinuation rate in PEBD

	Base case (5% loss of response)	**[redacted] loss of response (identical to odevixibat)**
Incremental LYs	1.86	1.74
Incremental QALYs	[redacted]	[redacted]
Incremental costs	[redacted]	[redacted]
ICER	[redacted]	[redacted]

B14. CS Section 12.2.1.4, page 178. It is stated that survival distributions other than the exponential were considered. Please clarify if this means that other survival distributions were fitted to the data and if so, which distributions were used and the resulting AIC and BIC statistics. Please justify further the assumption that hazards rates are constant over the period of the economic model and whether this aligns with clinical advice.

B14. Company Response

Other standard distributions were considered, and AIC and BIC statistics are presented in Table 9. Constant hazards were selected for simplicity and ease of interpretation. The model has 7 states and patients may experience up to 5 transitions that could be made time-dependent. The inclusion of time-dependent hazards would require the use on tunnel states for each health state with after the odevixibat response states was judged to add additional complexity and uncertainty without sufficient benefit to justify their inclusion.

Where event rates are clearly time-dependent in the rate of SBD in PFIC1, time-dependent hazards based on age have been included through the use of a piece-wise linear model. However, the inclusion of piece-wise linear models is much simpler than including other time-dependent models and is simpler in the case of transitions to PEBD as patients in the odevixibat arm may not undergo PEBD in the model.

Table 9: AIC and BIC statistics for alternative distributions for each model transition

Model transition		Exponential	Weibull	Gompertz	Generalised gamma	Log-normal	Log-logistic	Piecewise exponential
PFIC1 - NLS without SBD	AIC	132.72	133.46	126.47	120.36	127.15	129.47	N/A
	BIC	134.52	137.08	130.08	125.78	130.77	133.09	N/A
PFIC2 - NLS without SBD	AIC	551.05	550.80	546.88	539.06	538.20	543.22	N/A
	BIC	554.21	557.10	553.19	548.52	544.50	549.53	N/A
PFIC1 - NLS in SDB non-responders	AIC	20.60	21.84	22.55	21.93	20.74	21.08	N/A
	BIC	21.00	22.64	23.35	23.13	21.53	21.87	N/A
PFIC2 - NLS in SDB non-responders	AIC	551.05	550.80	546.88	-	538.20	543.22	N/A
	BIC	554.21	557.10	553.19	-	544.50	549.53	N/A
PFIC1 – rates of surgical diversion	AIC	350.78	342.66	332.85	305.81	325.74	332.58	326.93
	BIC	353.65	348.40	338.58	314.41	331.47	338.32	333.33
PFIC1 – rates of surgical diversion	AIC	526.43	525.45	515.89	501.11	510.60	518.68	N/A
	BIC	530.01	532.60	523.04	511.84	517.75	525.83	N/A
Post-LTx survival	AIC	85.80	78.07	79.17	80.06	78.35	78.18	N/A
	BIC	88.03	82.54	83.64	86.76	82.82	82.65	N/A

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; LTx, liver transplant; SBD, surgical biliary diversion.

B15. CS Section 12.2.1.4, page 178. Please explain more fully the following sentences, in order to explain why time-varying hazards could not be used: "*In addition, in some cases the timescale used is age, for example in the data on native liver survival with and without surgical diversion. As a proportion of patients treated with odevixibat will not be at risk of LTx until they discontinue treatment, using age-dependent transition probabilities may not accurately reflect a patient's risk.*"

B15. Company Response

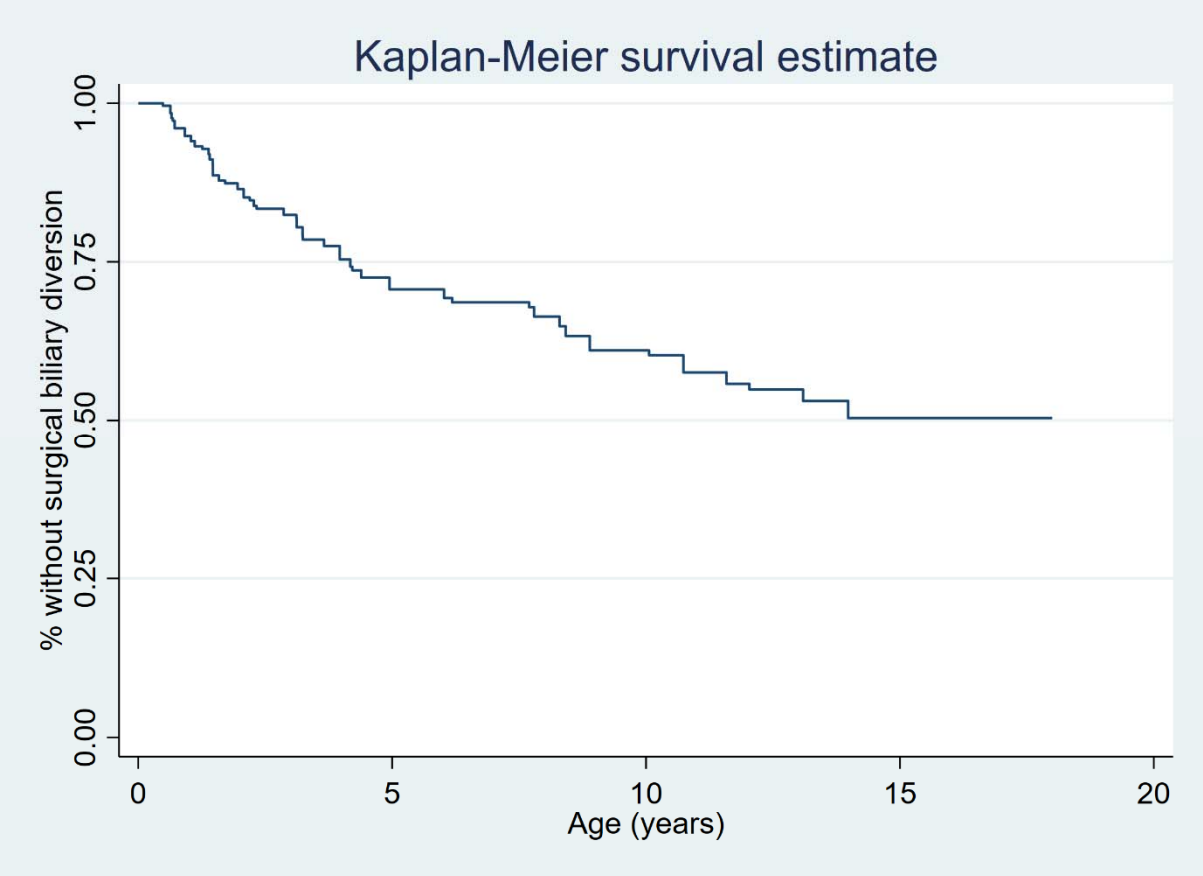
Where age is used as the time scale any non-constant survival model will produce age-dependent hazards. However, for transitions to LTx patients responding to odevixibat may become at risk at an older age, where hazards are larger or smaller depending on the time trend. This may not reflect actual disease progression after discontinuing as disease will progress differently while patients are on treatment. For example, a patient who loses response to odevixibat at age 10 and enters the non-response state may not have the same risk as a patient who did not receive or respond to odevixibat, who remains in the non-response state at age 10.

B16. Priority question CS Section 12.2.1.5, page 179. With reference to Figure 41, please present a plot of the combined data survival function that was used to inform the model.

B16. Company Response

The combined survival plot is presented in Figure 5.

Figure 5: Combined graph of SBD rates by age in PFIC2



B17. CS Section 12.2.1.5, page 180. Please clarify why the coefficients are presented on different scales between the two tables (Table 41 and 42) and whether it is correct that the PFIC1 hazard for age >3 is identical to that for PFIC2 at all ages, given that the two exponential models appear to have been fitted to different datasets.

B17. Company Response

The values presented are correct and similarity between the values is coincidental. Values are not the same when viewed with more decimal places (see Table 10).

Table 10: Table 43 in the CS, probability of PEBD based on NAPPED curve in PFIC1 and PFIC2

Age	PFIC1	PFIC2	Joint*
Up to age 3	18.1815%	4.7490%	8.4295%
3 and older	4.7498%	4.7490%	4.7492%

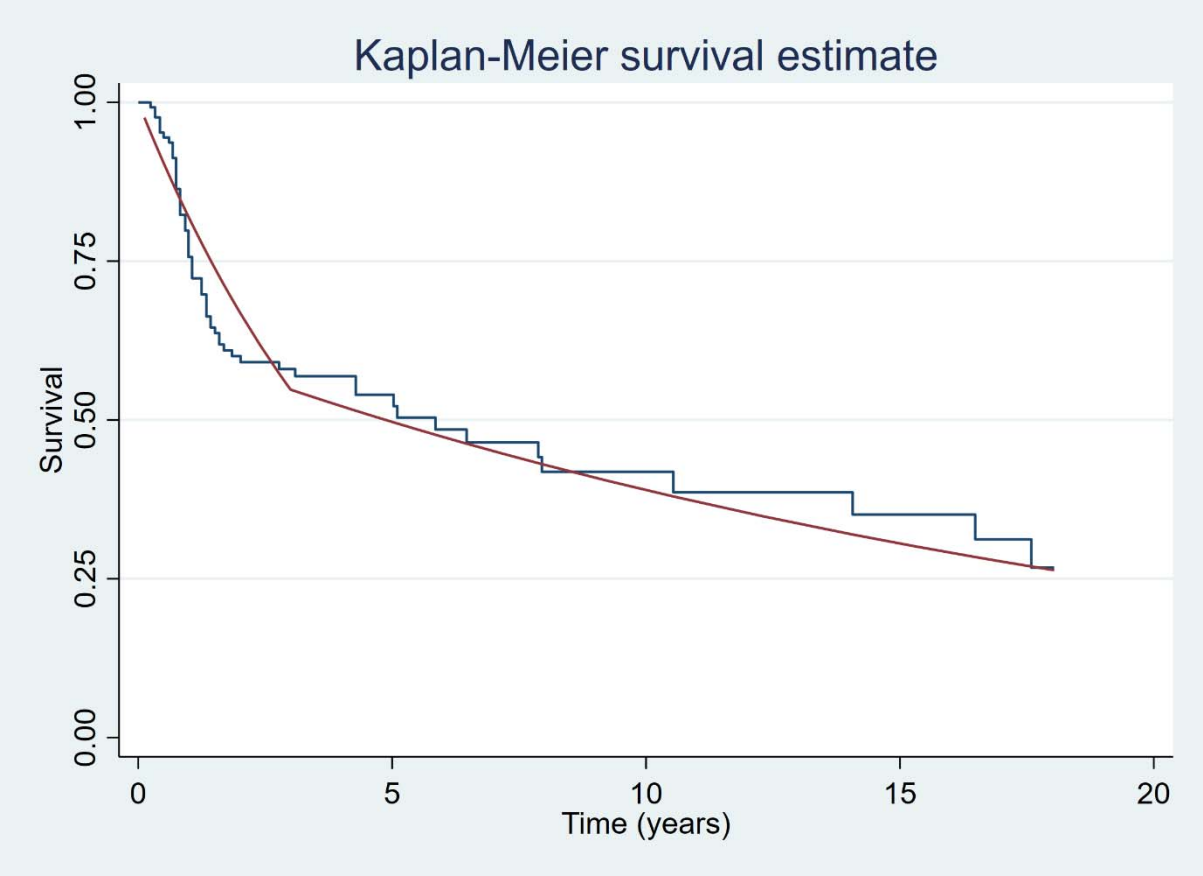
B18. Priority question CS Section 12.2.1.5, page 180. Figure 42 appears to suggest that the probability of having PEBD surgery between ages 3 and 18 seems to be roughly 40% which should translate to roughly around 3% per year assuming an exponential distribution, whereas Table 43 presents this value as 4.75%. Please check and amend if required, providing the rationale if no change is made. Our clinical experts suggested that PEBD is not very common in the UK so please clarify on the appropriateness of using probability of PEBD surgery estimated from NAPPED data. Please provide exploratory analyses assuming that the probability of PEBD surgery using a range of values between 0 and 3%.

B18. Company Response

While CS Figure 42 does show roughly a 40% change in the proportion of patients without SBD between ages 3 and 18, this change is based on the absolute difference in the proportion of patients without SBD, not conditional on not having an SBD at age 3. At age 3, approximately 60% of patients do not have an SBD, reducing to around 25% at age 18. This would indicate a probability of around 58% of having an SBD between 3 and 18.

Values in the model are correct based upon the piece-wise exponential model fit to the data. Figure 6 presents Kaplan-Meier estimates of SBD-free survival and predicted values from the piece-wise linear model. The graph shows good concurrence between observed and predicted survival at age 18.

Figure 6: Kaplan-Meier survival with predicted survival from the piece-wise exponential model



As documented in the in the company submission, NAPPED represents the largest genetically-defined cohort of PFIC patients to date, providing retrospective analysis of 130 PFIC1 and 264 PFIC2 patients (at latest data cut-off) in >50 centres globally, including centres in the UK. At the recent World Congress of Paediatric Gastroenterology, Hepatology and Nutrition, the presenter of the latest NAPPED data Dr Van Wessel as well as the NAPPED lead Prof HenkJan Verkade stated that there were no significant differences in outcomes observed between countries, regions and races. The validity of the NAPPED data to UK was also confirmed [redacted].

As such, NAPPED data is considered the most relevant source of rates of PEBD for the UK. While it is acknowledged that there is variation in care between patients, PEBD remains a part of the treatment pathway in the UK. Figure 39 of the company submission displays the current treatment pathway and has been validated by UK clinical experts.

However, clinical input has also stated that PEBD is not the preferred treatment option in the UK. As a sensitivity analysis, scenario analyses varying the annual probability of PEBD from 0% to 4% in 1% increments have been applied and are presented in Table 11 to
Table 15.

Table 11: Results assuming 0% annual probability of PEBD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.11	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	2.29	[redacted]	[redacted]

Table 12: Results assuming 1% annual probability of PEBD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.23	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	2.17	[redacted]	[redacted]

Table 13: Results assuming 2% annual probability of PEBD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.33	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	2.07	[redacted]	[redacted]

Table 14: Results assuming 3% annual probability of PEBD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)

Standard care	[redacted]	20.41	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	1.99	[redacted]	[redacted]

Table 15: Results assuming 4% annual probability of PEBD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.49	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	1.91	[redacted]	[redacted]

B19. CS Section 12.2.1.7, Table 47, page 182. Please give a full description of how the rate ratios were calculated.

B19. Company Response

Table 47 in the CS incorrectly reported the rate ratios corresponding to PFIC1 and PFIC2 pruritus responders. A corrected table is provided in Table 16. 56% and 68% of PFIC1 and PFIC2 patients were indicated for LTx due to intractable pruritus in NAPPED, respectively. A rate ratio of 1 minus this proportion was applied to patients with a pruritus response to reflect the proportion of patients who are indicated for LTx due to pruritus rather than other factors.

Table 16. Rate ratio for pruritus responders

Subgroup	Proportion indicated for LTx	Rate ratio
PFIC1	51/91 (56%)	0.44
PFIC2	19/28 (68%)	0.32
Joint population*	-	0.41*

*Joint rate ratio is calculated as a weighted average using the proportion of PFIC 1 and 2 in the PEDFIC trial.
Abbreviations: LTx, liver transplant.

B20. CS Section 12.2.1.7, page 182. The probability of LT in responders is assumed to be 0% whereas Figures 33 and 35 seem to suggest that responders do have LT. Please clarify why a 0% probability was assumed.

B20. Company Response

The data presented in Section 12.2.1.7 suggests a 0% probability of LTx in PEBD responders, however, this does not account for the annual 5% of patients who lose response (see Section 12.2.1.3). When patients have lost response to PEBD, they are subjected to the same probability of LTx as those presented in Table 48 of the CS (i.e. 6.34% in PFIC1, 11.24% in PFIC2). It is assumed that patients who later receive transplants have lost response to PEBD. This was confirmed by a UK clinical expert, in the same manner odvixibat responders should assume having a 0% probability for LTx.

B21. Priority question CS Section 12.2.1.7. There seems to be a discrepancy in the values reported for PFIC2 between Table 48 and Table 49. Table 49 suggests that annual rate is 0.0993 whereas an annual probability of 11.24% is reported in Table 48. Please check and amend accordingly.

B21. Company Response

The value presented in Table 49 of the CS is incorrect. Please find a corrected estimate in Table 17. The constant term of 0.1193 was used to derive the annual probability of 11.24% assuming an exponential distribution. This value was correct in the economic model.

Table 17: Exponential model results for LTx in PEBD non-responders, PFIC2

Definition of response	Constant term	Standard error	95% CI
≤75% sBA reduction	0.1193	0.040	0.062;0.229

Abbreviations: CI, confidence interval; LTx, liver transplant; PEBD, partial external biliary diversion.

B22. CS Section 12.2.1.9, Table 54. Please provide justification for using data from Bull *et al.* 2019 to estimate the re-transplantation rates.

B22. Company Response

Clinical opinion suggested that secondary LTx are expected to differ between PFIC1 and PFIC2. For this reason, it was preferred to use a source specific to PFIC rather than published estimates in UK adults. The cohort of patients used in Bull et al is described in Pawlikowska 2010[9] and includes patients enrolled in the UK.

Alternative estimates from the literature in UK adults do not present significant advantages or differences from the estimates used in the economic model and presented by Bull et al. In a paper by Bramhall et al (2001[10]), 10% of almost 2,000 LTx in the UK were found to be re-grafts. This is consistent with an estimate of 8% reported by Marudanayagam et al (2018[7]) in UK adults. A report by NHS Blood and Transplant reported 764 of 8,428 LTx to be re-transplants between April 2008 and March 2018 (9%). These estimates are consistent with the weighted average of 9.81% used in the model base-case.

B23. CS Section 12.2.1.9. Please clarify the source of the assumption used in the model that patients who require re-transplant have the same outcomes (acute and long-term mortality, quality of life, post LT complications) as those patients having a first liver transplant?

B23. Company Response

Estimates have been sourced from Bull et al., 2019. The assumption that re-transplantation is assumed to occur in the same year as the first liver transplant was due to the absence of available literature. Therefore, the company made a pragmatic assumption and applied the same assumption for both acute and long-term liver transplant.

Mortality

B24. Priority question CS, section 12.2.1.8, Table 51, page 183. See sub questions a) and b) below

a) Please provide more detail on how calibration methods were used to estimate the annual probability of death for pre-transplant mortality for PFIC1 and PFIC2 (Table 1). Please comment on the robustness of the method used to identify the parameters and whether it was sensitive to any assumptions made. Was consideration given to propagating the uncertainties on the estimated mortality rates through the calibration process instead of applying a +/-15% range for uncertainty in the model?

b) Please clarify where in the model the 'Goal Seek' calibration can be found? If it is not in the model submitted to the ERG, please provide the Excel file used for calibration.

B24. Company response

The model calculates the total proportion of patients that died prior to liver transplant in column S of the ‘Engine_SoC’ sheet, with cell S4 presenting the total pre-transplant mortality.

The following procedure was applied to calculate pre-LTx mortality for PFIC1 and PFIC2:

1. Select PFIC1 from the population dropdown on the ‘Key results’ sheet
2. Select cell S4 on the ‘Engine_SoC’ sheet
3. Go to the ribbon and select Data>What-If Analysis>Goal Seek and fill out as follows:
    - Set Cell: *S4*
    - To value: *0.09*
    - By changing cell: *'Clinical data - Efficacy'!$C$126*
4. Select OK
5. Select PFIC2 from the population dropdown on the ‘Key results’ sheet
6. Select cell S4 on the ‘Engine_SoC’ sheet
7. Go to the ribbon and select Data>What-If Analysis>Goal Seek and fill out as follows:
    - Set Cell: *S4*
    - To value: *0.04*
    - By changing cell: *'Clinical data - Efficacy'!$C$127*
8. Select OK

This approach assumes that all pre-LTx mortality above that captured in lifetables is experienced at a constant rate, regardless of age and is only applicable to patients that have not responded to odevixibat or SoC. The model is not overly sensitive to

these assumptions – excluding any excess mortality above that capture by lifetables leads to a small increase in the ICER, and 4.6% of PFIC1 patients and 1.9% of PFIC2 patients will die prior to liver transplant. If the excess mortality is applied to all pre-LTx health states, there is a slightly larger increase in the ICER of approximately 5%, to [redacted].

While it would be preferable to estimate pre-LTx mortality from published survival curves, none have been identified and the approach taken in the model was considered reasonable given the data available and the relative importance of this parameter for results. No measures of uncertainty around estimates of pre-LTx mortality were identified and so consideration was not given to propagating uncertainty through the calibration process.

Table 18: Results without excess mortality applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.96	[redacted]	-	-	-	-
Odevixibat	[redacted]	22.72	[redacted]	[redacted]	1.75	[redacted]	[redacted]

Table 19: Results with excess mortality applied to all pre-transplant states

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.43	[redacted]	-	-	-	-
Odevixibat	[redacted]	21.96	[redacted]	[redacted]	1.53	[redacted]	[redacted]

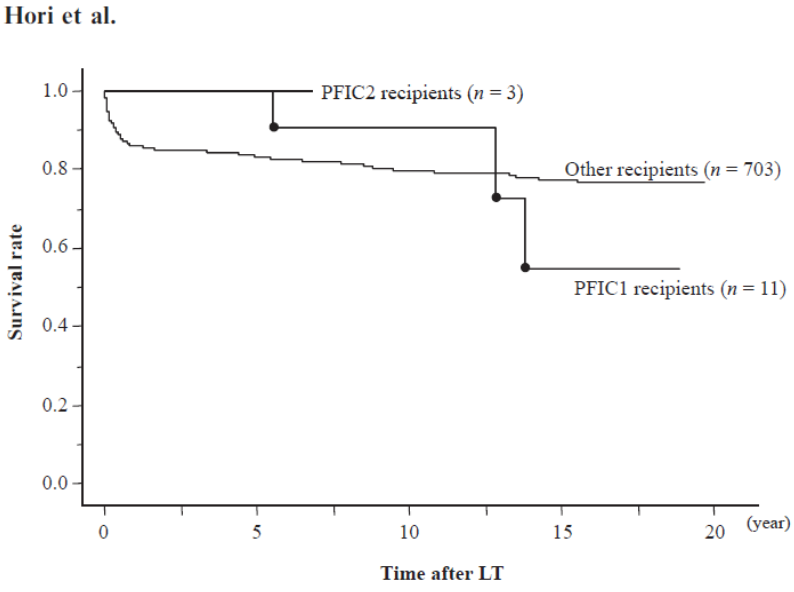
B25. CS Table 52 and 53, page 184-5 and Appendix 17.9. See sub questions a) to e) below

a) Please clarify the discrepancy between CS Table 52, page 184 which lists three studies used in the meta-analysis and the meta-analysis results presented in Appendix, Table 122, page 41 and section 17.9, Figure 55 which shows four studies, the additional one being Hori, 2010.

B25. a) Company Response

We acknowledge the question posed by the ERG, and can confirm that Hori et., 2011 was included in the weighting for the meta-analyses rate. The value used in the model was 0.13. CS Table 122 should have included the study conducted by Hori et al., 2011, although there were no events in year 1 (Figure 7). Section 17.9, Figure 55 of the CS correctly includes Hori et al., 2011. presents the patient survival data from Hori et al., 2011.

Figure 7: Kaplan-Meier survival presented in Hori 2011



b) Please give further information on the methodology for identifying the studies used to inform the acute and the long term LTx and why the particular studies were chosen. Please comment on the source of heterogeneity among the studies used in the meta-analysis for acute LTx mortality and in particular possible reasons why the annual probability of acute LTx morality is so much

less in the Wanty *et al.*, 2004 study compared to Valamparampil *et al.*, 2019 and Ayodgdu *et al*., 2007.

B25. b) Company Response

A systematic literature review informed the sources that were meta-analysed to obtain acute LTx mortality. The systematic review was performed in 2019 and was designed to identify sources for mortality in PFIC and BRIC among other outcomes. No large studies were identified. Given small patient numbers and variation between the estimates reported in each study, a meta-analysis was considered the most robust approach to aggregating the available evidence. Variation in the rates obtained is likely due to the small patient numbers, differences in study design (including differences in the number of PFIC1 and PFIC2 patients) and geography (see Table 8). Both Aydogdu and Valamparampil studies were primarily designed to consider the impact of LTx in PFIC patients, while the Wanty study aimed to review the experience of all patients in a single centre, regardless of transplant status.

Table 8: Study characteristics used for acute LTx mortality

Characteristic	Wanty et al	Aydogdu et al	Valamparampil et al
Country	Belgium	Turkey	India
Study type	Single centre retrospective analysis	Single centre retrospective analysis	Single centre retrospective analysis
Age at LTx	50 months	43.2 months	68 months
Patient numbers	49	12	34
Time frame (year)	15 years	1997 to 2016	2010 to 2018

Abbreviations: LTx, liver transplant.

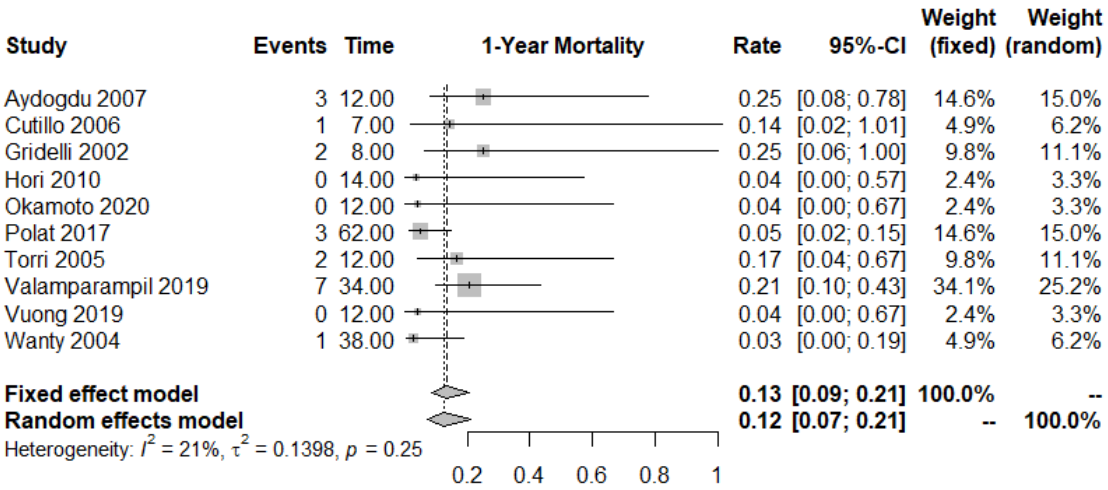
Six additional papers have subsequently been identified and incorporated into the meta-analysis. Table 20 summarises the additional studies. Additionally 2 data extraction errors in the Wanty and Aydogdu papers have been corrected.

Table 20: Additional studies incorporated into the one-year survival meta-analysis

Study	Country	Study type	Patient numbers	1-year survival
Cutillo 2006	Belgium	Single centre retrospective analysis	7	85.7%
Gridelli 2002	Italy	Single centre retrospective analysis	8	75%
Okamoto 2020	Japan	Single centre retrospective analysis	12	100%
Polat 2017	Turkey	Retrospective analysis	62	95.2%
Torri 2005	Italy	Retrospective analysis	12	83.3%
Vuong 2019	USA	Single centre retrospective analysis	12	100%

The updates to the meta-analysis result in a small decrease in the rate predicted in the random-effects model, and better concurrence between the fixed effects and random effects models. Figure 9 presents the results of the updated meta-analysis.

Figure 9: Updated meta-analysis for acute mortality following LTx



c) Please clarify what the numbers in the "Values reported" column represent in Appendix Table 122 and 123, - are they rates or probabilities or a mixture of both. How do they relate to the probabilities shown in CS, Table 52 and the rates shown in Figures 55 and 56 in the Appendix? Please provide details of the statistical model used in the meta-analysis for acute LTx. Please provide the R file with model code and data.

B25. c) Company Response

Inputs to the meta-analysis were provided as the number of deaths in the first-year post-transplant and the total number of transplanted patients. Inputs are summarised in Table 21.

Table 21: Meta-analysis of acute LTx mortality inputs

Study	n	N
Aydogdu 2007	3	12
Cutillo 2006	1	7
Gridelli 2002	2	8
Hori 2010	0	14
Okamoto 2020	0	12
Polat 2017	3	62
Torri 2005	2	12
Valamparampil 2019	7	34
Vuong 2019	0	12
Wanty 2004	1	38

Outputs of the meta-analysis are reported as a rate. This was used directly in the submitted model but in the updated base-case has been converted to an annual probability.

d) Please clarify the statement that only one death occurred in the timeframe 2-5 years (Appendix page 42) in relation to the KM plot in Figure 57 which appears to show at least two deaths in the pooled data between 2 and 5 years.

B25. d) Company Response

The KM plot in Figure 57 reports survival conditional on survival at 1-year post LTx, thus year 5 in the graph represents 6 years post LTx. No events occurred between year 2 and year 5 in the Wanty 2004 analysis. Hori 2010 reports a 5-year survival rate of 90.9% and it was assumed the first death was observed by year 5; however, upon review this death occurs at just after 5 years post-transplant. Thus in this analysis no deaths were observed in the time frame 2-5 years.

e) Please provide possible reasons for the difference between the long term LTx mortality rate obtained from the meta-analysis of two studies (0.0071) and that obtained from the pooled method (0.0145) and reasons for preferring the pooled method result. Accounting for censoring was one reason given but the ERG notes that using rates in the meta-analysis also accounts for censoring as it uses person-years at risk.

B25. e) Company Response

The meta-analysis was performed to consider the mortality rate between years 2 and 5 and discarded any data on patient survival occurring outside of this timeframe. Most mortality events occurred after 5 years and the meta-analysis is considered less reliable. The meta-analysis does not account for patients that may have been censored in the period Year 2-5, as only the number of deaths by year 5 were included. The pooled survival data allows all events to be included and does not discard data at the 5-year cut-off.

The pooled analysis has been updated to include 2 new studies, Okamoto 2020 and Gridelli 2002 which also report KM analysis of survival. Figure 10 presents the updated KM curve and Table 22 presents the updated survival analysis. The update results in a small increase in long-term mortality.

Figure 10: Updated Kaplan-Meier curve from the pooled analysis

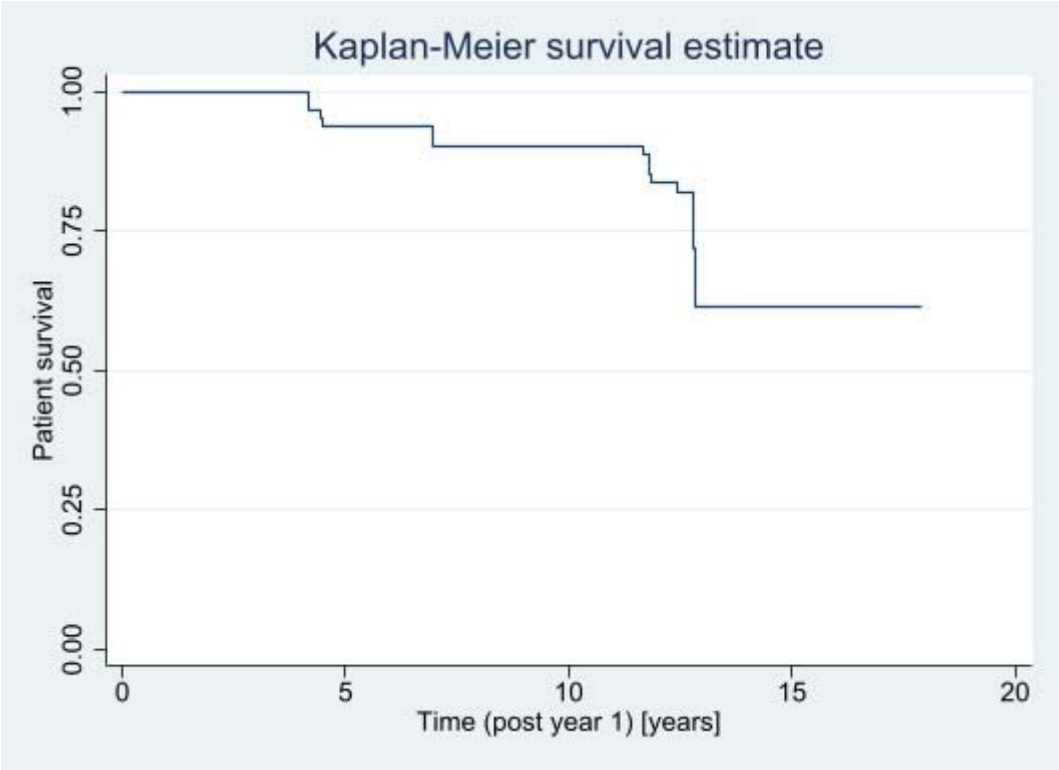


Table 22: Exponential model results for updated pooled, long-term post-liver transplant mortality

	Constant term	Standard error	95% CI
Coefficient	0.0196	0.0050	0.0116-0.0320

Abbreviations: CI, confidence interval

Costs

B26. CS, Section 12.2.4.1, page 186. Please clarify why adverse event costs related to odevixibat are not included in the model base-case.

B26. Company Response

We acknowledge the question posed by the ERG and can confirm no serious adverse events related to the study drug were observed in PEDFIC1 trial (please see Table 25 in CS), therefore adverse events were not applied in the model base case.

B27. Please explain why costs of pharmacy preparation and dispensing for odevixibat have not been included in the model.

B27. Company response

The general practice in both hospital and community pharmacy is that packs should not be split (minimising preparation of the product), especially high-cost drugs, due to the False Medicines Directive being introduced. No costs are associated with pharmacy preparation as odevixibat is an oral capsule and there will be no splitting of packs. In the dispensing process, there are no dispensing or preparation fees for capsules, the typical pharmacy dispensing process involves validation of the prescription by a pharmacist, once this is done it can be dispensed. The dispensing process usually involves the use of a robotic dispensing system. Medicines in the robotic system must be suitable for storage at room temperature and odevixibat does not require any special temperature storage conditions. Once the prescription has been dispensed there will be a final check by the pharmacist prior to counselling and giving the patient their medication.

The administration of the capsule may require splitting but this will be at point of administration, likely to be by the patient or parent/carer at the time of administration. The purpose of this splitting is for ease of administration for patients that cannot swallow capsules.

Odevixibat is initiated in a specialist centre (secondary care) and patients will be provided 3 or 6 months supply until their check-ups. FP10 scripts for outpatient dispensing will be very unlikely and courier services from the hospital will be offered as delivery service.

Odevixibat is licensed for children and the majority of the population is expected to be paediatrics, therefore they are exempt from paying any prescription charges. This has been informed and validated by an expert clinician.

B28. Priority question CS and Model, Section 12.3.6.1, Table 61, page 202. Please clarify why the daily dose is increased at set intervals (e.g., 7.5kg, 12.5 kg) rather than linking it to the recommended daily dose for the weight category. For example, it seems the daily dose is only increased to 1600 µg at 35.5kg while it should be increased to 1600 µg when the weight is over 30kg. Please estimate the daily costs by using the recommended daily dose based on weight.

B28. Company Response

Dosing in the model is in line with trial (PEDFIC1 CSR, Table 4) and the dosing schedule presented in the SmPC, presented in Table 2 of the CS. Table 23 presents the dosing schedule used in PEDFIC1.

Table 23: Dosing schedule used in PEDFIC1

Body Weight (KG)	Capsule Size	Number of Capsules per Day	Odevixibat				Placebo
			40 µG/DAY		120 µG/DAY		
			Capsule Strength, Low Dose (µG)	Total Dose (µG)	Capsule Strength, High Dose (µG)	Total Dose (µG)	Total Dose (µG)
5.0 to <7.5	0	1	200	200	600	600	0
7.5 to <12.5	0	2	200	400	600	1200	0
12.5 to <17.5	0	3	200	600	600	1800	0
17.5 to <19.5	0	4	200	800	600	2400	0
19.5 to <25.5	3	2	400	800	1200	2400	0
25.5 to <35.5	3	3	400	1200	1200	3600	0
35.5 to <45.5	3	4	400	1600	1200	4800	0
45.5 to 55.5	3	5	400	2000	1200	6000	0
>55.5	3	6	400	2400	1200	7200	0

B29. Priority question CS and Model, Section 12.3.6.1, Table 61, page 202. Please provide the actual costs of odevixibat based on the doses observed at the patient-level in the PEDIFIC1 study. Please also provide the mean dose used in the PEDIFIC1 study

B29. Company Response

Table 24. Summary of Average Daily Dose in PEDFIC1

	Odevixibat 40 ug/kg/day N=23	**Odevixibat 120 ug/kg/day N=19**	**Odevixibat All Doses N=42**
Average Daily Dose (ug)			
Mean	625.3	2113.4	1298.5
SD	393.96	1205.63	1132.85
Median	499.4	1800	800
Min	303	600	303
Max	2145	4800	4800
Average Daily Dose (ug/kg)			
Mean	38.56	115.5	73.36
SD	3.152	12.817	39.744
Median	39.27	112.99	43.63
Min	31.6	92.9	31.6
Max	43.8	141.1	141.1

Table 25 presents the number of odevixibat patients in each weight category at baseline. These lead to an average daily cost of [redacted] in the Odevixibat 40 ug/kg/day arm and [redacted] in the Odevixibat 120 ug/kg/day arm, using the PAS price. These values increase to [redacted] and [redacted] respectively using the list price.

Table 25: Weight categories at baseline

Weight category at baseline	Odevixibat 40 ug/kg/day N=23 n (%)	Odevixibat 120 ug/kg/day N=19 n (%)
5.0 to <7.5	1 (4.3)	1 (5.3)
7.5 to <12.5	11 (47.8)	6 (31.6)
12.5 to <17.5	5 (21.7)	7 (36.8)
17.5 to <19.5	3 (13.0)	0
19.5 to <25.5	1 (4.3)	0
25.5 to <35.5	1 (4.3)	4 (21.1)
35.5 to <45.5	0	1 (5.3)
45.5 to 55.5	1 (4.3)	0
>55.5	0	0

B30. Priority question

a) **Please clarify why no wastage costs for odevixibat are included in the model.**

B30. a) Company Response

Odevixibat is available as 200 µg, 400 µg, 600 µg and 1200 µg hard capsules. The recommended dose of odevixibat is 40 µg/kg administered orally once daily. The dose may be increased to 120 µg/kg/day, with a maximum daily dose of 7200 µg per day. The company does not anticipate capsule-splitting, therefore wastage costs are not included in the model. Patients falling into each weight category incur the full cost of the capsules used.

b) **Please clarify why average weights of patients were used to estimate the drug dosage. It is acknowledged that the mean patient characteristics (e.g. weight) led to an underestimation of drug cost compared with using patient-level data from clinical trials, please see https://www.sciencedirect.com/science/article/pii/S1098301516304387. Please also provide an updated mean dose for each age group using the distribution of patient characteristics.**

B30. b) Company Response

Average patient weights were initially applied in the model for two reasons:

- At baseline, patients are expected to be below average weight but responding patients are likely to catch up; thus the original model reflects patients starting in the 25th weight percentile and growing to the 50th percentile by year 2.

- Estimating a distribution for patient weight relies on making assumptions about the standard deviation in weight at each age in the model. The baseline standard deviation (SD) observed in the trial cannot be used, as it will underestimate variation in weight as patients grow and not all older age groups are observed in the trial.

Nevertheless, the model has been updated to apply a distribution of patient weights in each cycle, based on the average age. In order the calculate the SD in weight, the interquartile range (IQR) has been calculated from standard growth charts and the SD set equal to IQR/1.35. Table 26 presents the weight distribution by age applied in the model.

Table 26: Weight distribution by age applied in the model

Age	Mean weight	SD in weight	Weight category (kg)								
			4	7.5	12.5	17.5	19.5	25.5	35.5	45.5	55.5
2	11.75	1.481	0%	69%	31%	0%	0%	0%	0%	0%	0%
3	14.00	1.759	0%	20%	78%	2%	0%	0%	0%	0%	0%
4	16.38	1.852	0%	2%	71%	23%	5%	0%	0%	0%	0%
5	18.50	2.315	0%	0%	33%	33%	33%	0%	0%	0%	0%
6	20.63	3.148	0%	0%	16%	20%	58%	6%	0%	0%	0%
7	23.00	3.148	0%	0%	4%	9%	65%	21%	0%	0%	0%
8	25.75	3.889	0%	0%	2%	4%	42%	52%	1%	0%	0%
9	28.63	4.630	0%	0%	1%	2%	23%	68%	7%	0%	0%
10	31.88	5.833	0%	0%	1%	1%	12%	60%	26%	1%	0%
11	35.38	6.204	0%	0%	0%	0%	5%	45%	44%	5%	0%
12	39.25	7.315	0%	0%	0%	0%	3%	27%	50%	18%	1%
13	44.13	7.870	0%	0%	0%	0%	1%	13%	43%	36%	7%
14	49.63	8.519	0%	0%	0%	0%	0%	5%	27%	44%	25%
15	54.50	9.259	0%	0%	0%	0%	0%	2%	15%	38%	46%
16	58.13	8.889	0%	0%	0%	0%	0%	1%	7%	31%	62%
17	60.63	8.704	0%	0%	0%	0%	0%	0%	4%	24%	72%
18	62.25	8.611	0%	0%	0%	0%	0%	0%	2%	19%	78%
25	76.74	8.611	0%	0%	0%	0%	0%	0%	0%	1%	99%
35	79.82	8.611	0%	0%	0%	0%	0%	0%	0%	0%	100%
45	81.96	8.611	0%	0%	0%	0%	0%	0%	0%	0%	100%
55	80.98	8.611	0%	0%	0%	0%	0%	0%	0%	0%	100%
65	78.88	8.611	0%	0%	0%	0%	0%	0%	0%	0%	100%
75	73.83	8.611	0%	0%	0%	0%	0%	0%	0%	2%	98%

Abbreviations: SD, standard deviation.

c) **Please comment on the possibility of wastage associated with the patients not eating the food (e.g. fussy eaters) and the need to open a new capsule to meet the required daily dose.**

B30. c) Company response

The possibility of wastage associated with patients not eating the food (e.g., fussy eaters) and the need to open a new capsule can be minimized, as all capsules can be either swallowed whole with a glass of water or opened and sprinkled on food. However, the larger 200 and 600 micrograms capsules are designed to be opened to have the contents sprinkled on food.

The odevixibat pellets do not have any smell nor any taste. Only a small amount of soft food is needed in a bowl (2 tablespoons/30 mL of yoghurt, apple sauce, banana or carrot puree, chocolate pudding, rice pudding or oatmeal porridge). This will prevent a fussy eater from developing an aversion to food, due to the small amount of soft food needed, therefore reducing the possibility of wastage. “Picky” eaters and potential wastage was not an issue in PEDFIC1 nor in PEDFIC2 studies, which is consistent with the compliance data included. Precise instructions on the patients detailing methods of administration are provided in the patient information leaflet.[11]

Overall, compliance with daily dosing of odevixibat in PEDFIC1 was high, with a median overall compliance calculated from the eDiary of 93%. Compliance as calculated from the case report form (CRF) was also high, with a median overall compliance of 99%.[3] In PEDFIC2 daily dosing of odevixibat was also high, with a median overall compliance of 96% as calculated from the eDiary and 97% as calculated from the CRF.[4]

B31. CS and model, Section 12.3.6.1.2, Table 63. The model uses the same dosages for cholestyramine and rifampicin over the patient's lifetime, regardless of age. Please clarify if this is expected to be the case in clinical practice or if this is a simplifying assumption. If this is an error, please correct the model accordingly.

B31. Company Response

The application of paediatric doses throughout patients' lifetimes is an error. The model has been corrected to model the following doses in adulthood (>18 years):

- 10mg/kg/day of rifampicin in patients < 18 years (previously fixed dose of 10 mg/day)
- 6g/day of cholestyramine in patients ≥ 18 years, following guidance from the BNF on treating pruritus with partial biliary obstruction and primary biliary cirrhosis (4-8g recommended dose)
- 450mg/day of rifampicin in patients ≥ 18 years, following the literature on treating adults with cholestasis (300-600mg recommended dose)[12]

The use of adult doses did not significantly impact results, as the majority of patients have progressed to surgical treatment once adulthood is reached (+2% on ICER).

B32. Priority question CS and model, Section 12.3.6.4, Table 64. Please provide more rationale on the appropriateness and generalisability of data from Bjornland *et al*., 2020 to the UK setting. The data in the table suggests two-thirds of the patients have re-operations which seems quite high.

B32. Company response

As noted, the proportion of patients with complications following PEBD was informed by Bjornland et al., 2020. Due to lack of data from other sources including UK-specific studies, this study, which reported on a population of PFIC patients treated at four Nordic centres was considered appropriate, since clinical practice in the Nordics is not expected to vary significantly from the UK. The study was carried out at 4 centres seeing few patients and it is possible that they are less experienced than key UK centres in this type of surgery. Secondary surgeries were performed mainly due to variety of stoma problems (leakage, prolapse, stricture, and bleeding), patient's wish for removal of the external stoma, or inadequate bile drainage with persistent sever itching. In several cases the surgery was a conversion to another form biliary diversion. The high rate of the re-operations reflects the significant complications and inadequacies related to this type of surgery.

B33. CS, Section 12.3.6.5, page 204. Please clarify why the cost of LTx surgery is assumed equivalent to the cost reported in TA443 for patients diagnosed with chronic hepatitis C and B in the UK, and inflated from 2014, rather than searching for more recent and disease relevant costs or using NHS reference costs.

B33. Company Response

The cost for the LTx health state applied in the economic model is from semi-structured interviews collected by Singh et al, inflated to 2019/20. This cost reflects the total annual mean resource use rather than the cost of the procedure alone. NHS reference costs were not used, as it was not clear how a micro-costing approach could accurately capture all resources needed in the year of LTx. In addition, this cost has been used in other submissions, such as TA330 (Sofosbuvir for the treatment of chronic hepatitis C).

In 2017, Singh et al[13] also reported that observational data such as the data collected in Singh et al's interviews are potentially the most reliable reflection of current resource use associated with LTx in the UK. It was therefore preferred to use an estimate from the literature rather than NHS reference costs.

B34. Priority question CS Section 12.3.7. Please present the costs related to each health state in Table D8. Also, the costs presented in cells C14:J15 of the 'Costs data' sheet of the cost- effectiveness model do not seem to be representative of the costs used in the calculations in Engine sheets.

B34. Company Response

The calculated costs in cells C14:J15 of the "Costs data" sheet of the cost-effectiveness model have been used in various parts in the Engine sheets. Cells C14:D15 of the "Costs data" were not directly used in the engine calculations and will be rectified in the updated model. All costs in cells C15:J15 of the "Costs data" sheet represent the annual cost of medical resource use (excluding drug costs) associated with being in the defined health state. All other costs are separately accounted for in the Engine sheets. Please see Table 27 costs related to each health state.

Table 27: Health state costs (PAS price)

	SoC	Odevixibat
Response	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]
PEBD	[redacted]	[redacted]
LTx	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]
Immunosuppressants	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]
Death	[redacted]	[redacted]
Loss productivity	[redacted]	[redacted]

HRQoL

B35. Clinicians to the ERG suggested that patients who have a response to treatment will not have the same quality of life as a healthy child due to ongoing problems and symptoms of disease, contrary to the assumption used in the model. Please clarify why this simplifying assumption is made in the model.

B35. Company response

While it is accepted that patients that have responded to treatment will not experience the same quality of life as a healthy child, this simplifying assumption was applied due to a lack of available data on quality of life in children with PFIC generally and split by sBA response specifically. The data applied for non-responders in the model has been taken from a general PFIC cohort and the exact response and surgical status of these patients remains unknown. As such, the

difference in quality of life between the PFIC cohort and healthy children was judged to be an appropriate estimate of the impact of response on quality of life.

The updated analysis does not rely on these assumptions as the vignette study acknowledges that patients with response to treatment will continue to experience some symptoms. The outputs of the vignette study imply that the difference in quality of life between the response and non-response states presented in the submitted analyses was conservative. The original analyses assumed that the utility difference between responders and non-responders was 0.083, compared to 0.192 in the vignette study TTO analysis.

B36. Priority question CS, Section 10.1.4 , page 151 and CS, Appendix 17.8. Please clarify why the results of the mapping study were not used for base case analysis. Please provide an explanation for differences in HRQL at baseline in responders and non-responders (Tables 116 and 117). Clarify whether you considered using a common baseline value for responders and non-responders, and using the CFB (change from baseline) observed in the trial (e.g., as reported in Table 117) to estimate the utility values for responders and non-responders. If you did, provide the rationale for not selecting this approach.

B36. Company Response

There are many potential confounding variables that may be correlated with sBA or pruritus response and may explain the differences in QoL at baseline. Albireo is currently conducting further analyses to determine predictors of response, however no such predictors have yet been identified.

Mapped EQ-5D utilities from the trial were not applied in the model - PedsQL data were included as an exploratory endpoint in the PEDFIC1 as there was a lack of consistency in the results. Patient numbers were small, especially among self-reporting patients, and the mapping analysis was applied to aggregate data rather than patient-level data.

A sensitivity analysis assuming a common baseline EQ-5D utility for all patients and applying observed change from baseline is presented. The combined baseline utility observed in the mapping analysis was 0.633. Patients with an sBA response to treatment experienced a 0.244 increase from baseline, compared to 0.064 in non-responders. Utility scores applied in this scenario are presented in Table 28.

Table 28: Utility scores applied in the scenario using mapped utility scores

Health state		Utility
Without PEBD	sBA & pruritus response	0.858
	Loss of response	0.697
With PEBD	sBA & pruritus response	0.619
	Loss of response	0.503
LTx		0.710
Post-LTx		0.850

Abbreviations: LTx, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid.

B37. Priority question Model and CS, Section 10.1.9.2, page 157. In the model, there is the option to select [redacted]. Please clarify how the value used for the base-case was chosen, was this based on clinical opinion on the appropriateness of the two studies?

B37. Company Response

The disutility multiplier for colorectal cancer (0.945) seemed inappropriate for the base case, because colorectal cancer patients are far older (mean age 72 years) and likely at end of life, compared to the target population. An ulcerative colitis multiplier was used in lieu of this as the base case (0.722). This study represented younger patients with a stoma bag. Clinical opinion confirmed that a multiplier of 0.722 more accurately reflected the discomfort of carrying a stoma bag, and that this value was likely to decrease (i.e., worse quality of life) as children get older and become more aware of it. Our current base case therefore represents a conservative scenario, where a constant multiplier is applied for all age groups.

B38. CS, Section 10.1.9.4, page 157. The text in CS suggests that a disutility of -0.1 is applied to patients in the most severe health state of the model (PEBD non-response), however, the model seems to use a disutility of -0.05. Please check this discrepancy and amend appropriately.

B38. Company Response

In the base-case, a disutility of -0.1 is applied to patients in the most severe health state of the model (PEBD non-response).

The model presents three caregiver disutilities:

- Caregiver disutility, loss of response = -0.05
- Caregiver disutility, PEBD = -0.05
- Caregiver disutility, post-LT = -0.05

For the PEBD non-response state the model sums the PEBD and non-response utilities equating to -0.1 disutility.

B39. CS, Appendix 17.8. Please clarify the reason for differences between the utility values in Tables 116/117 compared with Table 121.

B39. Company Response

We acknowledge the question posed by the ERG and can confirm Table 116 and Table 117 are weighted across both patient-reported scores and parent-proxy scores in PEDFIC1. Table 121 represents all scores reported in PEDFIC1: self-reported, parent-reported and weighted scores (as see in Tables 116/117).

Model calculations

B40. Please clarify if 'FIC 1 deficiency' and 'BSEP-deficiency' in the model relate to PFIC1 and PFIC2 patients, respectively.

B40. Company Response

We can confirm “FIC 1 deficiency” in the model relates to PFIC1 patients and “BSEP-deficiency” represents PFIC2 patients.

B41. Model, worksheet “HRQoL data”. Cells C48:C144 calculate utility values for the general population which is then used in worksheets “Engine_Odevixibat” and “Engine_SoC”, column AG to calculate the age multiplier, to account for decreasing utilities with age. However, in the worksheet “HRQoL data” the formula in cell C48 sets a value of 1 if the age is the starting age of the model, instead of the general population utility at that age. This results in the age multiplier in worksheets “Engine_Odevixibat” and “Engine_SoC” being incorrect. Please confirm this is an error and correct in the model if so.

B41. Company Response

This was an error. The model has been corrected to reflect this change.

B42. Priority question Model, worksheets “Engine_Odevixibat” and “Engine_SoC”. The cost of liver transplant post 2 years is given an annual cost of £19,643 and is assumed to apply for the first 2 years post LT. In the model, this cost is only applied to “new patients in post-LT cycle”, (column AE) and not all patients in the “Post-LT” state (column Z) therefore only applying this annual cost for 1 year. Please confirm if this is an error and correct in the model if so.

B42. Company Response

This was an error. The model has been corrected to reflect this change.

Section C: Textual clarification and additional points

C1. CS Table 49, page 183. The constant hazard for PFIC2 here is different from the value used in cell C86 of sheet “Clinical data - Efficacy” in the company model. It

also doesn't appear to correspond to the probability of 11.24% shown in CS Table 48, page 182. Please clarify this apparent discrepancy.

C1. Company Response

This has been addressed in B21. An error has been identified in the value reported in Table 49 CS. The constant term of 0.1193 is the value used in the economic model to derive an annual probability of 11.24%. Please see revised table below.

Table 49: Exponential model results for LTx in PEBD non-responders, PFIC2

Definition of response	Constant term	Standard error	95% CI
≤75% sBA reduction	0.1193	0.040	0.062;0.229

Abbreviations: CI, confidence interval; LTx, liver transplant; PEBD, partial external biliary diversion.

C2. CS page 102. Please clarify the intended meaning of the sentence: "[redacted]."

C2. Company response

This refers to the other pruritus assessments (i.e. secondary endpoints) in PEDFIC1 that were [redacted] with the primary endpoint results, i.e. [redacted] were observed with odevixibat compared to placebo[14]. This included:

- [redacted] night-time and daytime scratching severity compared to placebo, based on the ObsRO
- [redacted] of patients achieving a clinically meaningful reduction in ObsRO pruritus score at weeks 12 and 24 based on the blinded psychometric analysis, compared to placebo
- [redacted] in pruritus symptoms (caregiver-reported scratching based on the ObsRO) with odevixibat over the first 4 weeks of treatment and by Week 8, the proportion of positive pruritus assessments at the patient level for both odevixibat dose groups [redacted] that observed in the placebo group

Data were limited for evaluation of pruritus scores based on the PRO; nonetheless, results for the proportion of positive pruritus assessments at the patient level through Week 24 based on the PRO [redacted] those reported for the ObsRO.

C3. CS Table 21, page 110. The mean percentage difference for [redacted] is inconsistent with that in the text [redacted]. Please clarify this apparent discrepancy.

C3. Company response

The figure in the text is incorrect and should read [redacted].

C4. CS Table 40. Transition probabilities for mortality are referenced as coming from 'Bull et al' and re-transplant as 'meta-analysed/pooled LY mortality sourced'. However, according to section 12.2.1.8 to 12.2.1.9, these sources are the other way around. Please amend the data in Table 40 to align.

C4. Company Response

This was an error and we have amended Table 40 accordingly, please see below.

Table 29. Summary of transition probabilities and their sources

Number on schematic	Transition	Reference
1	Loss of sBA/pruritus response	Assumption
2	PEBD, response	NAPPED study[5,6]
3	PEBD, no response	NAPPED study[5,6]
4	Loss of response to PEBD	Assumption
5	LTx without PEBD	NAPPED study[5,6]
6	LTx after PEBD response	Assumed 0%
7	LTx after PEBD non-response	NAPPED study
8	LTx to post-LTx	General population
9	Re-transplant	Bull et al [15]
-	Mortality	Meta-analysed/pooled LY mortality sourced[16-19]

Abbreviations: LT, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid; TP, transition probabilities.

Additional question asked during clarification call

Please provide additional analyses for PFIC1 and PFIC2 populations.

Please see Addendum A for full results.

Please explain why there were 2 resource/cost studies identified in Figure 38, but these were not subsequently reported in the submission.

This is an omission. The two studies identified are described in Table 30 and Table 31 below. The study by Valamparampil et el was also identified in a previous review that informed the economic modelling (also mentioned in response to A8).[1] Although the second study by Diao et al did report outcomes in patients with PFIC following surgery, the surgery used in the study was of a type not commonly used in the UK (laparoscopic cholecystocolostomy with antireflux Y-loop), and therefore was not considered appropriate for use in the economic model.

Table 30: Included resource identification, measurement and valuation studies

Reference
Diao M, Li L, Zhang JS, Ye M, Cheng W. Laparoscopic cholecystocolostomy: a novel surgical approach for the treatment of progressive familial intrahepatic cholestasis. Annals of surgery. 2013 Dec 1;258(6):1028-33.
Valamparampil J, Shanmugam N, Reddy MS, Rela M. Liver transplantation in progressive familial intrahepatic cholestasis: outcome analysis from a single centre. Transplantation. 2018 May 1;102:141-142.

Table 31: Resource identification, measurement and valuation outcomes

Study name (year)	Objective	Population characteristics	Country	Time period of the study	Population size	Cost outcomes	Resource use outcomes
Diao 2013	Conventionally, liver transplantation, ileoileal bypass, and partial external or internal biliary diversion are used in the treatment of progressive familial intrahepatic cholestasis (PFIC). However, postoperative recurrence, chronic diarrhea, and permanent stoma are the major concerns. We present a novel approach of laparoscopic cholecystocolostomy with antireflux Y-loop for the management of children with PFIC.	20 patients Female 11, male 9 PFIC 1: 10 PFIC 2: 7 PFIC 3: 3 Median (range) age: 1.47 years (10.8 months to 5.11 years)	China and Australia (based on author affiliations)	August 2003 to April 2011	n=20	NR	The mean postoperative hospital stay was 8 days (range: 5–10 days) The average operative time was 2.02 (0.18) hours (range: 2–2.5 hours) Average time for full resumption of diet was 3 days (range: 2–4 days) Patients were followed up in the clinic at 1, 3, 6, and 12 months postoperatively and at 6-month intervals thereafter. Physical examination, abdominal ultrasonography, and liver function tests were carried out at each visit. The median follow-up period was 54 months (range: 12–104 months). Contrast enema studies and colonoscopies were performed at 1- and 3-month follow-up, respectively, to assess the presence and severity of reflux from theY-

							type loop into the biliary system. No blood transfusion was required. Biliary irrigation was carried out with normal saline (10 mL, every day) via epidural catheter for 7 consecutive days. Operation staff were an operating surgeon, assistant, scrub nurse, camera assistant, and anaesthetist.
Valamparampil 2018	To analyse patient demographics, clinical profile, outcomes of 25 children with PFIC who underwent liver transplant and compare with 50 age and sex matched controls with biliary atresia.	25 children Gender NR PFIC1: 7 PFIC2: 7 PFIC3: 10 PFIC4: 1	India (based on author affiliations)	NR	n=25	NR	Duration of hospitalisation following liver transplant was 21 days

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Responses to clarification questions on the submission odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Addendum A – revised economic modelling

Table of contents

List of tables and figures

1 OVERVIEW

Due to the availability of supporting data from the additional studies carried out by Albireo AB, to develop and value vignettes in PFIC (vignette study) and to understand the burden of illness (PICTURE study), we are providing an update to all cost-effectiveness model results (CS section 12.5-12.8). An executive summary of the vignette study and PICTURE study are included within this document. Full study protocols, methodology and results can be found in Addendum B. In response to ERG clarification question B1, the revised base-case and scenario analyses will be described in this document. Further analyses will be presented for PFIC1 and PFIC2 populations; as requested by the ERG during the ERG clarification meeting on the 7th of June 2021. We have additionally submitted an updated PAS Evidence Submission template that reflects these changes and a two full Excel models (covering both list and PAS prices).

2 Executive summary

Burden of Illness study (PICTURE study)

The PICTURE study aims to examine the substantial burden and unmet medical need of PFIC and support the evidence base for this community. The primary object of the study is to estimate resource use and the financial burden of caregivers. Interim results were incorporated into the CS on the 10th May 2021. Final resource use and societal perspective results have been included in the updated model. Please see Addendum B for data and methodology used.

Vignette study

Albireo AB recently conducted a study to develop and value vignettes in PFIC (vignette study), following a recommendation from the BMJ Technology Assessment Group (BMJ-TAG) during the NICE decision problem meeting on the 23rd February 2021. During this meeting the limited amount of quality-of-life data available from the trial for both response

and non-response treatment groups was discussed; BMJ-TAG encouraged consideration of a vignette study to address this uncertainty.

A time-trade-off (TTO) approach was undertaken during the vignettes, interviewing 95 general public respondents. The final vignette results provide alternative data for considering the utility values and decrements associated with response and non-response health states.

However, the draft vignettes were found to not be fully descriptive of the presence of a primary external biliary diversion (PEBD), and fail to provide a strong foundation to assess the range of uncertainty in the additional quality of life (QoL) benefit from avoiding PEBD (in both the response and non-response states). Therefore, Albireo AB have commissioned additional vignette and patient/carer survey work to consider more fully the sensitive to the impact on QoL of the PEBD health state (please see below). This will be presented as an additional scenario analysis to our revised base-case. For full methodology and vignette data please see Addendum B.

Ongoing study - Estimation of the disutility associated with PEBD

Albireo AB are conducting a follow-up study with one leading physician and several families affected by liver disease in order to undertake qualitative research to better understand and characterise the burden of PEBD for children. The interviews will take place with a parent of an affected child, and they will be asked to describe how the PEBD has affected their child. This will explore symptom relief, and general liver health (since the drain was inserted) as well as the impact of the drain on the child, how they accommodate it, any problems experienced and if it limits their day-to-day life.

Following the qualitative component, the participants will be asked to review a vignette describing a PFIC patient with PEBD and a second vignette where there is no PEBD. For each vignette the parent or physician will be asked to complete the EQ-5D as a proxy assessment of how such a child (as described in the vignette) would be affected. The EQ-5D data will be scored and summarised.

3 List of amendments implemented

Table 1 lists the updates to the economic model since the company submitted in May 2021, to reflect the amendments made to the revised base case and scenarios in

response to the Evidence Review Group (ERG) clarification questions received in May 2021.

Table 1: Economic model updates

#	Updates	In response to	Sheet – cells reference
1	HRQoL scenarios using: 1) vignette study results (TTO and EQ-5D), 2) vignette study and PEBD multiplier in post-PEBD states, 3) change from baseline EQ-5D (PEDFIC 1)	B7, B35	Key results – C34:35 HRQoL data – E18:23 QoL mapping – rows 99:110
2	Approach to weight-based dosing updated using assumed standard deviation & age groups	B30	General population – B82:O108
3	Discount rate changed to 3.5%	B8	Key results – C14:15
4	Cholestyramine + rifampicin doses corrected for adults (>18) Rifampicin dose corrected for children	B31	Cost data – E24:F29 Engines – columns BE, BF and BG
5	Medical resource use updated with final burden of illness (PICTURE) study results	-	Cost data – C49:H61, C68:D80
6	Societal perspective updated with final burden of illness (PICTURE) study results	-	Cost data – C157:D157, C161:162
7	Correction to the application of general population age multiplier	B41	HRQoL data – C48:C144
8	Correction of post-liver transplantation (LTx) costs in all post-LTx patients	B42	Engines – column Z
9	Post-LTx mortality meta-analysis updated to include an additional 6 studies from a later SLR and pooled analysis of long-term mortality updated	A8, B25	Clinical data - Efficacy – G102, F111
10	Removed re-transplant health state column	B4	Transitions – column AA

4 List of scenarios

Albireo AB has examined the impact of varying and underlying data and assumptions in the model on the odevixibat versus standard of care (SoC) ICER; the data value and sources explored include. Table 2 which provides a summary of the different scenarios explored, as follows:

Perspective:

The perspective of costs and outcomes is that of NHS and PSS in England and Wales, in line with NICE guidance[1]. The perspective for outcomes and costs includes direct and indirect costs and health effects on patients and their caregivers. A scenario without societal costs and effects has been conducted, in line with the NICE reference case.

Utility values:

Patient reported estimates from the literature will remain in the company's base case. Albireo has recently conducted a study to develop and value vignettes in PFIC (vignette study). The vignette study was designed to elicit societal utility values for a series of health states in PFIC to support economic modelling for the odevixibat submission. The vignette study provides a valuable alternative source of utility data, demonstrating the significant impact of disease on patients as well as the difference in quality of life in patients responding to treatment. Due to the limited time conducting the vignette and limited literature available for patients with PEBD, the vignette approach was not sensitive enough to fully elicit the utility impact from having a PEBD. A single descriptive line was described in the response vignette, "*You have a small tube that drains fluid from your tummy into a bag",* alluding to a factual statement. The reality of living in the PEBD health state has therefore not been captured within the vignettes.

External stoma bags from PEBD contribute to a number of negative feelings among patients, including fears about social life and insecurity by reintegration of previous social roles and functions[2] (see CS section 8.2.5). Patients who have undergone PEBD will experience a psychosocial transition and will encounter various challenges along their journey.[3]

Stoma care has a tremendous impact on both patient and family.[4] Contrary to the vignette description, young patients report emotional distress and half of patients experience psychological problems in the long-term, manifesting into low moods and anxiety.[3] In addition to psychological problems, patients may encounter physiological complications associated with stomas such as leakage, infection, odour, fatigue, pain, deterioration of sleep and skin irritation.[5]

Although PEBD can be beneficial the impact of this procedure should not be underestimated.

Albireo AB is currently undertaking additional analysis, focusing on the impact of having a stoma bag in patients who have undergone PEBD and/or patients that have a liver disease. The objective of this study is to yield an accurate stoma bag disutility value that can be applied as a multiplier to patients in the “PEBD response and non-response” health states, reducing the uncertainty around the current vignette data for PEBD health state. This data will provide a range of values associated with stoma bag disutility. The values will be included as an additional scenario once the study meets completion (June 30th 2021) and will not affect the revised base case.

In summary, the current vignette results, both TTO and EQ-5D data have been informed by the vignette study conducted in May and provided as a scenario analysis, alongside PEDFIC1 baseline characteristics, as requested in ERG clarification question B36.

The current stoma bag disutility multiplier is applied to the current vignette data and has been included as an exploratory analysis. The source for the stoma-bag disutility multiplier will be informed by ulcerative colitis study, being the preferred source validated by an expert clinician.

Treatment duration:

In the model, treatment duration with odevixibat is assumed until loss of treatment response. In practice clinicians are likely to keep patients on 40µg/kg dose for a longer duration, therefore treatment until surgery is explored as a scenario.

Response to odevixibat:

Response to odevixibat is assumed equivalent to the primary trial endpoint observed in PEDFIC1 trial – sBA reduction. According to expert consultation, these patients are assumed to have an improvement in pruritus following their positive sBA response. Response to odevixibat is assessed using sBA and pruritus response in the model, however using pruritus as the definition of response is deemed more suitable than the primary trial endpoint of sBA reduction (see CS section 12.2.1.1).

Exploratory scenarios

Several exploratory analyses of scenarios were conducted – both optimistic and pessimistic, within the model as follows:

- Estimates for liver-transplantation (LTx)-related mortality have been sourced from meta-analyses and pooled estimates (see ERG clarification response B25)
    - NHS transplant data has been included as a scenario and reflects year-one mortality in children with LTx for any indication between 2013 and 2018 in the UK.
- Odevixibat is assumed clinically equivalent to PEBD
    - The model assumes if a patient does not respond to odevixibat they will not respond to PEBD
    - The option of receiving PEBD prior to odevixibat treatment has been explored
- Annual loss of response to odevixibat is assumed [redacted] (see ERG clarification response B9)
    - Odevixibat is expected to replace PEBD within the treatment pathway, therefore the same PEBD withdrawal rate is assumed – 5%
    - This has been validated by a clinical expert in the UK
- Annual loss of response to PEBD is assumed 5% (see ERG clarification response B13)
    - Odevixibat is expected to replace PEBD within the treatment pathway, therefore the same odevixibat withdrawal rate is assumed – [redacted], validated by a clinical expert
    - A 10% loss of annual response to PEBD rate is included as an exploratory analysis
- 27% of patients observed in PEDFIC1 were PFIC1 patients
    - In practice, the proportion of PFIC1 patients maybe higher than those seen in PEDFIC1
- Adverse event costs were not included in the base case (please see ERG clarification response B26)

    - Common treatment-emergent adverse events occurring in greater than 5% of patients were included as an exploratory analysis
- Growth curves used for weight-based dosing is currently 25th percentile until year 1, 33rd percentile until year 2, 50th percentile thereafter, UK growth curved
    - 25th percentile has been explored assuming patients are under-weight for age
    - Patients in the model start on odevixibat at 4.25 years as per the mean age at baseline in PEDFIC1 trial. In reality newly diagnosed patients will start odevixibat a lot earlier, categorising them in the lower weight band
- Probability of pruritus response in SoC
    - In response to ERG clarification question **B12a**
    - Pruritus response in SoC set to [redacted] with [redacted], [redacted] and [redacted] loss of response per year
    - Results are presented in the company's response to ERG clarification questions (June 2021), response **B12a**
- Probability of PEBD surgery
    - In response to ERG clarification question **B18**
    - Scenario analyses varying the annual probability of PEBD from 0% to 4% in 1% increments
    - Results are presented in the company's response to ERG clarification questions (June 2021), response **B18**

Table 2. Summary of scenarios

Scenario	Parameter	Base-case	Scenario
1	Perspective	Societal	NHS
2	LTx mortality	Meta analyses and pooled estimates from literature	NHS data
3	Quality of life	Patient reported estimates from the literature	Vignette – EQ-5D
4			Vignette - TTO
5			PEDFIC1 change from baseline (CFB)analysis
6			Vignette – TTO + stoma bag multiplier
7			Vignette – EQ-5D + stoma bag multiplier
8	Source of stoma bag disutility	Ulcerative colitis study	Colorectal cancer study
9	Time on treatment with odevixibat	Until loss of response	Until surgery
10	PEBD in odevixibat arm	Excluded	Include
11	Response assessment	sBA and pruritus	Pruritus only
12	Annual loss of response to odevixibat	[redacted]	5%
13	Annual loss of response to PEBD	5%	[redacted]
14			10%
15	Proportion of PFIC1	27%	50%
16	Adverse event costs	Not applied	Include
17	Growth curve used for weight-based dosing	25th percentile until year 1, 33rd percentile until year 2, 50th percentile thereafter, UK growth curved	25th percentile

5 Economic analysis

5.1 Results of economic analysis

5.1.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme.

In the base case, the ICER for odevixibat versus SoC is [redacted] per QALY gained. Total and incremental results for costs, life-years and QALY gains are presented in

Table 3 and Table 4. As per the response to ERG questions (see Table 1) the following changes have been applied to the base-case:

- Weight-based dosing has been updated and using standard deviation and age groups
- All model costs and effects have been discounted at 3.5%
- Doses for cholestyramine and rifampicin have been correct
- Updated results from the PICTURE study

Table 3: Base-case results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.54	[redacted]				
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 4: Base-case results – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.54	[redacted]				
Odevixibat	[redacted]	22.40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

5.1.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The following clinical outcomes were modelled:

- Years with response
- Years with loss of response
- Years in LTx
- Years in post-LTx

Modelled results could not be compared to those reported in the clinical trials, as long-term outcomes data are not available from the clinical studies (please see Table 5).

Table 5: Summary of model results

Outcome	**Standard of care**	**Odevixibat**
Years with response	0.00	14.88
Years with loss of response	7.93	12.84
Years in PEBD	8.38	0.00
Years in LTx	1.05	0.99
Years in Post-LTx	31.29	26.96

5.1.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The proportion of patients in response, loss of response, PEBD, LTx, post LTx and mortality for both odevixibat and SoC are presented in Figure 1 and Figure 2 for the full lifetime time horizon.

Figure 1: Health states - standard of care

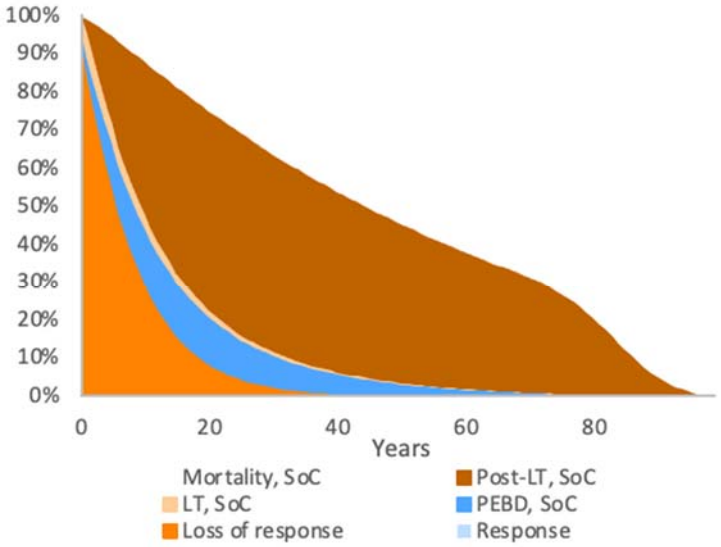
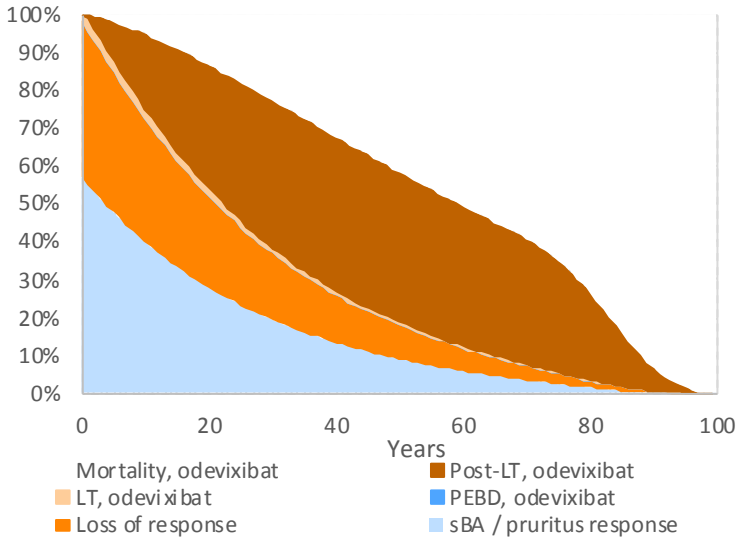


Figure 2: Health states - odevixibat arm



5.1.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time

The QALYs accrued over time for the first 20 years for both odevixibat and SoC are presented in Table 6. Graphical representations are presented in Figure 3 for the full-time horizon.

Table 6: Accrued QALYs (first twenty years only)

Year	Odevixibat	SoC
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]
19	[redacted]	[redacted]
20	[redacted]	[redacted]

Figure 3: Accrued QALYs

[redacted]

5.1.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 5 and Table 7 show life year gains and QALY gains disaggregated by health state.

Table 7: Model outputs by clinical outcomes - QALY

	Standard of care	**Odevixibat**
QALYs with response	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]
QALYs LTx	[redacted]	[redacted]
QALYs Post-LTx	[redacted]	[redacted]

5.1.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table 8 shows a summary of QALY gains by health state. Just over half of the QALY gains ([redacted]) were due to patients responding to treatment; post-liver transplant accounted for [redacted] of the QALY gains.

Table 8: Summary of QALY gain by health state

Health state	QALY Odevixibat	QALY Standard of care	Increment	Absolute increment	% absolute increment
QALYs with response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALYs LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrements	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

5.1.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

Total undiscounted QALYs for treatment with odevixibat was [redacted] compared to [redacted] for standard of care over a lifetime time horizon, resulting in an incremental benefit of [redacted].

5.1.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table D12.

A summary of costs by category per patient are provided in Table 9 and Table 10 for both odevixibat and SoC.

Table 9: Summary of costs by category of cost per patient – PAS price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 10: Summary of costs by category of cost per patient – list price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

5.1.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Table D13.

Costs for technology and comparator by health state are summarised in Table 9 and Table 10.

5.1.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Table D14.

Not applicable.

Sensitivity analysis results

5.1.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Results for the ten most influential parameters identified by univariate sensitivity analysis are presented in Table 11 and Figure 4 at PAS price; and Table 12 and Figure 5 at list price.

Table 11: One-way sensitivity analysis results – PAS price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
PAS discount	[redacted]	[redacted]	[redacted]	[redacted]
Response to odevixibat - sBA & pruritus response - uptitrators	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
PEBD hazard, PFIC 2	[redacted]	[redacted]	[redacted]	[redacted]
Work impairment - loss of response	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - school score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
% LT, without PEBD, PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
sBA≥118 PedsQL - school score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant - transplant phase cost (Singh et al)	[redacted]	[redacted]	[redacted]	[redacted]
% LT, with PEBD, no response, PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]

Table 12: One-way sensitivity analysis results – list price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
Response to odevixibat - sBA & pruritus response - uptitrators	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - emotional score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Post-LT PedsQL - school score	[redacted]	[redacted]	[redacted]	[redacted]
Post-LT PedsQL - social score	[redacted]	[redacted]	[redacted]	[redacted]
% LT, without PEBD, PFIC 2	[redacted]	[redacted]	[redacted]	[redacted]
Work impairment - loss of response	[redacted]	[redacted]	[redacted]	[redacted]
% LT, with PEBD, no response, PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
Pre-transplant mortality - PFIC 2	[redacted]	[redacted]	[redacted]	[redacted]
% PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]

Figure 4: Change in ICER - PAS price

Figure 5: Change in ICER – list price

5.1.12 Present results of deterministic multi-way scenario sensitivity analysis

Table 13: Scenario analysis

Parameter	Scenarios	ICER - List	ICER - PAS
Base case		[redacted]	[redacted]
Perspective	NHS	[redacted]	[redacted]
LTx mortality	NHS data	[redacted]	[redacted]
Quality of life	Vignette – EQ-5D	[redacted]	[redacted]
Quality of life	Vignette - TTO	[redacted]	[redacted]
Quality of life	PEDFIC1 CFB analysis	[redacted]	[redacted]
Quality of life	Vignette EQ-5D + stoma bag disutility multiplier	[redacted]	[redacted]
Quality of life	Vignetter TTO + stoma bag disutility multiplier	[redacted]	[redacted]
Source of stoma bag disutility	Colorectal cancer study	[redacted]	[redacted]
Time on treatment with odevixibat	Until surgery	[redacted]	[redacted]
PEBD in odevixibat arm	Include	[redacted]	[redacted]
Response assessment	Pruritus only	[redacted]	[redacted]
Annual loss of response to odevixibat	5%	[redacted]	[redacted]
Annual loss of response to PEBD	[redacted]	[redacted]	[redacted]
Annual loss of response to PEBD	10%	[redacted]	[redacted]
Proportion of PFC 1	50%	[redacted]	[redacted]
Adverse event costs	Include	[redacted]	[redacted]
Growth curve used for weight-based dosing	25th percentile	[redacted]	[redacted]

5.1.13 Present results of the probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) – PAS price

PSA simulations were plotted on the cost-effectiveness plane (**Error! Not a valid bookmark self-reference.**) and a CEAC was generated (

Figure 7). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted]

Figure 6: Cost effectiveness plane – PAS price

Figure 7: Cost-effectiveness acceptability curve – PAS price

PSA – List price

PSA simulations were plotted on the cost-effectiveness plane (**Error! Not a valid bookmark self-reference.**) and a CEAC was generated (Figure 9). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted] this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted] and [redacted] respectively.

Figure 8: Cost effectiveness plane – list price

Figure 9: Cost-effectiveness acceptability curve – list price

5.1.14 What were the main findings of each of the sensitivity analyses?

The most influential parameter for both list price and PAS is the response to odevixibat - sBA & pruritus response – up-titrators. As anticipated the quality-of-life impact of PEBD (stoma bag) is influential on the ICER, validating the need for the additional work commissioned by Albireo AB.

Scenario analyses demonstrated that the ICER is sensitive to treatment duration with odevixibat for both list and PAS price. The majority of ICERs remained below the maximum threshold of [redacted], in all scenarios modelled for PAS price.

The mean PSA results for PAS price lie very close to the deterministic base-case results (Table 4). Odevixibat accrued [redacted] at cost of [redacted] compared to SoC. The corresponding ICER was [redacted] QALY gained.

5.1.15 What are the key drivers of the cost results?

The key driver of cost results is the price of odevixibat, time spent on odevixibat, and the impact of a stoma bag.

Miscellaneous results

5.1.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

5.2 Validation

5.2.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

In line with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) taskforce report on model transparency and validation[1] [6], the following types of validation were conducted:

1) Face validation
2) Internal validation
3) Cross validation
4) External validation

[1] Note that no attempt was made to conduct a predictive validation (the fifth validation type specified in the ISPOR taskforce report)

Face validity

Interviews with clinical experts (including a [redacted]) and an academic health economist were conducted to review the model decision problem, structure, and data use. Following the availability of results from PEDFIC 1, additional interviews with experts and an advisory board were conducted to evaluate the data used in the model.

External validity

Outputs of the model were compared against the outcomes observed in the clinical trial to evaluate the internal consistency of the model.

5.3 Interpretation of economic evidence

5.3.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The economic model represents the most valid characterisation of PFIC modelling. Modelling decisions are based on the primary endpoint reported in PEDFIC1 and clinician input.

5.3.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The cost-effectiveness analysis does not include patients with subtypes of PFIC other than PFIC1 and PFIC2, however odevixibat will be used to treat all subtypes (see section **Error! Reference source not found.**). In addition, clinicians may wish to treat some patients with the episodic forms of PFIC1 and PFIC2 (BRIC1 and BRIC2).

5.3.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A key strength of this analysis is the use of trial endpoints in the model for a number of inputs, and their consistency with endpoints from the NAPPED study, which enabled modelling disease progression based on clinically meaningful sBA/pruritus thresholds.

An additional strength is that a wide range of scenarios have been considered, to test model sensitivity to parameters for which multiple sources were available (e.g. rate of LTx, mortality, and quality of life).

A key limitation of the analysis is the paucity of data and the vignette data for PEBD. Where possible, data specific to PFIC were used (e.g. NAPPED, PEDFIC 1), but small patient numbers and the limited number of studies available on outcomes in PFIC1 and PFIC2 result in a significant level of uncertainty in the model's outcomes.

5.3.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Albireo AB is currently undertaking further analysis to accurately estimate the QoL impact of patients having a stoma bag as a result of PEBD surgery and/or other patients that have a liver disease. Results from the study are intended to reduce uncertainty around QoL parameters and produce robust results. The results will be included as a scenario analysis at the end June.

[redacted] will provide further data that can be included in the economic analysis in the longer term.

6 Additional analysis requested by ERG

The ERG requested additional analysis for the separate populations, PFIC1 and PFIC2. This section will explore the different populations using both PAS and list price.

6.1.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme.

PFIC1

Table 14:Base case results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	21.18	[redacted]				
Odevixibat	[redacted]	22.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 15: Base case results – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	21.18	[redacted]				
Odevixibat	[redacted]	22.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

PFIC2

Table 16: Base case results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.34	[redacted]				
Odevixibat	[redacted]	22.27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 17: Base case results – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard care	[redacted]	20.34	[redacted]				
Odevixibat	[redacted]	22.27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

6.1.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 18: Summary of model results – PFIC1

Outcome	Standard of care	Odevixibat
Years with response	0.00	14.88
Years with loss of response	9.33	16.58
Years in PEBD	11.85	0.00
Years in LTx	0.95	0.89
Years in Post-LTx	29.06	25.04

Table 19: Summary of model results – PFIC2

Outcome	Standard of care	Odevixibat
Years with response	0.00	14.88
Years with loss of response	7.49	11.81
Years in PEBD	7.56	0.00
Years in LTx	1.09	1.03
Years in Post-LTx	31.78	27.42

6.1.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure 10: PFIC1 Health states – standard of care

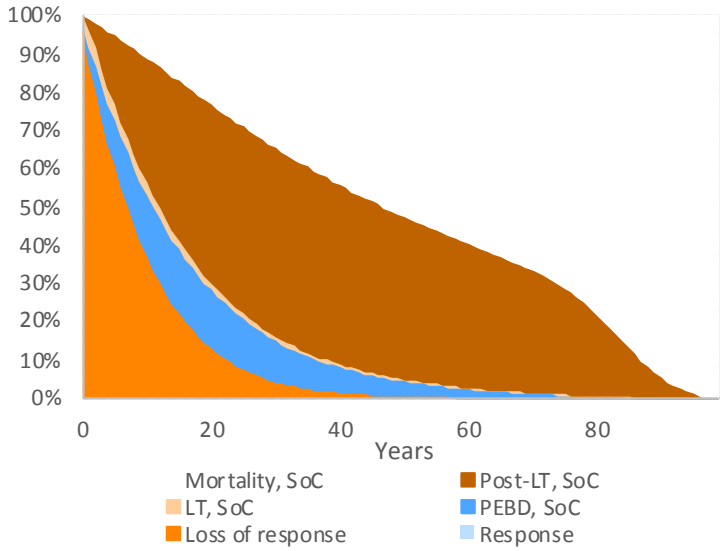


Figure 11: PFIC1 Health states - Odevixbat

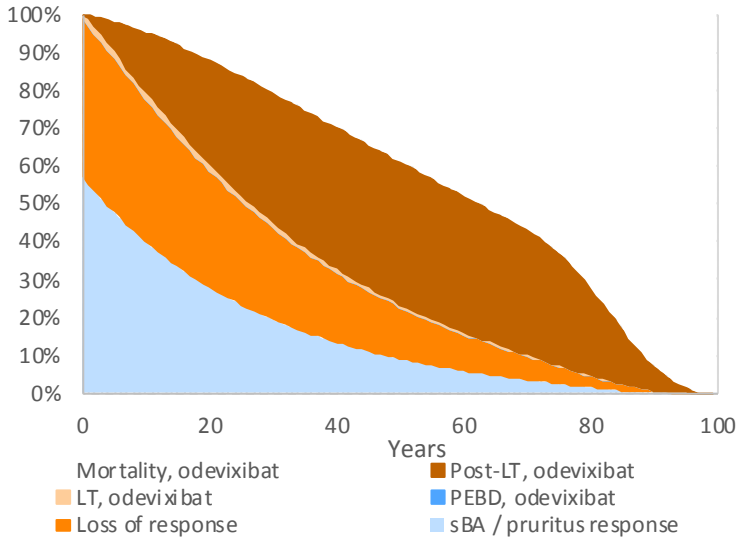


Figure 12: PFIC2 Health states – standard of care

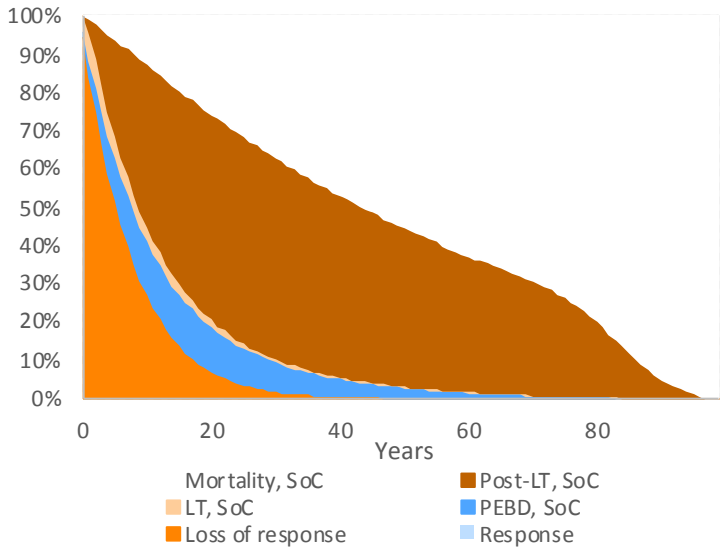
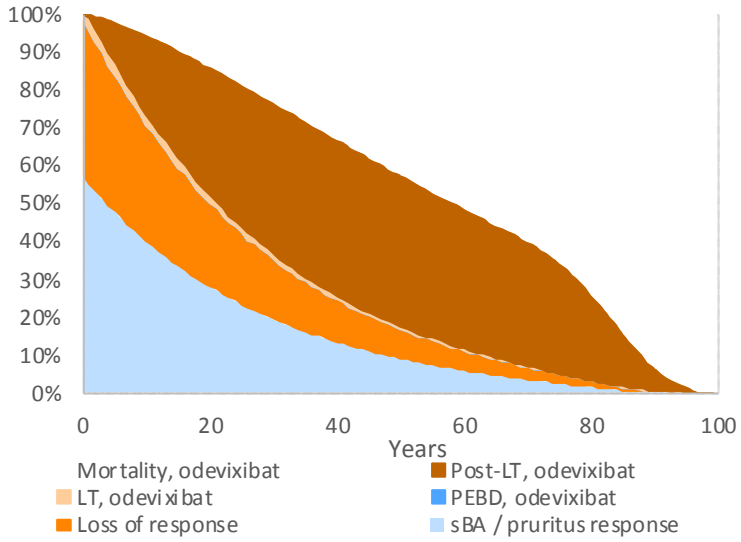


Figure 13: PFIC2 Health states - Odevixibat



6.1.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table 20: PFIC1 Accrued QALYs (twenty years only)

Year	Odevixibat	SoC
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]
19	[redacted]	[redacted]
20	[redacted]	[redacted]

Figure 14: PFIC1 Accrued QALYs

Table 21: PFIC2 Accrued QALYs (twenty years only)

Year	Odevixibat	SoC
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]
19	[redacted]	[redacted]
20	[redacted]	[redacted]

Figure 15: PFIC2 Accrued QALYs

6.1.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 22: PFIC1 Model outputs by clinical outcomes - QALY

	Standard of care	**Odevixibat**
QALYs with response	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]
QALYs LTx	[redacted]	[redacted]
QALYs Post-LTx	[redacted]	[redacted]

Table 23: PFIC2 Model outputs by clinical outcomes - QALY

	Standard of care	Odevixibat
QALYs with response	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]
QALYs LTx	[redacted]	[redacted]
QALYs Post-LTx	[redacted]	[redacted]

6.1.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table 24: PFIC1- Summary of QALY gain by health state

Health state	QALY Standard of care	QALY Odevixibat	Increment	Absolute increment	% absolute increment
QALYs with response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrements	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY, quality-adjusted life year Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 25: PFIC2 - Summary of QALY gain by health state

Health state	QALY Standard of care	QALY Odevixibat	Increment	Absolute increment	% absolute increment
QALYs with response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PEBD no response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALYs Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrements	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY, quality-adjusted life year
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

6.1.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

PFIC1

Total undiscounted QALYs for treatment with odevixibat was [redacted] compared to [redacted] for standard of care over a lifetime time horizon, resulting in an incremental benefit of [redacted]

PFIC2

Total undiscounted QALYs for treatment with odevixibat was [redacted] compared to [redacted] for standard of care over a lifetime time horizon, resulting in an incremental benefit of [redacted]

6.1.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table D12.

Table 26: PFIC1 Summary of costs by category of cost per patient – PAS price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 27: PFIC1 Summary of costs by category of cost per patient – list price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 28: PFIC2 Summary of costs by category of cost per patient – PAS price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 29: PFIC2 Summary of costs by category of cost per patient – list price

Item	Cost odevixibat	Cost standard of care	Increment	Absolute increment	% absolute increment
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost productivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Sensitivity analysis results

6.1.9 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Results for the ten most influential parameters identified by univariate sensitivity analysis are presented below.

Table 30: PFIC1 One-way sensitivity analysis results – PAS price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
PAS discount	[redacted]	[redacted]	[redacted]	[redacted]
Response to odevixibat - sBA & pruritus response - uptitrators	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
Post-LT PedsQL - emotional score	[redacted]	[redacted]	[redacted]	[redacted]
Average weekly wage	[redacted]	[redacted]	[redacted]	[redacted]
Response to PEBD - PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
Work impairment - response	[redacted]	[redacted]	[redacted]	[redacted]
Pre-transplant mortality - PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant - transplant phase cost (Singh et al)	[redacted]	[redacted]	[redacted]	[redacted]
Naltrexone - Mg/unit	[redacted]	[redacted]	[redacted]	[redacted]

Table 31: PFIC1 One-way sensitivity analysis results – list price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
Response to odevixibat - sBA & pruritus response - uptitrators	[redacted]	[redacted]	[redacted]	[redacted]

Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - emotional score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - school score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Response to PEBD - PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
Post-LT PedsQL - social score	[redacted]	[redacted]	[redacted]	[redacted]
% female	[redacted]	[redacted]	[redacted]	[redacted]
% PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
Work impairment - response	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant - transplant phase cost (Singh et al)	[redacted]	[redacted]	[redacted]	[redacted]

Figure 16: PFIC1 Change in ICER - list price

[redacted]

Figure 17: PFIC1 Change in ICER - list price

Table 32 PFIC2 One-way sensitivity analysis results – PAS price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
PAS discount	[redacted]	[redacted]	[redacted]	[redacted]
Response to odevixibat - sBA & pruritus response - uptitrators	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - emotional score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Average weekly wage	[redacted]	[redacted]	[redacted]	[redacted]
% LT, without PEBD, PFIC 2	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - school score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant - transplant phase cost (Singh et al)	[redacted]	[redacted]	[redacted]	[redacted]

Work impairment - response	[redacted]	[redacted]	[redacted]	[redacted]
Re-transplant rate - PFIC 2	[redacted]	[redacted]	[redacted]	[redacted]
Naltrexone - Mg/unit	[redacted]	[redacted]	[redacted]	[redacted]

Table 33 PFIC2 One-way sensitivity analysis results – list price

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change from base-case at lower value	% change from base-case at upper value
Response to odevixibat - sBA & pruritus response - uptitrators	[redacted]	[redacted]	[redacted]	[redacted]
Healthy PedsQL - emotional score (Kamath 2015)	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of stoma bag - ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
Post-LT PedsQL - school score	[redacted]	[redacted]	[redacted]	[redacted]
Post-LT PedsQL - social score	[redacted]	[redacted]	[redacted]	[redacted]
Response to PEBD - PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
Re-transplant rate - PFIC 2	[redacted]	[redacted]	[redacted]	[redacted]
% female	[redacted]	[redacted]	[redacted]	[redacted]
% PFIC 1	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant - transplant phase cost (Singh et al)	[redacted]	[redacted]	[redacted]	[redacted]

Figure 18:PFIC2 Change in ICER - PAS price

Figure 19: PFIC2 Change in ICER - list price

6.1.10 Present results of deterministic multi-way scenario sensitivity analysis

Table 34: PFIC1 Scenario analysis

Parameter	Scenarios	ICER - List	ICER - PAS
Base case		[redacted]	[redacted]
Perspective	NHS	[redacted]	[redacted]
LTx mortality	NHS data	[redacted]	[redacted]
Quality of life	Vignette – EQ-5D	[redacted]	[redacted]
Quality of life	Vignette - TTO	[redacted]	[redacted]
Quality of life	PEDFIC1 CFB analysis	[redacted]	[redacted]
Quality of life	Vignette EQ-5D + stoma bag disutility multiplier	[redacted]	[redacted]
Quality of life	Vignette TTO + stoma bag disutility multiplier	[redacted]	[redacted]
Source of stoma bag disutility	Colorectal cancer study	[redacted]	[redacted]
Time on treatment with odevixibat	Until surgery	[redacted]	[redacted]
PEBD in odevixibat arm	Include	[redacted]	[redacted]
Response assessment	Pruritus only	[redacted]	[redacted]
Annual loss of response to odevixibat	5%	[redacted]	[redacted]
Annual loss of response to PEBD	[redacted]	[redacted]	[redacted]
Annual loss of response to PEBD	10%	[redacted]	[redacted]
Adverse event costs	Include	[redacted]	[redacted]
Growth curve used for weight-based dosing	25th percentile	[redacted]	[redacted]

Table 35: PFIC2 Scenario analysis

Parameter	Scenarios	ICER - List	ICER - PAS
Base case		[redacted]	[redacted]
Perspective	NHS	[redacted]	[redacted]
LTx mortality	NHS data	[redacted]	[redacted]
Quality of life	Vignette – EQ-5D	[redacted]	[redacted]
Quality of life	Vignette - TTO	[redacted]	[redacted]
Quality of life	PEDFIC1 CFB analysis	[redacted]	[redacted]
Quality of life	Vignette EQ-5D + stoma bag disutility multiplier	[redacted]	[redacted]
Quality of life	Vignette TTO + stoma bag disutility multiplier	[redacted]	[redacted]
Source of stoma bag disutility	Colorectal cancer study	[redacted]	[redacted]
Time on treatment with odevixibat	Until surgery	[redacted]	[redacted]
PEBD in odevixibat arm	Include	[redacted]	[redacted]
Response assessment	Pruritus only	[redacted]	[redacted]
Annual loss of response to odevixibat	5%	[redacted]	[redacted]
Annual loss of response to PEBD	[redacted]	[redacted]	[redacted]
Annual loss of response to PEBD	10%	[redacted]	[redacted]
Adverse event costs	Include	[redacted]	[redacted]
Growth curve used for weight-based dosing	25th percentile	[redacted]	[redacted]

6.1.11 Present results of the probabilistic sensitivity analysis

PFIC1

PSA – PAS price

PSA simulations were plotted on the cost-effectiveness plane (**Error! Not a valid bookmark self-reference.**) and a CEAC was generated (

Figure 7). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted]

Figure 20: PFIC1 Cost effectiveness plane – PAS price

Figure 21: PFIC1 Cost-effectiveness acceptability curve – PAS price

PSA – list price

PSA simulations were plotted on the cost-effectiveness plane (**Error! Not a valid bookmark self-reference.**) and a CEAC was generated (Figure 23). The average

incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted]

Figure 22: PFIC1 Cost effectiveness plane – List price

Figure 23: PFIC1 Cost-effectiveness acceptability curve – List price

PFIC2

PSA – PAS price

PSA simulations were plotted on the cost-effectiveness plane (Figure 24) and a CEAC was generated (Figure 25). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted]

Figure 24: PFIC2 Cost effectiveness plane – PAS price

[redacted]

Figure 25: PFIC2 Cost-effectiveness acceptability curve – PAS price

PSA – list price

PSA simulations were plotted on the cost-effectiveness plane (

Figure 26) and a CEAC was generated (Figure 27). The average incremental costs over the simulated results were [redacted] and average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs. The proportion of simulations considered cost-effective at a threshold of £100,000 and £300,000 per QALY was [redacted]

Figure 26: PFIC2 Cost effectiveness plane – List price

Figure 27: Cost-effectiveness acceptability curve – List price

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Responses to clarification questions on the submission odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Addendum B

Table of contents

List of tables and figures

1 Introduction

This addendum presents two studies in children with progressive familial intrahepatic cholestasis (PFIC) that support the revised economic case for odevixibat:

- The PICTURE study characterised the economic, humanistic and societal burden of PFIC experienced by caregivers, patients, health systems and society across the United Kingdom (UK), France, Germany and United States (US).
- A vignette study was conducted to estimate the benefits of treatment with odevixibat in children with PFIC in terms of gains in quality-adjusted life years (QALYs). QALY estimation requires utility data, and a vignette study is designed to capture this type of data.

Data from these two studies have been incorporated into the updated economic model – please see file *ID1570 odevixibat response to clarification questions Addendum A (revised economic modelling).docx*.

2 PICTURE study

2.1 Introduction

Although PFIC is an ultrarare disease, the burden it places on paediatric patients and their caregivers, as well as the high mortality rates in this population highlight that there is a high amount of unmet need for more efficacious treatments. At the moment, there is no comprehensive study to document the clinical, humanistic and socio-economic burden faced by patients and their families, on a societal level.

With a high unmet need comes a great potential for new therapies to offer dramatic changes in HRQoL. However, without data on the 'real life' burden and costs of PFIC, it is difficult to gauge the potential impact and gains that new lines of treatment could offer. Therefore, a thorough examination of all aspects of the PFIC disease burden is needed to fill the current research gap. To gain a patient- and caregiver-level understanding of the PFIC burden, a cross-sectional, observational burden of illness study is being conducted across four countries: UK, France, Germany and US.

The aim of the PICTURE (**P**rogressive Familial **I**ntrahepatic **C**holes**t**asis Disease B**ur**d**e**n of Illness) study was to characterise the economic, humanistic and societal burden of PFIC experienced by caregivers, patients, health systems and society across the UK, France, Germany and US (Ruiz-Casas et al. 2021). PICTURE is a non-interventional study conducted in accordance with University of Chester (UoC) ethical standards. The study is completed and its results have recently become available, which are shown in the present document in Section 2.9.

The primary objective of the PICTURE study is to quantify the overall economic and humanistic burden on PFIC patients, on their caregivers and ultimately on society overall. The secondary objectives are to determine (a) the existing PFIC-related resource use and associated costs for patients and their caregivers and ultimately societies, and (b) the

impact of PFIC on patients and caregiver's quality of life using patient and caregiver-reported outcomes measurements for each country.

2.2 Protocol synopsis

The study protocol is summarised in Table 1 and described in the next subsections.

Table 1: PICTURE study protocol synopsis

Title	PICTURE Study: Progressive Familial Intrahepatic Cholestasis Disease Burden of Illness: Quantifying the socio-economic burden in the United Kingdom, France, Germany and United States
Principal investigator	Prof. Alan Finnegan
Collaborators	HCD Economics M3 (Fieldwork Company) University of Chester Children's Liver Disease Foundation Progressive Familial Intrahepatic Cholestasis Advocacy and Resource Network
Supporter	Albireo
Rationale	There is a lack of extensive up-to-date real-world evidence documenting the clinical, humanistic, economic and societal burden of progressive familial intrahepatic cholestasis (PFIC) patients and caregivers.
Primary objectives	The primary objective of this study is to quantify the overall economic and humanistic burden on PFIC patients and their caregivers, and ultimately on society overall.
Secondary objectives	Determine the existing PFIC-related resource use and associated costs for patients and their caregivers, and ultimately societies. Determine the impact of PFIC on the quality of life of patients and their caregivers using caregiver-reported outcomes measurements for each country.

Study design	Observational and cross-sectional, international (United Kingdom, France, Germany and United States of America), and multi-site burden of illness study consisting of a retrospective patient chart review with abstraction of natural history of disease data also capturing patient direct medical resource utilisation profile over a period of 12 months. Cross-sectional patient- and caregiver-reported outcomes to document the health-related quality of life (HRQoL) and non-medical direct or indirect costs for the same patients (and their caregivers) at the index date.
Study population	Patients with known genetic diagnosis of PFIC (progressive familial intrahepatic cholestasis) including: Main population: PFIC subtypes 1 and 2 (minimum quota required, see Section 2.4.4) Additional subgroups allowed: PFIC 3 (no minimum quota required)
Study duration	Main enrolment period from September 2020 to March 2021 (included). Documentation period: Diagnosed population data analysis and results by May 2021.
Statistical methods	Descriptive analysis: minimum, maximum, mean/median, interquartile range values for continuous variables and frequencies and percentages for categorical variables with 95% confidence intervals.
Sample size	Approximately 225 patients in total will be enrolled in the study (main sample). As the study is descriptive, no power calculation was undertaken.
Endpoints	The existing PFIC-related costs for patients will include: • Health direct PFIC costs: prescribed drugs including concomitant medications, healthcare professional visits, hospitalisations, procedure for disease management. • Non-health direct costs: travel and accommodation costs, other over-the-counter/alternative treatments or therapies, professional caregivers/long-term care homes, home alterations, transfer payments, etc. Indirect and societal costs: loss of productivity and absenteeism costs The impact of PFIC on patients' health-related qualify of life (HRQoL), the following will be quantified using the following validated patient-reported outcomes tools: • The impact of providing informal care on caregivers via the care-related quality of life seven dimensions (CareQol-7D).

	• The impact of PFIC on patients' and companion/caregivers' productivity using the Work Productivity and Activity Impairment (WPAI)-Caregiver v2.0. • The level of pruritus and interference with activities on patients via the 5-D itch scale Each endpoint will be analysed by country and disease subtype (PFIC 1, PFIC 2, PFIC 3)
Limitations	Despite recruiting and sampling of participating physicians and patients will aim to be representative of the real-world clinical practice in PFIC, the voluntary nature of participation on this study implies that there is a risk of selection bias in physicians and patients. The patient and caregiver Patient Public Involvement Engagement (PPIE) information will come from a subsample of the main sample. The PPIE questionnaires are self-completed by patients and caregivers and are non-compulsory. The possibility of recall bias for participants is low, given that physicians will directly look at their patients records to provide case report-form data. This might happen for patients/caregivers, though the number of questions where recalling data is needed will be kept to a minimum to reduce this bias and to prevent survey fatigue.

2.3 Methodology

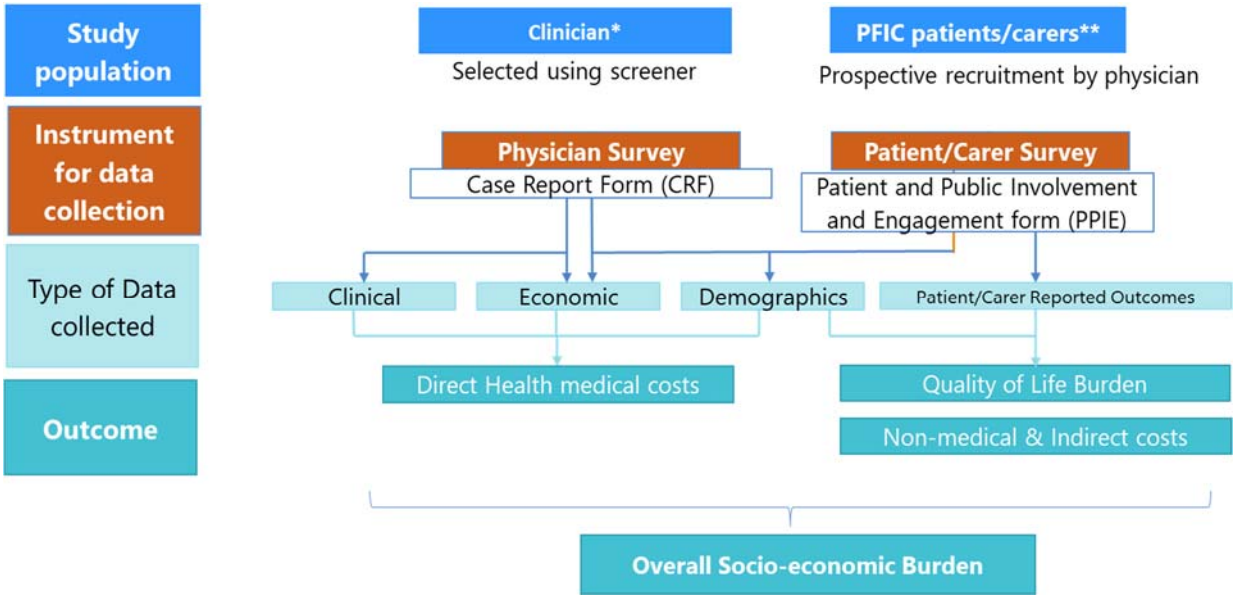
2.3.1 Study design

The study is a descriptive, retrospective and cross-sectional, international (UK, France, Germany and US) burden of illness study.

The study will be guided by an Expert Reference Group (ERG, hereafter called Study ERG), consisting of a representative of academia as principal investigator (University of Chester), partnering charity representatives; Children's Liver Disease Foundation (CLDF), patient advocacy representative; Progressive Familial Intrahepatic Cholestasis Advocacy and Resource Network (PFIC Network), as well as experts in the field of liver diseases.

For the PFIC patient population, data will be collected at 2 levels: the physician - via an electronic Case Record Form (eCRF) and the caregivers – via a survey called Patient Public Involvement Engagement questionnaire (PPIE). Caregivers will be asked to complete on the burden of PFIC on the patients and on themselves, as seen from their own perspective and experience. Information about the questionnaire is detailed in the following section. The nature and structure of outcomes that will be reported can be observed in Figure 1 below.

Figure 1: Proposed study workflow design



2.3.2 Study materials

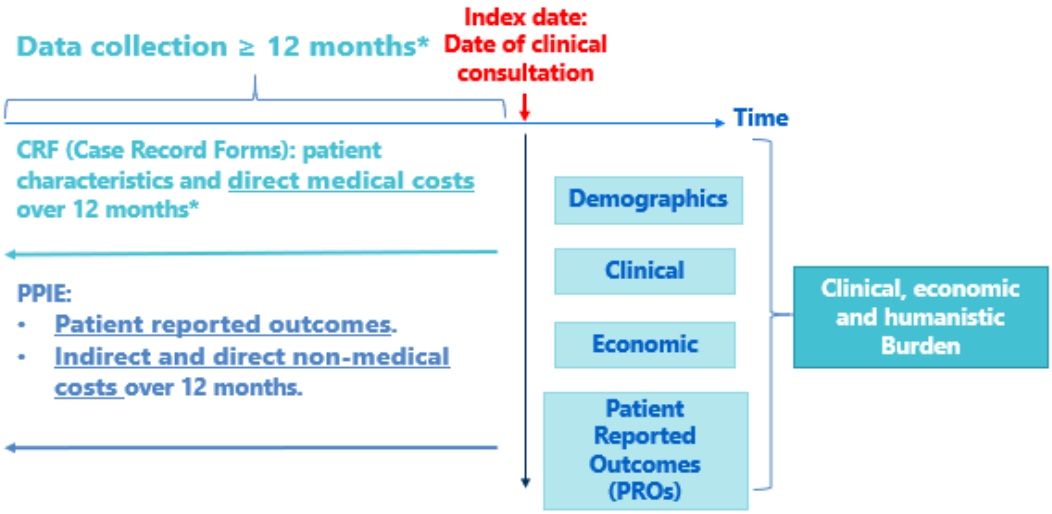
2.3.2.1 Electronic Case Report Forms (eCRFs)

For each patient seen during the clinical consultation, physicians will complete an eCRF. Eligible recruited physicians (see Section 2.4.2 on physician eligibility) will be invited to retrospectively enrol approximately three PFIC patients seen during clinical consultation (i.e., index date). The enrolment period will last for five to six months from the start of the field work, which is expected to begin in September 2020.

Physicians will retrospectively extract real-world information from the patients' health medical records to document direct health PFIC-related resource use over the 12 months prior the date of clinical consultation which is defined as the index date. These 12 months are usually called the documentation period.

The types of data collected from the physician completed CRF will be clinical, economic and demographic. As commented, economic data will be mostly limited to a 12-month period, but data such as diagnosis, disease history and symptomatology will be abstracted from diagnosis where possible, in order to provide an accurate understanding of the disease and clinical pathway from a longitudinal point of view. Time to completion is expected to be on average 20 minutes per patient. The proposed study time framework for the PICTURE study is shown in Figure 2.

Figure 2: Proposed study time framework*



*Some variables will be abstracted since the date of diagnosis or ever (e.g., symptoms, comorbidities, changes in severity status…) with the aim to capture relevant milestones in disease natural history.

2.3.2.2 eCRF variables

Variables to be included in the eCRF include clinical and economic data and are as follows:

- Diagnosis and disease history
  - Other family relatives with PFIC
  - Recorded symptoms
  - Course of disease (time elapsed from first symptoms to definitive diagnosis)
- Consultations
  - Specialists
  - Primary care physician
  - Other healthcare professionals
- Hospitalisations
  - Day Case
  - Inpatient and outpatient
  - Length of stay and intensive care unit (ICU)
- Current and previous treatment
  - Conventional therapies (ursodeoxycholic acid, rifampicin, cholestyramine, phenobarbital)
  - Dietary interventions (vitamin supplements, nasobiliary feeding/drainage)
- Surgical procedures
  - Number/type of surgery (partial external/internal biliary diversion, ileal exclusion)
- Tests and/or examinations to diagnose/monitor PFIC
  - Lab Tests

    - Imaging, biopsy
    - Other tests/examinations
- Comorbidities
- Insurance details (where relevant)
- Demographic data

2.3.2.3 Patient Public Involvement Engagement (PPIE) questionnaire

The PPIE questionnaire will account for the burden of PFIC on both the patient and the main caregiver. The caregivers will provide information about the socioeconomic and humanistic burden of PFIC, as well as data on direct and indirect costs associated with PFIC, lifestyle changes and the impact of PFIC in the child's education. For patients, the questions will be focused exclusively on the measurement of pruritus and its impact on the patients' life.

The caregiver will be the responsible to complete the PPIE questionnaire, including the section that relates to the patient's pruritus, completing it as proxy, at least for all patients <18 years old. The reason for this is that the validated tool chosen to measure pruritus (5-D Itch scale, explained below) was originally worded for adult population, but also due to the disabling nature of disease on patients. If the patient is 18 years old or older, they will be allowed to complete the pruritus 5-D Itch scale on their own, should they wish.

After clinical consultation, eligible caregivers and patients who accepted to be enrolled in the study will be invited to complete a corresponding pen and paper or online PPIE questionnaires, in the clinic or at any other place of their convenience. For the pen & paper version, the PPIE will be returned to the physician on the same day as clinical consultation or after the clinical consultation (index date) in a sealed envelope. For the online version, the physicians will be notified when participants complete the surveys.

Once collected, all anonymised eCRF will be encrypted and matched with corresponding PPIE questionnaires. All anonymised PPIE questionnaires will be collected and sent back to our fieldwork partnering company for coding. Once collected, all the eCRF and PPIE data will be analysed by a team of experts at HCD Economics. A copy of the signed caregiver informed consent form will be sent to UoC via the fieldwork company and retained over a period of 10 years.

The PPIE questionnaire includes the following validated patient-/caregiver-reported outcomes (PRO) questionnaires:

- CarerQol-7D for caregivers (Brouwer et al. 2006): Care Related Quality of Life (CarerQol-7D) is a tool to measure and value the impact of providing informal care on carers and comprises five negative dimensions of providing informal care (relational, mental, physical health and financial problems and problems combining daily activities with care) and two positive (fulfilment from caregiving and support with lending care). For each item, caregivers are asked to indicate whether an item applies to them with three possible responses: no, some, a lot.

- WPAI for caregivers (Reilly et al. 1993): The Work Productivity and Activity Impairment (WPAI) – Adapted for Companion or Caregiving V2.0 questionnaire is a validated and widely-used instrument for measuring the impact of a condition on an individual's work, and is in turn a helpful tool for estimating the indirect costs of PFIC on society. This is particularly useful in many types of economic studies, helping to reveal the true impact of a health problem within a society. The WPAI will be administered to caregivers.
- 5-D itch scale for patients (completed by parent proxy) (Elman et al. 2010): it is a brief multidimensional questionnaire measure of itching. It has five dimensions: degree, duration, direction, disability and distribution of pruritus. The 5-D has demonstrated ease of use, content validity, test–retest reliability, internal consistency and ability to detect change in itch over time in patients with liver disease.

2.3.2.4 PPIE variables

The PPIE will collect the following information:

- PRO: WPAI and CarerQol-7d
- Sociodemographic information
    - Gender and age of the patient
    - Family relationship
    - Socio-demographic variables (age, marital status, level of schooling, household income, area of residency)
- Travel costs
    - Distance to treatment centre
    - Transportation mode
- Work productivity impact (school-child with PFIC and work-caregiver)
- Home adaptations/devices
- Alternative therapies
- PFIC Medications – prescribed and non-prescribed
- Insurance type, coverage, cost, excess
- State/ non-state benefits for child and caregiver
- Educational adaptations
    - Home education
    - School costs
- Informal/Caregiver time
    - Hours per week
    - Impact in career for main caregiver (respondent)
- Professional/contracted care
    - Hourly Wage
    - Hours per week
- Caregiver health (sleep deprivation due to child's itch)

- PRO: 5-D itch scale: a patient-reported outcome to be completed by the caregiver by proxy (due to the questionnaire being originally worded for adults)
- Impact of COVID-19 in health resource use/ physical health/mental health

2.4 Study settings

2.4.1 Study population and representativeness

In order to minimise bias and provide accurate estimates of burden for patients and their caregivers, the PICTURE study population should be representative and generalisable of the real world PFIC population. For this, applying broad inclusion and criteria will aim to capture a representative sample of the PFIC population in the real world. Study population will only exclude patients that are not subtypes 1, 2 or 3 (out of scope in the present study) and that previously participated in PFIC-related clinical trials in the last 12 months before inclusion in this study (due to the bias this may entail in the resource consumption and patient health outcomes).

However, despite recruiting and sampling of participating physicians and patients will aim to be representative, the voluntary nature of participation on this study implies that there is a risk of selection bias in physicians and patients. Additionally, the PPIE information will come from a subsample of the main sample, and the questionnaires are self-completed by caregivers and are non-compulsory.

The possibility of recall bias for participants is low, given that physicians will directly look at their patients records to provide CRF data. However, this may happen for caregivers, though the number of questions where recalling data is needed will be kept to a minimum to reduce this bias and to prevent survey fatigue.

The observational and descriptive nature of this study does not allow for hypothesis testing; therefore, a formal calculation of sample size and statistical power is not applicable. Sample size has been informed by assessing similar burden-of-disease studies in the literature (O'Hara et al. 2017) and based on the information provided by fieldwork partners about distribution of PFIC patients and physicians across the studied countries (UK, France, Germany and US). The expected numbers are outlined in Table 2 below; this option could yield an estimated 225 eCRF and 135 PPIE forms for data collection. However, these estimates are to be taken cautiously given the disease ultra-orphan status. Feasibility of these numbers will be regularly monitored and updated in case this is deemed necessary.

Table 2: Expected/aspirational sample size by country and participant

Country	Physicians	eCRF (physician)	PPIE (caregiver)
United Kingdom	15	45	27
Germany	15	45	27
France	15	45	27
United States	30	90	54
TOTAL	75	225	135

eCRF, electronic case report form; PPIE, Patient Public Involvement Engagement

2.4.2 Physician eligibility

Physicians will be identified and recruited via a fieldwork company. HCD Economics will ensure that they are recruited from a representative sample of physicians that manage PFIC patients for each country.

The following criteria must be met by all participating physicians:

- The physician must be a qualified physician, preferably a (paediatric) hepatologist or a (paediatric) gastroenterologist. Due to the nature and rapid progression of the disease, it has been decided these specialists are most likely to know the patient's history of disease, as well as the previous and current therapy line.
- Recruited physicians must be the main point of contact for these patients (i.e. they must have the lead role in managing and coordinating care for these patients).
- Physicians must have at least 2 years of experience and must manage at least one patient of either type 1 or 2.
- Physicians must agree to comply with the study protocol and the documentation procedure.

2.4.3 Patient eligibility – inclusion and exclusion criteria

The caregiver/patient inclusion criteria are as follows:

- Adult caregivers/guardians of patients (of all ages) with genetic diagnosis of PFIC subtypes 1, 2 or 3 for at least 12 months.
- Caregivers must be willing and able to complete the study questionnaires and give informed consent (and assent) as appropriate.
- Patients of all ages with genetic diagnosis of PFIC types 1, 2 or 3 for at least 12 months.
- Patients (only if they are 18 or older) must give informed consent (and assent) as appropriate.

Patients will be excluded from participation in the study if they exhibit the following characteristics:

- Patients on clinical trials for PFIC or PFIC-related symptoms currently or 12 months before the index date.

2.4.4 Stratification

Patient enrolment stratification will be performed according to disease type (PFIC1, PFIC2 or PFIC3). It is expected that each physician will enrol on average around **67% patients with PFIC1 or PFIC2** and approximately 33% patients with PFIC3, based on the available data from the literature (Davit-Spraul et al. 2009). Subgroup data analyses will be done for each country by PFIC type.

Although a quota on patients based on their pre- or post-liver transplant status has been discussed, this was finally discouraged due to several reasons:

- Existence of the previous quota on PFIC subtypes makes an additional quota complex for recruiting physicians, especially in the context of an ultra-rare disease.
- PFIC1,2,3 subtypes quota is based on literature findings on the real-world proportion of these subtypes, but there is no initial evidence that can support a quota to improve sample representativeness.
- Study ERG members discouraged this quota given the heterogeneity of transplant rate in the subtypes and complexity of recruiting.

Final decision included close monitoring of recruitment to observe % of recruited patients pre- and post- liver transplant, and possibility of adjustment later (and subsequent protocol amendment).

2.4.5 Physician and patient remuneration

The work the physicians undertake as part of this study will be outside of the clinical consultation and undertaken in their own time. They will be paid for this work (in a similar process to a completion of a legal report). The incentive remuneration system is based on country, specialty, and length of interview and is based on the principle of fair market value. The incentives will plan to offer will be as follows in each local currency:

- £157/€175/$200 per physician that completes three eCRFs

Companion/caregivers will be also offered remuneration to complete the PPIE. The incentives will plan to offer will be as follows in each local currency:

- £25/€28/$31 per completed caregiver PPIE, for the caregiver

2.4.6 Language

All study materials (profiling questions, eCRFs, caregiver ‘Invitation to Participate’ information sheet and PPIE) will be developed in English (UK) and translated into native languages using a third-party translation service. Study materials will be reviewed for

content and accuracy by the HCD Economics and a representative of the fieldwork agency of each country.

2.4.7 PPIE hybrid approach to increment PPIE completion

In December 2020, due to difficulties in obtaining a minimum sample size of PPIE completions, an alternative approach was agreed and implemented to obtain an extra sample of PPIE caregivers surveys. Within this approach, caregivers of PFIC 1 and 2 paediatric patients (prioritised sample size) would be invited to participate directly by the Patient Association Groups (PAGs). The main PAGs are the Children's Liver Disease Foundation (CLDF) and PFIC Network (UK- and US-based, respectively), but other country specific associations from France and Germany will be contacted for collaboration in recruitment; they will inform caregivers/patients of the study via their main communications channels: email list, website, newsletter and social media. Partnering PAGs have a network of potential patients/families willing to collaborate and might be able to enhance the final sample size achieved via the Fieldwork matched CRF-PPIE approach.

Once registered and recruited, caregivers will complete the same PPIE survey with a minimum of extra questions, to ensure essential clinical and medical resource use is collected. These extra questions will be adapted from the CRF form, using appropriate, non-medical language. Due to the collection of these items, a cost of illness calculation from the medical/health-system perspective will be possible (and added to the direct non-medical and indirect resource use/costs categories captured in the PPIE). The questions are:

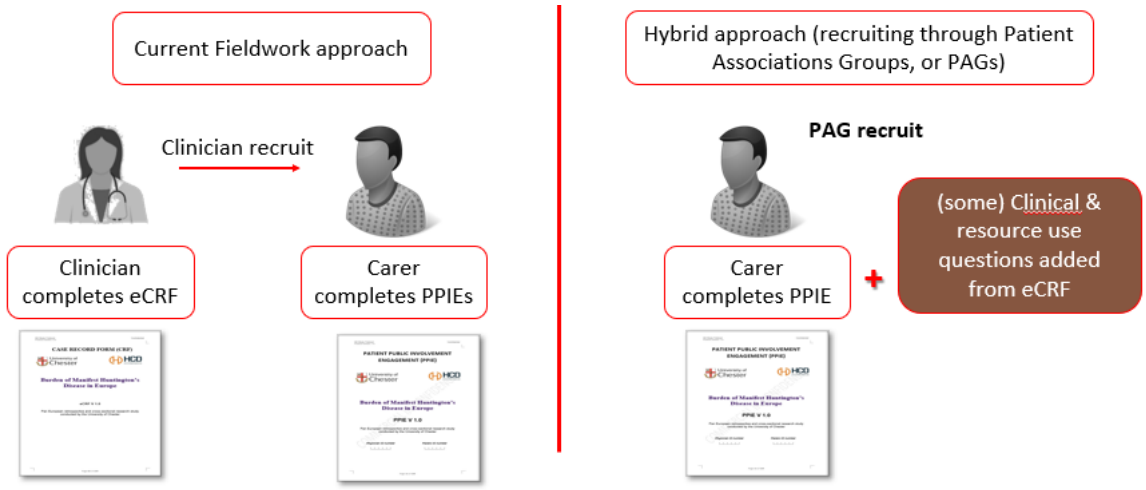
- PFIC subtype
- Patient's comorbidities
- Number of clinical consultations with different health care professionals (last 3 months)
- Medications (last 12 months)
- Selected surgical procedures (ever and last 12 months)
- Hospitalisation (last 12 months)

The potential limitations of this approach are as follows:

- Non-matched physician – patient data, hence there is a loss of clinical and disease history details.
- Caregiver perspective may be subject to recall bias on resource use.

Despite the stated limitations, one of the main benefits of gathering matched physician-caregiver data (the classic fieldwork approach) is to be able to understand the relationship between different levels of health system total resource use/costs and corresponding levels of patient/caregiver reported impact. This relationship will be still achieved by means of the PPIE hybrid approach (Figure 3).

Figure 3: Hybrid strategy to obtain PPIE data



Furthermore, with this hybrid strategy approach, an average cost per year can still be derived, and used for costing and health technology assessment purposes, despite losing some details on patient's clinical pathway.

2.5 Data collection

2.5.1 Data management

The fieldwork agency is responsible for assigning a unique patient number to each eCRF and PPIE in order to match them accordingly. All patient level data will be anonymised, and participants will be assigned a unique patient identification number. No written records of participant identification numbers will be made or retained by the fieldwork company, project team or HCD Economics.

The fieldwork agency will provide the list of patient numbers to each physician. Physicians will be responsible for assigning a patient identification number to each enrolled patient/caregiver and must ensure consistency and validity between eCRF and its corresponding PPIE. Therefore, there is a patient tracking system in place in case patients raise a complaint, but importantly, the fieldwork agency and HCD Economics will not have access to identifiable patient information. The completed original eCRFs are the sole property of the client and will not be made available in any form to third parties.

At no time during the study are the names or addresses of participants requested. No information on residence other than country will be revealed at the patient level. The identities of respondent clinicians are always held by the fieldwork company; no identifiable information about the respondent clinician is obtained by or disclosed to the individuals involved in analysing the data.

2.5.2 Data quality

Each physician has ultimate responsibility for the patient consent and the collection and reporting of all data entered on the eCRFs and any other data collection forms (PPIE and ICF). They must ensure that the data are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The eCRFs must be validated by the physician to attest that the data contained in them are correctly recorded. Any corrections to entries made in the eCRFs, source documents must be dated, initialled, and explained (if necessary) and will not obscure the original entry.

2.5.3 Data security

HCD Economics provides security measures against unauthorised access to client systems including programmes, files and information. The security measures provided include:

- User security: Users logging into the system gain level-specific access to information based upon assigned rights.
- Network security: Users are required to log into the network before accessing any information.
- Survey security: All surveys use SSL (Secure Sockets Layer)
- Laptop security: All laptops are encrypted
- Database security: Our databases provide security features that permit users to access only the information that is relevant to their position, including encrypted passwords, internal and external user authentication, IP address restrictions, fine-grained database privileges, and group level access control.
- Materials: All study materials reside in restricted-access areas of our networks. Only specific project staff has access to these folders.
- Building security: All buildings are secure and require fob access at all times and have security on reception.

To support the security infrastructure, HCD Economics also:

- Has established governance structures with roles and responsibilities
- Keeps detailed records of all data processing operations
- Documents data protection policies and procedures
- Completes data protection impact assessments (DPIAs) for high-risk processing operations
- Implements appropriate measures to secure personal data
- Ensures that all staff are sufficiently trained
- Appoints a data protection officer
- Ensures data protection safeguards are in place at the design stage of any new process, system or technology implemented

2.6 Statistical analysis methods

The study incorporates a mixture of demographic, clinical, and economic information about each patient, as well as demographic, economic and psychological/ emotional burden about their caregivers. With the collation of patient-level and caregiver-level data, the following three-step process has been used in order to calculate the overall annual cost of PFIC across the UK, France, Germany and US.

1. The equation below is applied to identify the total cost at the individual level (commonly used in bottom-up approach to cost of illness studies) (Jo, 2014):

$$P_j \times Q_{ij} = TC_i$$

In this equation, P denotes the price of one unit of a specific resource in the previous 12 months to the patient's consultation date, while Q is the quantity of the resource used. This formula will yield the total cost (TC) for an individual – denoted with the subscript i. TC can be used as a variable for summary statistics. This equation can be applied to all resource use items where unit costs and resource use items are available.

2. To calculate the mean total cost (MTC), the following equation is applied:

$$MTC = \frac{1}{n} \times \sum_{i=1}^{n} TC_i$$

Here, *n* represents the specific country sample size. The inclusion of this variable ensures that the results reported from this study will be specific to each included country (UK, France, Germany and US), facilitating comparisons between the different MTCs.

For both populations, tables will be generated by country and by disease type and subtype. Quality control on all data collected will be performed regularly, prior to data analysis and actions will be taken when necessary. A comparison of HRQoL measures between disease stages, types and country will be made by comparing means and standard deviation.

An additional aim of the descriptive analysis is to help to describe and understand the data collected in order to generate hypothesis and identify unmet needs for further investigation. HCD Economics value high standard statistical analysis and our team uses two main statistical software packages, STATA® 16 and R, to deliver products. When appropriate, univariate comparisons will be tested for significance. Additionally, multivariate analysis can be conducted using standard linear regression (ordinary least squares [OLS]) or generalised linear models (GLMs) where the choice of the method will depend on the nature of the relationship.

2.6.1 Summary statistics

Given the descriptive nature of the study, the study outcomes will be analysed using exploratory statistics. Country specific data analysis and pooled data analysis for the European countries will be carried for the primary and secondary study objectives as follows:

- Continuous variables and study outcomes will be summarised using the following summary statistics, as appropriate:
    - Non-missing sample size (n) and percentage of non-missing
    - Mean and standard deviation (SD)
    - Median, interquartile range (IQR) and extremes values (minimum, maximum)
    - 95% confidence intervals
- Categorical variables and study outcomes will be summarised using the following summary statistics, as appropriate:
    - Non-missing sample size (n)
    - Count and percentage by category for the non-missing sample size

Resource use and cost data are commonly positively skewed with a small number of people consuming a disproportional amount of resources. In this case bootstrapping techniques can be applied to standard parametric statistics, which do not require the assumption of normality.

2.6.2 Missing data

Collected data will be constantly and consistently audited for completeness, accuracy and clarity. Data clean-up and cross-checking will be performed prior to data analysis. The frequency and percentage of missing data will be quantified for all variables.

The pattern of missing data across the sample will be evaluated. If considered missing at random, case wise deletion or imputation may be implemented using:

- Overall mean
- Subgroup mean (e.g., ethnicity, disease type, treatment strategy etc.)
- Regression on non-missing values for imputation

Decisions on imputation techniques will be discussed internally prior to implementation and the process of data imputation will be reported transparently; this statistical analysis tool will only be used when deemed necessary, in order to obtain accurate results.

2.6.3 Sourcing and applying costs

In order to calculate aggregated economic healthcare outcomes, a dataset of unit costs will be created for the resource use items captured in the study questionnaires for each country. From this dataset, costing profiles will be developed. These costs will be collated via access to public tariff information and general public data sources.

Unit costs will be assembled for each non-drug resource use item included in the survey, including, but not limited to the costs of medical consultations, hospitalisations, surgery

and professional care. For the medication costs, and because only molecule level information is collected (e.g., no branded medication), the lowest available list price will be used for total costs computation within the different country specific sources. Estimates of the cost of working days lost will be undertaken using the human capital method (i.e. using relevant daily wage rates).

Although all PFIC-related resource use will be quantified, it is proposed to restrict PFIC drug costing to relevant supportive treatment only. These costs will be collated using national datasets and through discussions with Study ERG members and subscribers.

2.7 Ethical standards

This research study will be reviewed and approved in accord with the UoC's Faculty of Health & Social Care research ethical requirements. This will ensure that the study is conducted in accordance with UoC ethical standards.

2.8 Project governance

2.8.1 Overview

The governance of the study will be overseen by the Study ERG, to ensure quality standards are maintained and to provide overall study oversight on behalf of UoC, subscribers and the partnering PFIC organisations: Childrens Liver Disease Foundation (CLDF), Progressive Familial Intrahepatic Cholestasis Advocacy and Resource Network (PFIC Network).

The Project Team will deliver and report to the Study ERG on the progress of the study against the project timelines and will be resourced from UoC and any sub-contractors.

2.8.2 Expert Reference Group

2.8.2.1 Terms of reference

The Study ERG will ensure quality standards are maintained and provide expert input and review of the study on behalf of the UoC, sponsors and charities. The Study ERG shall review and approve the fieldwork materials and recommend any changes. The Study ERG shall facilitate all interactions between the different participants in the study and shall periodically review progress including corrective action as necessary. HCD Economics with the UoC will design and carry out the burden of illness (PICTURE) study, hold and manage all funds for the project.

2.8.2.2 Frequency and location of meetings

The Study ERG plan to hold three meetings during the study. Importantly, additional meetings should be scheduled if some material issues arise outside of the scheduled meetings.

- First meeting: Discussion of protocol and materials, including topics such as inclusion criteria, data completeness, representativeness, etc. (via teleconference).
    - review of the protocol (to be finalised via email)
    - review of the study questionnaires (to be finalised via email)
- Second meeting: to discuss data return and interim results of analysis (via teleconference)
- Third meeting: at the end of the project to discuss results and report (via teleconference)

2.8.2.3 Meeting conditions

Prior to the first meeting, the CLDF president will act as Chair. At its first meeting the Study ERG shall appoint one of its members as an independent Chair and a member of UoC/HCD Economics as the Secretary. The Chair shall act as the chair of meetings, but in his or her absence, another representative of the Study ERG will be identified prior to the meeting and detailed in the minutes. The Secretary shall be responsible for circulating the agenda and papers before meetings and for producing and circulating minutes.

2.9 Results

After six months of recruitment, a total of [redacted] patients were included in the standard-approach population.

2.9.1 Patient socio-demographics at baseline

In the standard-approach population (n=[redacted]), most (approximately [redacted]%) patients were from the US, with [redacted] ([redacted]%) patients enrolled from UK centres. The majority of patients were PFIC 1 ([redacted]%) and around [redacted]% of patients were younger than 18 years old. Of those, [redacted] children had *missing/don't know* information regarding their surgical history.

In the hybrid-approach population (n=[redacted]), no patients were enrolled from French centres, over [redacted]% of patients were younger than 18 years old and most patients were PFIC 2 ([redacted]%).

2.9.2 eCRF variables

Laboratory tests and procedures and consultations in the last 12 months, both by surgery category, are shown in Table 3 and Table 4, respectively.

Table 3: Laboratory tests and procedures by surgery category

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_1 : Serum bilirubin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_2 : Serum bile acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_3 : Complete blood count (CBC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_4 : Alanine aminotransferase (ALT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_5 : Alpha fetoprotein (AFP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_6 : Gamma glutamyl transpeptidase (GGT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_7 : Aspartate aminotransferase (AST)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_8 : Prothrombin (PT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_9 : Glucose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_10 : Albumin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
CRF15_11 : Vitamin (A, E, D, K) status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_12 : Thyroid stimulating hormone (TSH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_13 : Serum thyroxine (T4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_14 : Metabolic disease markers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_15 : Canalicular immunostaining	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_16 : Electron microscopy (EM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_17 : Liver biopsy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_18 : Liver histology	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_19 : Transient elastography (FibroScan®)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_20 : FibroTest®/ FibroSure®	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_21 : Spleen size	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_26 : Abdominal ultrasound	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_27 : Magnetic resonance elastography (MRE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_28 : Magnetic resonance cholangiopancreatography (MRCP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
CRF15_29 : Magnetic resonance imaging (MRI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF15_30 : DNA sequencing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CRF, case report form; LT, liver transplantation; PBD, partial (external/internal) biliary diversion
Data in **bold** have been used in the revised base-case economic model.

Table 4: Consultations in the last 12 months by surgery category

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
Consultations with other specialists - past 12 months (N=106)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
No	[redacted]						
CRF19a_1 : Paediatrician							
No							
Yes							
CRF19b_1 : Paediatrician (CRF19b - Number of visits) (N=21)							
CRF19a_2 : (Paediatric) Hepatologist							
No							
Yes							
CRF19b_2 : (Paediatric) Hepatologist							
CRF19a_3 : (Paediatric) Gastroenterologist							
No							

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19b_3 : (Paediatric) Gastroenterologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19a_4 : Gastro-intestinal surgeon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19b_4 : Gastro-intestinal surgeon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19a_5 : Dietitian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19b_5 : Dietitian (CRF19b - Number of visits) (N=13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
CRF19a_6 : Emergency medicine practitioner	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19b_6 : Emergency medicine practitioner	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19a_7 : General Practitioner	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19b_7 : General Practitioner	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19a_8 : Orthopaedist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
CRF19b_8 : Orthopaedist (CRF19b - Number of visits) (N=1)							
CRF19a_9 : Palliative care specialist							
No							
CRF19b_9 : Palliative care specialist							
CRF19a_10 : Physiotherapist							
No							
Yes							
CRF19b_10 : Physiotherapist (CRF19b - Number of visits) (N=4)							
CRF19a_11 : Psychologist							

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19b_11 : Psychologist (CRF19b - Number of visits) (N=4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19a_12 : Speech and language therapist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19b_12 : Speech and language therapist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRF19a_13 : (Paediatric) Oncologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Surgeries						
	With no LTx/PBD	With LTx	With PBD	With both LTx and PBD	Don't know	Missing	Total
CRF19b_13 : (Paediatric) Oncologist							
CRF19a_14 : (Paediatric) Psychiatrist							
No							
CRF19b_14 : (Paediatric) Psychiatrist							
CRF19a_15 : Endocrinologist							
No							
Yes							
CRF19b_15 : Endocrinologist (CRF19b - Number of visits) (N=3)							
CRF19a_16 : Surgeon							

	Surgeries						
	With no LTx/PBD	**With LTx**	**With PBD**	**With both LTx and PBD**	**Don't know**	**Missing**	**Total**
No							
Yes							
CRF19b_16 : Surgeon (CRF19b - Number of visits) (N=1)							
CRF19a_17 : Internal medicine practitioner							
No							
Yes							
CRF19b_17 : Internal medicine practitioner (CRF19b - Number							

CRF, case report form; LT, liver transplantation; PBD, partial (external/internal) biliary diversion

Data in **bold** have been used in the revised base-case economic model.

2.9.3 Patient socio-demographic characteristics

WPAI scores by surgery category and PFIC-related transportation costs by country are presented in Table 5 and

Table 6, respectively.

Table 5: WPAI scores by surgery category

	Surgeries				
	With no LTx/PBD	**With LTx**	**With PBD**	**With both LTx and PBD**	**Total**
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Are you currently working for pay (N=22)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAIscore_absent (N=16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAIscore_present (N=13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAIscore_workprod (N=13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAIscore_activimpair (N=22)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LT, liver transplantation; PBD, partial (external/internal) biliary diversion; WPAI, Work Productivity and Activity Impairment
Data in **bold** have been used in the revised base-case economic model.

Table 6: PFIC-related transportation – types and costs by country

	Country			Total
	DE	UK	US	
	[redacted]	[redacted]	[redacted]	[redacted]
CQ29x1_1PrivatevehicleCQ2_v2 (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Average number of journeys (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost per journey (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost in total (for all journeys) (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
CQ29x1_2TaxiCQ29x1Numbe_v2 (N=2)	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Average number of journeys (N=2)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost per journey (N=1)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost in total (for all journeys) (N=1)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
CQ29x1_3TrainCQ29x1Numbe_v2 (N=4)	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Average number of journeys (N=4)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost per journey (N=3)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

	Country			
	DE	UK	US	Total
	[redacted]	[redacted]	[redacted]	[redacted]
Cost in total (for all journeys) (N=3)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
CQ29x1_4FlightCQ29x1Numb_v2 (N=2)	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Average number of journeys (N=2)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost per journey (N=1)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost in total (for all journeys) (N=1)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
CQ29x1_5Publictransportation_v2 (N=3)	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Average number of journeys (N=3)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost per journey (N=2)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost in total (for all journeys) (N=2)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
CQ29x1_6AmbulanceCQ29x1N_v2 (N=5)	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Average number of journeys (N=5)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Cost per journey (N=4)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

	Country			
	DE	UK	US	Total
	[redacted]	[redacted]	[redacted]	[redacted]
Cost in total (for all journeys) (N=4)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
CQ29DK_97 : Not applicable (CQ29DK) (N=22)	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]

Data in **bold** have been used in the revised base-case economic model.

3 Vignette study

3.1 Introduction

Albireo has recently conducted a study to develop and value vignettes in PFIC (vignette study). The vignette study was designed to elicit societal utility values for a series of health states in PFIC to support economic modelling for the odevixibat submission. Economic evaluations of new treatments often assess outcomes in terms of QALYs, which require the impact on health-related quality of life (HRQoL) to be expressed in utility weights. These weights are scaled so that 1 represents full health, 0 represents dead and worse than dead is represented by a negative value. Utility weights should reflect the patient experience and are best captured using a validated measure of HRQoL such as the EuroQol 5-Dimension (EQ-5D) questionnaire. A further requirement of most health technology assessment (HTA) bodies, including NICE, is for utility weights to reflect outcomes that the general public value. Various methods can be used to capture utility weights, including the time trade-off (TTO) interview method. The TTO method can estimate health-state utilities for different disease states using vignettes that describe the patient health in a given disease state. The method asks participants to consider 10 years in the target health state against the prospect of X years in full health. Time in full health is then varied until the point is reached where participants think they are the same.

The vignette study aimed to develop vignettes for PFIC related disease states and then to complete a valuation of those vignettes using the TTO method among members of the general public.

3.2 Methodology

3.2.1 Vignette development

Health-state vignettes were developed to describe typical patients with PFIC in terms of their symptoms, functioning, and HRQOL. Vignettes were varied previous history of partial external biliary diversion (PEBD) and pharmacological treatment response. Two states described HRQOL after liver transplant.

PFIC (pre-transplant) states were developed using data from the Pediatric Quality of Life Questionnaire™ (PedsQL™) (Varni et al, 2001). The PedsQL data came from the PEDFIC1 trial, which is a double-blind, randomized, placebo-controlled, phase 3 study to demonstrate efficacy and safety of odevixibat in children with progressive Familial Intrahepatic Cholestasis Types 1 and 2. Additionally, daily diary data (referred to as the Albireo ObsRO) were used to describe patients' experience of itch. Both assessments were made by the patients' parent or caregiver.

The PedsQL has age-appropriate versions. In this trial, the versions used included the Parent report for toddlers (age 2-4), Parent report for young children (ages 5-7), Parent report for children (age 8-12) and Parent report for Teens (age 13-18). The dataset (including baseline and week 24) included the following distribution of participants:

Toddlers (age 2-4) n=36; Young children (ages 5-7) n=19, Parent report for children (age 8-12) n=12 and Parent report for Teens (age 13-18) n=5. The wording of the different age versions differs slightly to make it age appropriate and some items are not present in the version for younger children. Despite these small differences the concepts overlap very heavily. The data from children of different ages is designed to be combined, so it was felt to be appropriate here. Table 7 provides some examples.

Table 7: Comparison of the language used in different age versions of the PedsQL

In the past ONE month, how much of a problem has your child had with ...			
Toddlers 2-4	**Young children 5-7**	**Children 8-12**	**Teens**
Walking	*Walking more than one block*	*Walking more than one block*	*Walking more than one block*
Playing with other children	*Getting along with other children*	*Getting along with other children*	*Getting along with other teens*
Worrying	*Worrying about what will happen to him or her*	*Worrying about what will happen to him or her*	*Worrying about what will happen to him or her*

In the trial after dosing, patients' PedsQL was assessed at baseline and week 24. The daily diary data from baseline and week 24 were extracted. Descriptive analyses were performed to determine the median response options for the PedsQL and Diary for patients (regardless of trial arm). Trial patients were sub-divided into non-responders and responders defined in terms of a response on a pruritis scale (defined as a scratching score of ≤1 or at least a one-point drop from baseline on the Albireo ObsRO instrument) or a response in terms of serum bile acid levels (defined as a 70% reduction in fasting levels). The PedsQL and ObsRO data were summarised for both groups.

The trial data were used to develop the 4 vignettes which contrasted treatment response and PEBD status. The vignettes were based on a combination of PedsQL items and median response options for response and non-response. The PEBD states also included a description of the PEBD drain and bag. No trial data were available to describe children post liver transplant and so as a starting point the treatment response state was used for the physician review.

3.2.2 Validation of health state vignettes

Feedback from clinical experts was sought to ensure accuracy of the vignettes as well as balance, so that the experience of PFIC was neither exaggerated nor understated. Interviews were conducted via online video call (i.e., Zoom) to obtain feedback on the draft vignettes. An interview discussion guide was developed for the purpose of this study.

Questions were designed to validate and refine the content of the vignettes, as well as to review in more detail the post-liver transplant states. The interviews were also used to establish whether the vignettes were a fair representation of the experiences of children living with PFIC or post transplant.

The experts who consented to take part were sent all health-state vignettes for review. The interviews were summarised to inform the final health state development, detailing the feedback on the descriptions, but not formally analysed. The clinical experts were reimbursed for their time in line with fair market value.

Comments on each element of the health states from each expert were considered together. Changes were made to the content of the vignettes in line with the comments or a majority view where there were disagreements. The source data from the PedsQL and the itch ObsRO were considered the primary source as well. So, if the data suggested that patients have a problem on a question and one of the doctors suggested that they shouldn't then, the patient data was considered to be more accurate. If all or most of the doctors felt that a change should be made, then it was made. The exception to this was the two liver transplant states which were not based on patient data. For these states, most suggested changes were made.

3.2.2.1 Estimation of health utilities

Members of the general public were recruited through (online) advertisements, informal and online social networks and/or snowballing. The study aimed to recruit up to 100 members of the general public to take part in the TTO interviews. Interviewers were set quotas to ensure the sample is representative of the population in the UK in terms of age and sex.

3.2.2.2 TTO method

TTO is a standardised interview method for valuing health states, which was used to generate health utility weights for each vignette (Torrance, 1987; Drummond and McGuire, 2001). The method is designed to determine the point at which participants consider 10 years in the target health state to be equivalent (or indifferent) to the prospect of X years in full health. Time in full health is varied until this point of indifference is reached where the participant thinks they are the same. To minimise possible bias, the amount of time in full health is alternated between high and low values, decreasing by six-month intervals. If a participant indicates that they believe that being dead is preferable to any time living in a health state, then this indicates that the participant thinks the state is worse than dead. At this point the interviewer switches to a lead-time TTO exercise, which asks participants whether they would prefer to live for 10 years in full health followed by 10 years in a health state, or to live for 20 years of full health. This lead-time procedure allows the participant to trade more years of life to determine how much worse than dead they consider the health state to be.

3.2.2.3 TTO data collection

All TTO interviews were conducted using online video calls (Skype or Zoom) to minimise health risks associated with the Covid-19 pandemic. Before the TTO interview, participants were provided with information about the study and asked to complete a consent form to confirm that they agreed to take part. They also completed a brief background questionnaire about themselves and were provided with an opportunity to ask questions. Prior to the interview, all participant study materials were sent by email (or post, at the request of the participant) to all who took part in an online video interview.

Participants were requested to print the vignettes in preparation for the interview or to look at the study materials on one screen (monitor/laptop/tablet) and conduct the online video chat on a second screen (e.g., phone/tablet/laptop/monitor), so that the interviewer and participant could see each other at all times. This enabled the interviewer to show the VAS scale and TTO board alongside him/her on the screen. Throughout the interview, interviewers were instructed to ask participants regularly if they could see the board clearly and to maintain eye contact.

All interviews were conducted by trained TTO interviewers. The first exercise used a visual analogue scale (VAS) ranging from 0 (worst possible health) to 100 (full health). Health state vignettes and ‘dead’ were then presented one-by-one and participants were asked to rank them on the scale. A vignette, described as ‘Dead’, was included to allow participants to indicate if they considered any of the vignettes to be worse than dead.

Following the VAS exercise, participants completed a TTO interview for all vignettes. For each vignette, the interviewer recorded the utility value at the point of indifference. If participants rated any vignette as worse than dead, they were asked to confirm that they believed that this was the case. They then completed the lead time TTO procedure for any states worse than dead. Lastly participants rated each state using the EQ-5D.

The content of the states was driven in large part by the PedsQL and because of this the health states had child specific language in them. In order to be true to the source data this was not changed. In the valuation task an initial pilot phase explored whether participants could imagine themselves as a child and rate the state as such. This involved trading years of life as a child. The initial results from the pilot suggested that participants could not easily imagine themselves as a child and were unwilling to trade years of life in the TTO task. Therefore, for the remaining interviews, participants were asked to consider the quality-of-life burden of each vignette and to consider that when making choices in the TTO exercise.

3.2.2.4 Analysis of valuation data

Socio-demographic data were summarised descriptively using means and standard deviations or percentages and frequencies as appropriate.

The VAS ratings for each vignette were rescaled such that the value for the dead state was fixed at zero and all other values varied between 100 and the worse health state. The following formula was used to rescale the data.

$$V' = \left(\frac{V - V_{Dead}}{100 - V_{Dead}}\right) * 100$$

Where *V'* is the rescaled VAS value, V is the original VAS value and V_{Dead} is the value given to the Dead state. After rescaling the VAS data were summarised descriptively.

The TTO data were scored according to the point of indifference. The TTO data were summarised descriptively and presented as smoothed histogram distributions. The EQ-5D data were scored using the van Hout mapping function (van Hout et al. 2012).

3.3 Results

3.3.1 Clinical expert interviews

Four clinical experts with experience in treating patients with PFIC were interviewed. All four were paediatric liver specialists working in university teaching hospitals in the UK. All experts were provided with the complete set of draft health state vignettes prior to the interviews. Table 8 describes the changes that were made to the vignettes based on the expert feedback.

Table 8: Summary of changes to health state vignettes informed by expert interviews

Vignette	Original wording	Change requested
All	[redacted]	[redacted]
Non-responder states	[redacted]	[redacted]
PEBD states	[redacted]	[redacted]
Response states	[redacted]	[redacted]
Liver transplant within last 12 months	[redacted]	[redacted]

	[redacted]	[redacted]
Liver transplant over 12 months ago	[redacted]	[redacted]

3.3.2 Health-state valuation

3.3.2.1 Sample characteristics

Demographic characteristics of the participants who took part in the TTO valuation interviews are presented in Table 9, along with data for age, sex and ethnicity from the most recent UK census 2011 data. The UK sample characteristics were broadly similar to the UK census data in terms of age, sex and ethnicity.

Table 9: Sample characteristics from valuation interviews (N=100)

Characteristic		UK sample for TTO valuation	UK population*
		Mean (SD)	**Median**
Age		[redacted]	[redacted]
		n (%)	**%**
Sex	Male	[redacted]	[redacted]
	Female	[redacted]	[redacted]
Ethnicity	White	[redacted]	[redacted]
	Asian	[redacted]	[redacted]
	Black	[redacted]	[redacted]
	Mixed	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Occupation	Employed	[redacted]	[redacted]
	Retired	[redacted]	[redacted]
	Student	[redacted]	[redacted]
	Unemployed	[redacted]	[redacted]
	Homemaker/carer	[redacted]	[redacted]
Long-term condition	Yes	[redacted]	[redacted]

SD, standard deviation; TTO, time trade-off; UK, United Kingdom

*Figures based on data from the 2011 United Kingdom national census (Office for National Statistics https://www.ons.gov.uk/census)

3.3.2.2 Vignette ratings

The mean VAS ratings for each PFIC health state vignette along with estimates of dispersion for the total sample are shown in Table 10. Table 10 also shows the TTO weights and derived EQ-5D based weightings for each PFIC health state vignette alongside estimates of dispersion. The TTO scores show a similar pattern of results to the VAS values.

Table 10: VAS, EQ-5D and TTO ratings of each health state vignette

	VAS			EQ-5D			TTO		
	Mean	SD	95%CI	Mean	SD	95%CI	Mean	SD	95%CI
Non-responder, no PEBD	[redacted]								
Non-responder, with PEBD	[redacted]								
Responder, no PEBD	[redacted]								
Responder, with PEBD	[redacted]								
Liver transplant within 12 months	[redacted]								
Liver transplant over 12 months	[redacted]								

CI, confidence interval; PEBD, partial external biliary diversion; SD, standard deviation; TTO, time trade-off

The TTO and EQ-5D scores provided a consistent ordering of the states, as shown in

Figure 4.

Figure 4: Health state utilities for PFIC-related states assessed by TTO and EQ-5D

EQ-5D, EuroQol 5 Dimension; PEBD, partial external biliary diversion; PFIC, progressive familial intrahepatic cholestasis; TTO, time trade-off

3.4 Discussion and conclusions

3.4.1 TTO vignette valuation study

This study reports the findings of a vignette-based utility survey which was designed to estimate the impact of PFIC on the quality of life experienced by children with the condition. The vignette methodology is a recommended approach to estimate utility weights in rare diseases when it is not feasible to collect utility data using self-reported EQ-5D responses from patients across a number of relevant health states. In line with the NICE Task and Finish group recommendations, the present study has used available published literature, primary trial data from the PedsQL and qualitative information from clinical experts to develop vignettes for use in a general public TTO valuation exercise.

The vignettes described a range of PFIC experiences, including treatment response and the presence or absence of PEBD. In addition, two liver transplant states were also included. the content of the vignettes was driven by a summary analysis of the PedsQL

data from the recent trial completed by Albireo. Parents completed the PedsQL for their child at each visit and these data were used to determine the median response to each item on the PedsQL for children who were classified as responders and non-responders according to trial criteria. In addition, using a similar approach, data from the itch diary was also summarized and used in the vignettes. The reliance on the PedsQL items meant that the content of the vignettes clearly referred to a child. This meant in the TTO valuation task participants were asked to imagine the quality-of-life impact of each state on a child and provide their rating on that basis. This is a limitation of the study. Partly for this reason and in line with the NICE Task and finish report on measuring HRQoL we recommend that the EQ-5D ratings be considered the primary source of utility data.

The vignettes were reviewed by several clinical experts who all provided detailed feedback on their content. This was particularly important for the liver transplant states because no trial data were available in order to describe them. In the interview a treatment response state was presented as a ‘straw man’ for the transplant state and for each bullet point the clinicians were asked to comment on its accuracy. This process provided quite consistent feedback which allowed us to revise the states with some confidence. However, it should be noted that this is also a limitation of this study.

The TTO and EQ-5D scores provided a consistent ordering of the states (

Figure 4). However, the utility weights were quite different using the two methods. The EQ-5D weights are probably closer to the NICE reference case. Both set of weights could be included in sensitivity analyses of the cost effectiveness model to explore what impact they have on the final results. We are not aware of any other published utility weights in PFIC which these results could be compared to.

To conclude, quality of life of PFIC related states was rated by the general public in a TTO valuation task. This produced logically consistent TTO, EQ-5D and VAS weights that can be used in cost effectiveness modelling. The vignettes were developed in line with the NICE Task and finish group recommendations for generating utility estimates using vignettes when EQ-5D data are unavailable. This is relatively novel method for developing vignettes which we believe has merit for future studies.

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Additional scenario analysis on the submission odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Addendum C – Additional analyses (estimation of the disutility associated with PEBD)

Table of contents

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1 Overview

This document provides the methodology and results of an additional targeted scenario analysis conducted to address the issue of the underlying uncertainty of the impact on health-related quality of life (HRQoL) for patients with partial external biliary diversion (PEBD). This analysis is based on supporting data from the follow-up vignette study carried out by Albireo AB and estimates the most likely range for the disutility multiplier associated with PEBD. In response to ERG clarification question B1, the revised base-case will remain the same as reported in Addendum A. Further analyses are presented for progressive familial intrahepatic cholestasis type 1 and type 2 (PFIC1 and PFIC2) populations as requested by the ERG during the ERG clarification meeting on the 7th of June 2021. We have additionally submitted two full Excel models, reflecting the different scenarios (covering both list and PAS prices).

2 Introduction

Patients with PFIC often experience severe itch and significant liver damage. This can be ameliorated by a partial external biliary diversion (PEBD), an invasive procedure which consists of a surgical drain inserted into the liver connected to an external bag via a stoma. This can be an effective treatment for the itch and delay the need for a transplant. However, as these patients are often young children or teenagers, they can often struggle to live with such a drain on a permanent basis, and the drain itself can be associated with complications impacting patients' HRQoL. The previous vignette study conducted in May 2021 described PEBD as a single line in the health-state descriptors (for responders and non-responders alike) and did not adequately capture the wider impact on HRQoL (see Addendum A). The HRQoL estimates were also based on the views of the general public without experience of PEBD. The aim of this additional study is to derive a more informed view on the range for a stoma bag multipliers, and explore the potential impact on the ICER, reducing uncertainty for the NICE committee.

3 Methodology

A follow-up study was conducted by Albireo AB, including interviews with a leading physician and several families who have a child diagnosed with liver disease and who

have had a PEBD. Interviews were undertaken with the doctor and families to explore various issues, as follows:

- Quality of life and symptom burden related to liver disease prior to the PEBD
- The benefits experienced following the PEBD
- Challenges that the PEBD causes for children and how they meet those challenges. Limitations to day-to-day life, problems related to the drain, and any psychological or social impact of having a stoma and drain fitted were explored.

An interview guide was used to frame this discussion (see Appendix). Following the initial qualitative component, the participants were presented with two vignettes describing a PFIC patient. They were based on the non-responder state from the original valuation study. The two vignettes varied in terms of presence or absence of a PEBD but in all other regards the two vignettes were the same. For each vignette the parent or doctor was first asked to imagine describing a child who is 7 years old and complete the EQ-5D-5L as a proxy rating of how such a child would be affected. They were also asked to imagine that the vignette described a young person who was 15 years old, and then provided a second EQ-5D-5L rating for each state.

The EQ-5D data were scored using the van Hout algorithm[1] and then summarised. One parent preferred to provide a range of scores (e.g., sometimes moderate sometimes severe) and in this case we estimated utilities for the best response and the worst response to reflect this range.

4 Findings

Our clinical expert had worked with PFIC patients for [redacted], was based [redacted] and [redacted]. More recently he reported that PEBD is not a procedure they use very often because they are aware that its effectiveness is very much influenced by mutations, and generally prefer children to undergo a liver transplant. Pharmacological options were the preferred route for treating mild symptoms. PEBD was only considered after confirming that pruritus was

[1] van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. Value Health. 2012 Jul;15(5):708-15

severe and it correlated with serum bile acid (sBA) levels. The expert noted that most patients saw an improvement in their pruritus, but for some (20-25%) this did not last forever.

He explained and described problems that children may experience. Children did not like the stoma which can get sore or infected. The bags were unpleasant and could leak, especially at night. PEBD is a big issue in adolescents as they become more conscious of their bodies and start having relationships.

Three parents of children with liver disease were also interviewed.

Parent A's child (now aged [redacted]) [redacted]. A second procedure was unsuccessful, and a third drain was in place for several years although it was not as effective as the first drain. He has now undergone a liver transplant. The experience of this child seems similar to children with PFIC.

Parent B's child (now aged [redacted] years old) [redacted]. He experienced [redacted].While this boy had a drain fitted, the experience seems to be different to children with PFIC and the drain was only in for [redacted]. Parent B found it difficult to consider the vignettes and so in the interview she was asked to consider and rate the health of her own son currently and then also rate it if he still had a PEBD fitted.

Parent C's child (aged [redacted] years old) was diagnosed with [redacted] early in her life and experienced very [redacted]. Her PEBD was fitted at the age of [redacted] and since then she has never experienced itch. It is just as effective now [redacted] years later.

Table 1: EQ-5D-5L ratings of PFIC vignettes describing a 7yr old and a 15yr old and contrasting the presence of PEBD

	Doctor's view	Parent A [redacted]	Parent B [redacted]	Parent C [redacted]	Mean
PEBD					
7 yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 yr	[redacted]	[redacted]		[redacted]	[redacted]
Non-PEBD					
7 yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 yr	[redacted]	[redacted]		[redacted]	[redacted]

5 Stoma bag multipliers

Albireo AB has calculated a value range for the stoma bag multiplier informed by the follow-up vignette data presented in Table 1. These data report wide variations, but ultimately treating pruritus is the main objective for patients with PFIC and patients do opt for PEBD for this reason despite it being a potentially problematic intervention.

The range of multipliers used in the scenario analysis is summarised in **Error! Reference source not found.**. The mean multiplier is [redacted] (compared to 0.71 used in the base case analysis and derived from literature). The confidence interval remains wider due to limited data)

Table 2: Vignette study stoma bag multipliers

	Multiplier
Mean	[redacted]
Min	[redacted]
Max	[redacted]

The EQ-5D-5L ratings were based on a limited sample and showed some clear inconsistencies in scoring. As discussed in Section 4, Parent B's child suffered with [redacted] which can cause serious complications such as [redacted], the PEBD in this case was only [redacted] potentially driving the patient's negative PEBD experience and scores. The clinician mainly considered PEBD in the most severe cases and stated how he preferred patients to undergo a liver transplant rather

than long-term PEBD. [redacted]. It is also worth noting that the vignettes both described a non-responding patient, but the [redacted]

Due to these variations the results from Parent A and Parent C were deemed to be those most consistent and representative of a typical child with PFIC symptoms, and where a permanent / long-term PEBD is being considered.

The multipliers calculated in this analysis were therefore derived from Parent A and Parent C's reported ratings (see Table 1).

6 Scenario analysis

The range of multipliers in **Error! Reference source not found.** has been applied to patients in the PEBD health state when selecting the vignette study data in the model. Table 3, Table 4 and Table 5 show the results from this scenario for both list and PAS price.

Table 3: Joint population scenario analysis

HRQoL parameter	Scenarios	ICER - List	ICER - PAS
Base case		[redacted]	[redacted]
Vignette EQ-5D	+ stoma bag disutility multiplier (**vignette study mean)**	[redacted]	[redacted]
Vignette EQ-5D	+ stoma bag disutility multiplier (**vignette study min**)	[redacted]	[redacted]
Vignette EQ-5D	+ stoma bag disutility multiplier (**vignette study max**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study mean**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study min**)	[redacted]	[redacted]

Vignette TTO	+ stoma bag disutility multiplier (**vignette study max**)	[redacted]	[redacted]

Table 4: PFIC1 scenario analysis

HRQoL parameter	Scenarios	ICER - List	ICER - PAS
Base case		[redacted]	[redacted]
Vignette EQ-5D	Vignette EQ-5D + stoma bag disutility multiplier (**vignette study mean)**	[redacted]	[redacted]
Vignette EQ-5D	Vignette EQ-5D + stoma bag disutility multiplier (**vignette study min**)	[redacted]	[redacted]
Vignette EQ-5D	+ stoma bag disutility multiplier (**vignette study max**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study mean**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study min**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study max**)	[redacted]	[redacted]

Table 5: PFIC2 Scenario analysis

HRQoL parameter	Scenarios	ICER - List	ICER - PAS
Base case		[redacted]	[redacted]
Vignette EQ-5D	+ stoma bag disutility multiplier (**vignette study mean)**	[redacted]	[redacted]
Vignette EQ-5D	+ stoma bag disutility multiplier (**vignette study min**)	[redacted]	[redacted]
Vignette EQ-5D	+ stoma bag disutility multiplier (**vignette study max**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study mean**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study min**)	[redacted]	[redacted]
Vignette TTO	+ stoma bag disutility multiplier (**vignette study max**)	[redacted]	[redacted]

7 Appendix: PEBD health state valuation - Interview script

Instructions for the interviewer are shown using **CAPITALISED TEXT**. These should **not** be read to the participant.

Instructions for the participant are shown using plain text. These should be read aloud to the participant.

Thank you for taking the time to participate in this study. The purpose of this study is to gain an understanding of the benefits and burden for children and teenagers who have received a partial external biliary diversion. Are you familiar with this device?

In the first part of the interview, I would like to get your insights into how this has affected your child. We are interested in the benefit that they get from it – and also if they experience any difficulties. At the end of the interview, I will ask you to read two different health descriptions and I will ask you to rate each one.

Before we begin, I would like to tell you a few things about the interview.

1. All the information you provide us will remain confidential.
2. Are you happy for the interview to be recorded so that I can capture what you say?
3. The interview will take approximately 30 minutes in total to complete.
4. Please take your time answering the questions.
5. If there any questions that you don't wasn't to answer, then please say so and we can move on to the next one.
6. Please remember that there are no right or wrong answers. We are interested in your opinion and that is what is important to us. Do not worry about being consistent with previous answers and feel free to change your mind if you want to.
7. If you have any questions throughout the interview, please feel free to ask. We may have to wait until the end of the interview to answer some questions.
8. Your participation in this study is voluntary, so if at any time you would like to stop the interview, please let me know.

9. Do you have any questions before we start?

Confirm participant is happy for interview to be recorded.

Can you tell me about your child with liver disease?

Age

Gender

Caregiver

Has your child had a PEBD fitted?

When was it fitted?

START RECORDING

State participant ID and date.

[redacted]

STEP 2: HEALTH STATE VALUATION TASK

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

ON SCREEN SHOW THE EQ-5D-5L

[redacted]

NOTE THEIR RATINGS IN THE SCORE SHEET

NOTE ANY COMMENTS ON AND REASONS FOR THE RATINGS

[redacted]

State 2

[redacted]

[redacted]

[redacted]

ON SCREEN SHOW THE EQ-5D-5L

[redacted]

NOTE THEIR RATINGS IN THE SCORE SHEET

NOTE ANY COMMENTS ON AND REASONS FOR THE RATINGS

[redacted]

STEP 4: DEBRIEF QUESTIONS

Thank you for answering these questions and rating the descriptions.

Do you have any other comments on the interview? _____

I would like to arrange payment for your time today.

Are you happy to do a bank transfer?

PayPal?

Any other method?

NICE National Institute for Health and Care Excellence

Patient organisation submission

Odevixibat for progressive familial intrahepatic cholestasis ID1570

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Children's Liver Disease Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Children's Liver Disease Foundation (CLDF) is the only UK charity dedicated to fighting all childhood liver diseases. We do this by providing information to families and to health professionals, emotional support to young people with liver disease and their families, funds for research and a voice for all affected. CLDF currently provides emotional support and practical assistance to approximately 4,000 children, young people and their families affected by a childhood liver disease. We have 90 children and young people diagnosed with PFIC engaged with our organisation however this does not include those who have not signed up to us as a member and their families, who may still access our online services and support without signing up to the charity. CLDF is reliant on voluntary donations to fund the work of the charity. This is provided largely by the fundraising efforts of the families and young people we support.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	**Albireo** Amount – £25,988 Purpose – To provide financial support with costs relating to CLDF's Support services– Reaching Families, Children and Young People with liver disease and our Voice work – Representing the needs of families, young people and children affected by liver disease in childhood. **Mirum pharmaceuticals (also developing products for this cohort)** Amount – £13914 Purpose – To provide financial support with costs relating to CLDF's information services and yellow alert programme.

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	▪ Discussions with CLDF's Family Support Team who provide 1:1 support service, information, signposting and events/residentials to those affected by a childhood liver condition including PFIC. ▪ Direct conversations with parents of children with PFIC 1,2,3 ▪ Survey sent to parents of children with PFIC 1,2,3 ▪ Parent views collected through a review of the CLDF pruritus leaflet
Living with the condition	
6. What is it like to live with the condition? What do carers	In many cases, PFIC impacts all areas of not only the life of the child diagnosed with the condition but also their parents/carers and siblings. A PFIC diagnosis and the associated symptoms and complications can affect sleep, the child's education, social relationships and the work and home life of family. There is also the psychological impact of living with, at times, a debilitating condition especially where pruritus and muscle wasting occur. This can be difficult for young children and

experience when caring for someone with the condition?	their carers to cope with and manage. In our discussions with those affected, the impact on siblings was also highlighted. School life for the children can be severely impacted, this can not only affect their educational attainment but their social development, peer groups and friendship circles. **Impact on child:** "Before transplant the quality of my son's life was really poor. He couldn't eat/drink/sleep properly, his physical development was very delayed, his itching was unbearable. He needed 24/7 care and attention." "My child was diagnosed at 16 weeks with PFIC 2. He was extremely jaundiced, fed every 3 hours as a baby and was then sick, wasn't gaining weight, distressed with itchy skin, broken sleep. He also broke his leg the day after he started walking due to lack of absorption of vitamin D. He had physical developmental delay with crawling and walking. He had a gastrostomy tube to feed him overnight to help with weight gain. He also had extremely runny stools due to his lack of absorption of foods, this then led to delayed toilet training." **Impact on education:** "It's challenging, she was constantly tired, in pain and missed school due to hospital appointments. Regarding school there was a lack of concentration when she was not feeling well which caused her anxiety as teachers don't understand the condition and put pressure on her when getting behind with work." In a discussion with another parent, C, they stated that their child, because of not sleeping for days due to pruritus, missed many days of school which in turn impacted her exam results. **Impact on carers:** "It impacts both mentally and physically on parents/carers and due to severe itching that never really stops, sleep deprivation has a huge impact on wellbeing. Please don't forget the impact on siblings, although they might not articulate it at the time, but it is a very traumatic experience for them to see their sibling suffering."

	"It takes over the whole family including our older child. Lots of hospital visits, sleepless nights, lots of washing with sickness and loose stools. My child tired easily with walking and was in a pushchair until he was 6. The itching was distressing to see. My child's skin was raw and bleeding. I was unable to return to work as my child needed constant care. When he went to school/nursery, he had a 1:1 pupil support assistant to help him with his movement and toilet needs." "Feelings of guilt watching your child suffering and pressure not to neglect other children's needs."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments are not specific to PFIC patients (off label) so have varying levels of success. Often families are calling out for other practical ways to support their children to manage symptoms as they are aware there are currently no treatments specifically for their child's diagnosis. "Treatments seem very limited." "As far as we know there is no real treatment for Type 2 PFIC, other than transplant. 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."
8. Is there an unmet need for patients with this condition?	No treatment currently available specifically for PFIC patients. Off label treatments may support with aspects such as pruritus and vitamins and dietetic services can support with nutrition but with varying degrees of success.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	A specific drug for PFIC provides some hope and another option to patients and their families. Many rely on practical solutions unless/until it reaches the point of liver transplantation which carries risk and many hope to delay the need for this as long as possible. Transplant although lifesaving is not a cure, those patients need a lifetime of care. The ongoing immunosuppression has its own risks in the longer term and the child and family live with the ongoing concern that the new liver may fail at some stage leading to the need for further lifesaving transplants. "Any treatment to slow down the progression of the disease sound promising. We were initially informed that our child would need a transplant prior to his 10th birthday otherwise he wouldn't survive. His transplant ended up being just after his 4th birthday, much sooner than we had expected. Anything to slow the disease down would be extremely helpful to lots of families." "If the itching and other symptoms can be controlled fairly well, the PFIC child and families would get a much better quality of life and progression of the disease can be slowed down." "The new treatment being discussed for PFIC with it being available to all types of the condition sounds great. If it helps with itching and slows down the progression of the disease, then brilliant."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	"Perhaps young children would not benefit with it only being available in capsule form." "Having to take so many tablets which are large everyday is not easy."

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Possibly may not benefit PFIC 3 population as much due to side effects/symptoms usually being mild with current medication compared to other PFIC types. Pruritus can be slightly less severe in PFIC3 in comparison to PFIC1 and 2 but the severity of the condition can differ between individuals.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	**No**

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • The symptoms and complications of PFIC can often be debilitating and affect all areas of the child's life as well as those of their family and carers. • There are currently no treatments available specifically for this group of patients. Therefore, any possible safe treatment to slow down the progression of PFIC is vital

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Odevixibat for progressive familial intrahepatic cholestasis ID1570

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: British Association for the Study of the Liver (BASL)

Are you (tick all that apply):

- √ a specialist in the treatment of people with the condition for which NICE is considering this technology?

- √ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- √ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

  [redacted]

- other? (please specify)

  Not applicable

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

I have no links to and in receipt of funding from the tobacco industry

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Odevixibat for progressive familial intrahepatic cholestasis ID1570

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition.

How many of them would be expected to receive treatment with the technology?

80% would be expected to receive treatment with the technology. Approximately 20% of the children would not have severe enough symptoms to receive treatment with the technology as they would be managed with medications that are currently being used

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision?

The condition is currently treated in NHS within the three designated tertiary paediatric liver units. These units are funded within highly specialised service provision of NHS.

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There is no significant geographical variation in current practice.
Paediatric hepatologists who manage this condition have a standardised approach to management of pruritus.
The medications that are currently used for management of pruritus can be roughly divided into the following:

First group:	Ursodeoxycholic acid
	Cholestyramine
	Anti-histamines
Second group	Rifampicin
	Phenobarbitone
Third group	Ondansentron
	Naltrexone

The paediatric hepatologists start with medications from first group and if pruritus is not controlled than may use a combination of medications from first group, second group and third group. The combination of medications for children is based on trial and error depending on the symptom management of pruritus and quality of life of the individual family.

Advantages: Easily available within NHS on prescription
Clinicians familiar with side effects
Cost effective

Disadvantages: Intense uncontrolled pruritus despite a combination of medications may affect
quality of life of child, family
behaviour of the child
Social isolation
Need for non-transplant surgery (biliary diversion) and transplant Surgery (liver transplantation)

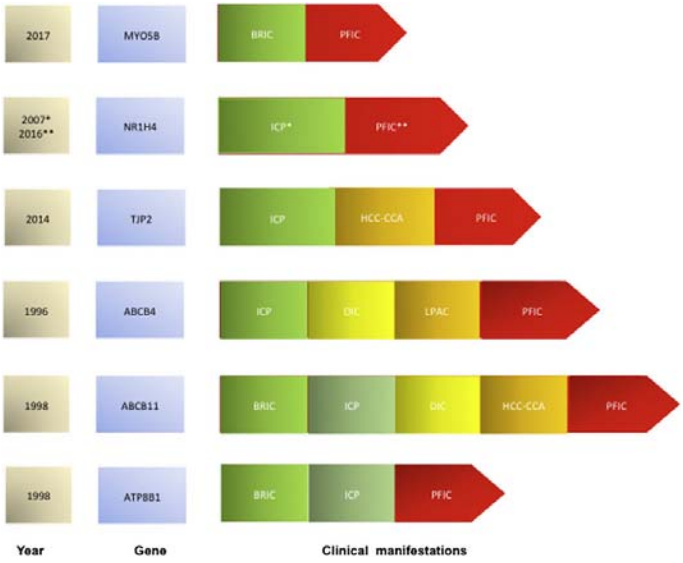
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

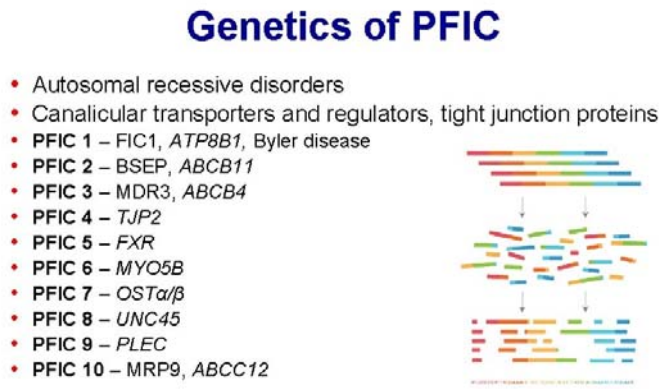
Odevixibat for progressive familial intrahepatic cholestasis ID1570

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

PFIC is a condition with different subgroups with newer subgroups being identified as there is an expansion in understanding genetics and mechanisms of the disease in the last 10 years. The evolution of diagnosis of PFIC can be summarised in the slides below



Slide showing the evolution of understanding of the genetics of PFIC and clinical manifestations



Slide showing the various mutations that are associated with PFIC

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	PFIC type 1	PFIC type 2	PFIC type 3
Age of onset	Early infancy	Early infancy	Later in childhood or young adulthood
Extrahepatic manifestations	Watery diarrhea Pancreatitis Sensorineural hearing loss	Uncommon	None
Pruritus	Severe	Very severe	Moderate
Cholesterol stone formation	Absent	Increased	Increased
Progression of PFIC subtypes	Liver cirrhosis and rapid progression to ESLD Patients do not have increased risk for development of liver tumors.	Progression even more quickly to end-stage liver disease, require liver transplantation during the first decade of life. Risk of development of liver tumors are high.	Insidious Risk of development of liver tumors are mildly increased.

Slide showing the various clinical manifestations of the condition

There is a considerable heterogeneity within the presentation and symptoms associated within each individual subgroups

As clinicians with the expansion of genetics, we are beginning to understand the genotype- phenotype corelation better within individual subgroups especially with relation to the various treatment options available

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Yes there are considerable differences in the capacity of different subgroups to benefit from the technology as it will depend on the individual condition and medications used in the treatment

What is the likely impact of the technology on the delivery of the specialised service?

The impact of the technology on the delivery of the specialised service is likely to be positive as it will improve patient symptoms thereby minimising the patient contact with various MDT teams involved in the care

Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

No, there would not any requirements for additional staffing and infrastructure or professional input

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If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

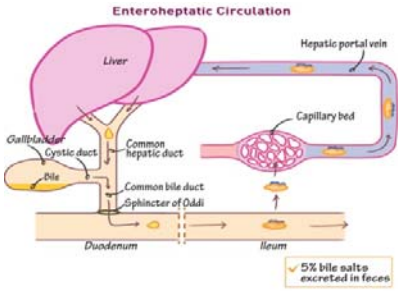
There are a subgroup of children who have PFIC like condition and symptoms but where the genetic diagnosis is not established. The children may have intractable pruritus and may not be responsive to other treatment for pruritus. It may be used for these children
Alagille syndrome is a rare, genetic condition. It can affect different parts of the body including the liver, heart kidneys, eyes, face and bones. It can affect around one in every 30,000 live births

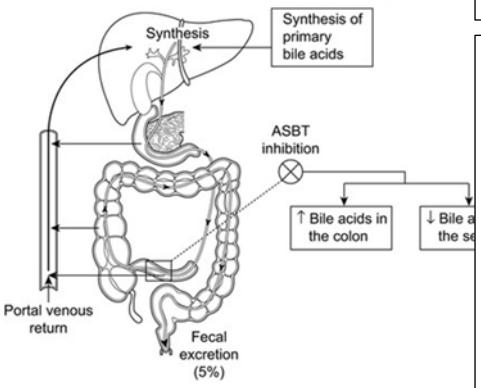
Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no national clinical guidelines of treatment for PFIC established within the paediatric society such as the BSPGHAN.

To understand the appropriateness of the methodology used in developing the guideline, a background information of enterohepatic circulation of bile is important

Enterohepatic circulation





Bile salts pass down the length of the small intestine to the ileum
ASBT mediate reabsorption of 95 % of bile acids within the terminal ileum (: enterohepatic circulation).
Travel through the hepatic portal vein back to the liver where they are recycled and re-secreted into newly formed bile.
Small amount of bile salts continues through the rest of the digestive tract; approximately 5% of bile salts

Mechanism of Odevixibat- ASBT (Apical sodium dependent bile acid transporter) inhibitor drug: Interruption of enterohepatic circulation of bile selectively inhibiting the ASBT protein located in the terminal ileum thereby reducing the levels of bile within the systemic circulation

Appropriateness of methodology used in development of medication

What is ASBT ?
ASBT is a plasma mem-brane glycoprotein with a molecular mass of 39− 41 kDa, which consists of 348 amino acid residues. The functioning of membrane transporters depends on their “targeting” to specific (micro)domains of the plasma membrane, as well as on the lipid and cholesterol composition of these microdomains. The ASBT polypeptide is present in insoluble fractions of the plasma membrane associated with raft microdomains (lipid raft); the destruction of these microdomains by cholesterol depletion significantly reduces ASBT activity. The secondary structure of ASBT consists of seven transmembrane domains (TM 1–7), three intracellular loops (IL 1-3), and three extracellular loops (EL 1-3) [24] . ASBT is N-glycosylated at the N10 asparagine residue in the first extracellular loop of the protein. N-glycosylation of ASBT provides protection against digestion by luminal proteases.

In vitro studies of ASBT

Compound	Inhibition (IC_{50})	Parameter studied	Experimental conditions
A3309	0.53 ± 0.17 nM	Transport of [^{14}C]glycocholic acid	Human embryonic kidney derived cell line (HEK293) expressing human ASBT
SHP626	No information		
A4250	No information		
264W94	0.25 µM	Transport of [^{3}H]taurocholic acid	Chinese hamster ovary (CHO) cell line expressing human ASBT
GSK2330672	42 ± 3 nM	Transport of [^{3}H]taurocholic acid	Human embryonic kidney derived cell line (HEK293) expressing human ASBT
SC-435	1.5 nM	Transport of [^{14}C]taurocholic acid	Baby hamster kidney (BHK) cell line expressing human ASBT
S-1647	4 µM	Transport of [^{3}H]cholyltaurine	Chinese hamster ovary (CHO) cell line expressing rabbit ASBT
	1.52 ± 0.12 µM	Transport of [^{3}H]taurocholic acid	Transformed embryonic kidney cells human, containing the SV40 virus T antigen (HEK293T), expressing human ASBT

Studies on A4250 in humans

The efficacy and tolerability of the A4250 inhibitor in humans was evaluated in a randomized, double-blind study involving 40 volunteers receiving either a single dose of A4250 (0.1 mg, 0.3 mg, 1 mg, 3 mg, or 10 mg) or placebo, as well as 24 people treated with A4250 (1 mg or 3 mg once a day or 1.5 mg twice a day) or placebo for one week. At the end of the one-week experiment, the total amount of BAs in blood plasma decreased by 47% in the case of the 3 mg/day dosage ($p < 0.01$) and by 15% in the case of the dosage 1.5 mg twice a day ($p < 0.05$); the 3 mg/day dosage caused a 5-fold increase in the total amount of BAs in feces, and primary BAs

represented about 75% of them. No serious adverse events occurred and all participants finished the trial per protocol, with diarrhea being the most common adverse drug reaction.
Pruritus is one of the common complications of cholestatic liver disease. Nine patients with primary biliary cholangitis participated in a pilot study evaluating the tolerability and effect on pruritus of A4250 0.75 mg (n = 4) or 1.5 mg (n = 5) taken daily for four weeks. All nine patients treated with A4250 reported a significant reduction in pruritus starting from the second day of taking the inhibitor. Five patients completed the study prematurely due to abdominal pain (5/5) and diarrhea (4/5), which was probably associated with the too high dose of A4250 used in the study

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Appropriateness of medication:

As can be demonstrated from the above in-vitro studies and other human studies, the medication would have a rationale for use in children with pruritus

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

When it becomes available, it will complement the therapies available for the management of PFIC. The clinicians treating this condition feel helpless in managing the children with intractable pruritus and it is distressing for the families and children as it affects the quality of life. The technology of using medications will give an

alternative to clinicians and families before proceeding to surgical (transplant and non-transplant) options.
There are no practical implications for concomitant treatment or additional clinical requirements or the need for additional blood tests.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The rules for starting and stopping the use of the technology is dependent on the indications for starting the treatment. At present the enrolment in the clinical trials were based on genetic testing. Genetic testing is done as routine in the patients who will be considered for treatment and hence there is no additional testing to identify subgroups for treatment or to assess response. The discontinuation of treatment is not based on additional testing in the use of this medication.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.

The use of technology (in this case the medication) under clinical trial conditions reflects that observed in clinical practice.

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

In my opinion the trials conducted reflect current UK practice and the results can be extrapolated easily to UK setting.

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The most important outcomes according to me in the subgroup of patients was
Pruritus and pruritus score
Serum bile acids reduction
Development of HCC in children with PFIC type 2
Need for surgical intervention (transplant or non-transplant)

The first two outcomes were measured in trials and were the most important outcomes to be measured in my opinion.

The other two outcomes are important but are long term outcomes and will need to be measured in ongoing long-term studies.

What is the relative significance of any side effects or adverse reactions?

The side-effects seen with the use of drug were mainly mild to moderate in severity and were as follows: diarrhea, raised transaminases, fever, upper respiratory tract infection etc. The raised transaminases or fever with upper respiratory tract infection are not directly related to the medication but can be seen in childhood frequently. In a small minority of patients when raised transaminases were seen, it did not progress to needing liver transplantation

In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

They did not affect the management of the condition or the patient's quality of life adversely. There are no other adverse effects that were not apparent in clinical trials, but came to light subsequently during routine clinical practice.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The standard of care being delivered at present will continue and hence if the technology is not available, then it would not affect the delivery of care at present. In the long term there may be implications that clinicians may need to exercise other treatment options such as – non transplant surgery or liver transplantation. There would be no need for extra education and training for staff or for example extra facilities or equipment.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Appendix D - professional organisation statement template

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Highly Specialised Technology Evaluation

Odevixibat for progressive familial intrahepatic cholestasis ID1570

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Odevixibat for progressive familial intrahepatic cholestasis ID1570

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NHS ENGLAND & IMPROVEMENT

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **X**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no NHSE clinical commissioning policies for this indication.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is highly specialised (HSS) specialist paediatric liver disease service commissioned from three providers. The aim of the service is to provide family-centred specialist care for children and families with all forms of medical and surgical liver disease, including metabolic liver disease, acute liver failure and pre-and post liver transplant management. The pathway of care is well defined.
8. What impact would the technology have on the current pathway of care?	The technology, if approved, would not alter the pathway of care.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	The technology is not commissioned for routine use.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology, if approved, would provide an additional treatment option for patients with this condition.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It is anticipated the technology would be administered through the HSS under existing arrangements
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	N/A

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No additional equality issues identified
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Deirdre Kelly**
2. Name of organisation	**Birmingham Women's and Children's Hospital**

3. Job title or position	**Professor of Paediatric Hepatology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ x a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ x yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Neonatal liver disease is the commonest presentation of liver in infants, and the majority have a genetic basis. Progressive familial intrahepatic cholestasis (PFIC) is one of the more common. It has a variable phenotype but is usually progressive with the eventual development of end stage liver disease. The majority of children need liver transplantation, which is not always a definitive cure as recurrence may occur. The early symptoms are prolonged jaundice, cholestasis with fat soluble vitamin deficiency, failure to thrive with malnutrition and severe debilitating pruritus. The effect of this severe pruritus should not be underestimated as it significantly affects quality of life. Whereas we have therapy to correct fat soluble vitamin deficiency and malnutrition, to date we have no effective therapy for pruritus or PFIC. Odevixibat is one of the first drugs to effectively treat this distressing symptom and by reducing the bile salt toxicity in the liver, also reduces the rate of liver damage, thus improving outcomes, and possibly delaying and reducing the need for liver transplantation
8. What do you consider a clinically significant treatment response with regards to a reduction in serum bile acid level and pruritus? In your experience, does a reduction in bile acid levels always correspond to a reduction in pruritus?	The most clinically significant treatment response is alleviation of pruritus, which is usually (not always) associated with a reduction in serum bile acids. The reduction in serum bile acids using surgery (biliary diversion) has been associated with outcome and native liver survival (ie without transplantation) and hence this is an important endpoint

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Definitely
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The early symptoms of PFIC are prolonged jaundice, cholestasis with fat soluble vitamin deficiency, failure to thrive with malnutrition and severe debilitating pruritus. Treatment includes: Intensive nutritional support, fat soluble vitamin replacement, treatment of pruritus with a number of different medications and strategies which include ursodeoxycholic acid, bile acid sequestrants (colestyramine), rifampicin, ondansetron and occasionally naltrexone. If medical therapy fails then surgical intervention with external or internal biliary diversion, or ultimately liver transplantation.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESPGHAN and NASPGHAN have guidelines for the management of cholestatic liver disease
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes. In the UK there are 3 national centres which are funded to treat these patients. There is good agreement on the therapy and the pathways of referral

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would significantly improve the patients' symptoms and QoL, possibly also their liver function and slow down the progress of their disease. It may also prevent or delay the need for liver transplantation.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is only currently available through clinical trials. Yes it will become part of routine clinical care.
• How does healthcare resource use differ between the technology and current care?	It may reduce the need for hospitalisation, the need for additional medications as detailed above. It may reduce the necessity for liver transplants thus improving mortality, morbidity and cost.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist centres only should prescribe, but patients should be jointly managed with their referral centre
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. All the three national centres are involved with the clinical trials and the use of this drug

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. See above
• Do you expect the technology to increase length of life more than current care?	Yes see above
• Do you expect the technology to increase health-related quality of life more than current care?	Yes see above
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology would be of value for all patients (adults or children) with cholestasis. It is not relevant for the general population.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No difference to current care other than the benefits mentioned above
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There will be a need to decide when to discontinue the medication in non-responders. If no response after 6 months, it should be discontinued
16. Do you consider that the use of the technology will result in any substantial health-	Yes see above

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes it is an entirely new drug with a novel mechanism as described in the scope
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are very few side effects or adverse effects which affect the management and QoL. Abdominal pain and constipation have been reported.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in pruritus, serum bile salts
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. How do data on real-world experience compare with the trial data?	N/A
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. How many subtypes of PFIC have been identified to date?	6
24. For people with PFIC types other than PFIC1 and 2, would you expect: a) A different treatment pathway? b) A different response to standard care treatment (as demonstrated by reduction in serum bile acid and pruritus)?	a) No b) There may be an improvement in pruritus but nor an associated fall in serum bile salts c) An improvement in growth and QoL. Reduction in the progression of liver disease

c) Other important response markers not captured in the clinical trials?	
25a. Would nutritional management ever be the sole PFIC treatment, or always be given in combination with oral therapies? 25b. Would nutritional management and off-label oral therapies continue after surgical biliary diversion or liver transplant? 25c. Would you ever observe an ongoing pruritus response to off-label therapies?	a) No -it will be part of a combination therapy b) Possibly after SBD and shortly after liver transplantation but not long term c) it is possible depending on the disease and the response to therapy, but it is unusual

26. In the NHS, how frequent is surgical biliary diversion in people with: a) PFIC 1 b) PFIC2 c) Other subtypes of PFIC	It is most effective in PFIC2. All centres vary in their use of this strategy. I could not give an estimate for the other centres, but it is rarely used in my centre (1-2 operations/year)
27. How often are non-PEBD surgeries (e.g. partial internal biliary drainage, internal ileac exclusion) conducted in the NHS? What factors influence the choice of surgery for a patient?	I do not have this data
28. What symptoms necessitate re-transplant in people with PFIC1 and 2? Would you associate more complications and a poorer	This is complicated. There are many reasons for re-transplantation but specifically for PFIC it may also be for recurrence of the disease

quality of life with a second transplant compared with the first?	QoI may be just as good post 2nd Tx but it depends on a number of other issues (eg other complications, technical issues, recurrent rejection etc)
29. How would you classify a lack of response to treatment with odevixibat?	No improvement in pruritus or inadequate reduction in SBA
30. How frequently do people with PFIC develop hepatocellular carcinoma (HCC)? Would these people follow the standard HCC treatment pathway?	I do not have the exact data. Yes they would be monitored regularly for this recurrence
31. Does treatment for PFIC differ in the UK to that in America, Canada and Europe? If so, how?	No
Key messages	

32. In up to 5 bullet points, please summarise the key messages of your statement.

- PFIC is a rare untreatable disease requiring liver transplantation
- The symptoms of severe debilitating pruritus significantly affect quality of life.
- Odevixibat is one of the first drugs to effectively treat this distressing symptom and improve QoI
- By reducing bile salt toxicity in the liver, it reduces the rate of liver damage and may reduce the need for liver transplantation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**CLAIRE BRINKLEY**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☒ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	CHILDREN'S LIVER DISEASE FOUNDATION
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☒ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☒ I have other relevant personal experience. Please specify what other experience: MOTHER OF A CHILD WITH THE CONDITION ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	NO

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	MY DAUGHTER'S CONDITION IMPACTED UPON THE WHOLE FAMILY. EMOTIONALLY RELATIONSHIPS WITHIN THE FAMILY SUFFERED. I HAD TO GIVE UP A MANAGEMENT JOB AND GO SELF EMPLOYED TO FIT WORK AROUND MEDICAL COMMITMENTS AND UNPLANNED HOSPITAL ADMISSIONS. MY DAUGHTER NEEDED FLEXIBLE/PART TIME SCHOOLING AS HER CONDITION DETERIORATED. HER BROTHER SUFFERED PSYCHOLOGICALLY WITH ANXIETY AND SIGNIFICANT TIME AWAY FROM HOME/STAYING WITH FRIENDS AND EXTENDED FAMILY. HIS EDUCATION ALSO SUFFERED AS WE WERE IN HOSPITAL FOR NEARLY 3 MONTHS AROUND THE TIME OF HIS SATS AND 11 PLUS EXAM. MY HUSBAND AND I SUFFERED LOSS OF EARNINGS WHEN ELEANOR NEEDED A TRANSPLANT. LACK OF SLEEP DUE TO ELEANOR'S ITCHING WAS A MAJOR ISSUE WHEN SHE WAS YOUNGER. ELEANOR HAS MILD LEARNING ISSUES DUE TO TIME WHEN HER LIVER WAS VERY POORLY.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	VERY LITTLE OPTION IN TERMS OF TREATMENT. ELEANOR'S ONLY TREATMENT OPTION WAS A LIVER TRANSPLANT. THIS HAS LEFT HER WITH ONGOING MEDICAL ISSUES WHICH WILL CONTINUE THROUGHOUT HER LIFE. NHS HAS BEEN AMAZING, PARTICULARLY AT THE SPECIALIST LEVEL, HOWEVER, WE DO NOT 'FIT' INTO THE USUAL SYSTEMS AT A LOCAL LEVEL (EG, FOR GETTING EMERGENCY BLOODS DONE ETC) AND HER CONDITION IS NOT UNDERSTOOD LOCALLY, OFTEN RESULTING IN HER NEEDING A & E SUPPORT WHEN NOT NECESSARY.
11. Is there an unmet need for patients with this condition?	YES – BETTER TREATMENT OPTIONS THAT ARE LESS INVASIVE AND LESS LONG TERM HEALTH CONSEQUENCES.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also	HOPE FOR PATIENTS – A POSSIBLE ALTERNATIVE TO TRANSPLANT. REDUCED ITCHING. LESS EMOTIONAL HEALTH ISSUES FOR CARERS.BETTER QUALITY OF LIFE AND EDUCATION OPPORTUNITIES. IMPROVED FAMILY LIFE.

include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	N/A
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they	N/A

long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	NOT SURE
Equality	
16. Are there any potential equality issues that should be taken into account when	**NOT SURE**

considering this condition and the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	NO
Topic-specific questions	
18. Please comment further on the psychological impact of living with PFIC symptoms for patients and family members? What symptoms cause the most distress?	THE ITCH WAS A HUGE ISSUE WITH SIGNIFICANT IMPACT ON THE WHOLE FAMILY. THE ANXIETY, PARTICULARLY IN THE EARLY DAYS AFTER DIAGNOSIS. THE UNPREDICTABILITY OF THE CONDITION – NOT KNOWING HOW QUICKLY IT WILL PROGRESS. PORTAL HYPOTENSION WAS EXTREMELY SCARY TO LIVE WITH. THE BEHAVIOURAL ISSUES FOR MY DAUGHTER AS SHE DETERIORATED.
19. If you or your child has received (or was scheduled to receive) a liver transplant for PFIC, would you have any concerns about this, and if so	HUGE CONCERNS – MY DAUGHTER SUFFERED SEVERE, LIFE THREATENING POST TRANSPLANT COMPLICATIONS. SHE IS NOW IMMUNOSUPPRESSED WHICH BRINGS A NEW SET OF WORRIES. CONCERNS ABOUT REJECTION AND PTSD.

what would these concerns be?	
20. If you or your child had a partial external biliary diversion, what impact does a stoma bag have on your/their quality-of-life?	N/A
21. What are the most important outcomes of a new treatment for PFIC to patients and carers?	IT GIVES HOPE OF AVOIDING TRANSPLANT AND A BETTER QUALITY OF LIFE.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your statement:

- PFIC IS A CONDITION THAT HAS HUGE, LONG TERM IMPACT ON THE WHOLE FAMILY.
- PFIC IS SUCH A RARE CONDITION THAT FAMILIES FEEL ISOLATED AND SCARED.
- A LIVER TRANSPLANT IS AN EXTREMELY SCARY AND TRAUMATIC PROCEDURE FOR A CHILD AND THE FAMILY.
- WE NEED BETTER OPTIONS FOR TREATMENT OF PFIC THAT CAN BE DELIVERED LOCALLY.
- PFIC IMPACTS UPON A CHILD'S DEVELOPMENT IN EVERY WAY.

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Penny North-Lewis**
2. Name of organisation	**Leeds Teaching Hospital NHS Trust**

3. Job title or position	**Paediatric Liver Pharmacist**
4. Are you (please tick all that apply):	☐**x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ **x** other (please specify): Specialist pharmacist managing children with this condition
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **x** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve quality of life (by reducing pruritus), stop progression to biliary diversion, slow progression to liver transplant
8. What do you consider a clinically significant treatment response with regards to a reduction in serum bile acid level and pruritus? In your experience, does a reduction in bile acid levels always correspond to a reduction in pruritus?	A clinically significant response is improvement of itch. Serum bile acid levels do not always correlate with degree of itching and it is difficult to assign an absolute number that could be deemed significant. However in practice a reduction in serum bile acid levels is usually associated with an improvement in itch scores. In addition, any reduction may slow the damage to the liver caused by high serum bile acid levels.
9. In your view, is there an unmet need for patients and healthcare professionals in this	Pruritus associated with PFIC (and other profoundly cholestaic conditions) has no completely reliable medical treatment options. Pharmacological management of itch is usually of limited benefit and the effect is often lost as cholestasis worsens. Whilst agents such as colestyramine may be of benefit in reducing bile acid levels, by interrupting enterohepatic recirculation, they are almost unpalatable and difficult for

condition?	children to take and in practice are rarely successful. Rifampicin use carries concerns around antimicrobial stewardship and the agents used more rarely have limited effect. These children have no good medical treatment available to them, and we have little to offer, and as a result come to liver transplant, with all of its inherent risks, because of the impact of pruritus on their quality of life. There is a huge unmet need for alternative therapies.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Current treatment options are medical management with ursodeoxycholic acid (to improve bile flow), colestyramine (bile acid sequestrant), rifampicin (interrupt bile acid recirculation), ondansetron (5HT3 receptor antagonist that may have an impact on itch receptors at the epidermis). Other agents may be used very rarely such as naltrexone (opioid antagonist - inhibiting itch response but tachyphylaxis occurs so short term use only) and sertraline (central effect on itch response - rarely used in children). If medical management fails then biliary diversion or liver transplant is required
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	In-house guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is	As far as I am aware the pathway of care for these children varies little across the NHS.

from outside England.)	
• What impact would the technology have on the current pathway of care?	The current therapies are not effective in all children and are used because we have nothing else to offer. This technology is expected to have a significant impact on the quality of life of children (and their carers) by reducing pruritus. If the secondary effects of improving weight gain, preventing need for biliary diversion and delaying the need for liver transplant are as anticipated then this would have a huge impact on the welfare of families of children with this condition as well as on clinical outcomes for the child.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is currently on in use within clinical trials
• How does healthcare resource use differ between the technology and current care?	Similar resource in terms of monitoring and follow up. However, may delay or prevent the need for biliary surgery or transplantation thus reducing NHS burden
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It needs to initiated in specialist centres. Ongoing monitoring and supply could be through secondary or primary care (hub and spoke model).
• What investment is needed to introduce the technology? (For example, for facilities,	If prescribing is to remain in the tertiary centres then funding to support homecare delivery would be required (large geographical areas covered by each tertiary centre). No special training or facilities needed

equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes - liver transplantation carries risks (e.g. graft failure, rejection, infection, mortality approx 5% at 5 years) and if that can be delayed or prevented then those risks would be averted
• Do you expect the technology to increase health-related quality of life more than current care?	Definitely
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with PFIC or potentially other severe cholestatic conditions
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	I think it will be about the same as current therapies with the advantage of being licensed. The treatment is a once a day medicine, easy to administer in granule or capsule form (so suitable for all age ranges). There are no drug interactions (unlike colestyramine or rifampicin) and there appear to be minimal side effects. Monitoring is similar to monitoring currently undertaken in terms of blood tests and frequency of visits needed
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stop rules should include: - deterioration of liver function and/or development of liver nodules and progression to liver transplant - this would be routinely monitored for this condition regardless of treatment - failure of treatment to improve itch scores (these are routinely measured informally in the clinic setting)
16. Do you consider that the use of the technology will	Need to ensure consideration given to the impact of the therapy on the family as well as the patient

result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes - current treatments do not work universally or for any length of time. They do not have any impact on the progression to end stage liver disease

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile is minimal for this technology. The drug is not absorbed so systemic side effects are not seen other than loose stools and abdominal pain. These can also be a feature of some types of PFIC. As we develop experience using the agent we may find ways of mitigating these side effects for example by splitting the dose
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in pruritus - yes Reduction in serum bile acid levels - yes Improvement in liver function tests - yes Improvement in growth - yes
• If surrogate outcome	The reduction in serum bile acid levels, improvement in liver function tests and growth seen in the trials

measures were used, do they adequately predict long-term clinical outcomes?	suggest a benefit beyond just treating itch and that is likely to predict longer term benefits. It is too early to have that data.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	N/A
Equality	
22a. Are there any potential equality issues that should be taken into account when	No, other than to ensure the technology is also available for adults with this condition if these children thrive without needing liver transplant and reach adulthood or for those who present later in childhood/early adulthood

considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	Current care is unaffected by age
Topic-specific questions	
23. How many subtypes of PFIC have been identified to date?	
24. For people with PFIC types other than PFIC1 and 2, would you expect: a) A different treatment pathway? b) A different response to standard care treatment (as demonstrated by reduction in serum bile	No but too few patients in each subtype

acid and pruritus)? c) Other important response markers not captured in the clinical trials?	
25a. Would nutritional management ever be the sole PFIC treatment, or always be given in combination with oral therapies? 25b. Would nutritional management and off-label oral therapies continue after surgical biliary diversion or liver transplant? 25c. Would you ever observe an ongoing pruritus response to off-label therapies?	No - additional therapies always needed Nutritional therapies would continue as would urodeoxycholic acid after biliary diversion but other antipruritics would be expected to stop. After transplantation these would not be necessary in the long term (may require short term nutritional management to establish normal feeding) except in some children with type 1 who have ongoing malabsorption . Only occasionally in children with mild symptoms

26. In the NHS, how frequent is surgical biliary diversion in people with: a) PFIC 1 b) PFIC2 c) Other subtypes of PFIC	
27. How often are non-PEBD surgeries (e.g. partial internal biliary drainage, internal ileac exclusion) conducted in the NHS? What factors influence the choice of surgery for a patient?	
28. What symptoms necessitate re-transplant in people with PFIC1 and 2? Would you associate more complications and a poorer	Same indications for re-transplant as for other conditions. In BESP the development of anti-BSEP antibodies has been noted resulting in apparent recurrence of disease. This may require rituximab therapy or re-transplant Not overall

quality of life with a second transplant compared with the first?	
29. How would you classify a lack of response to treatment with odevixibat?	No improvement in itch score or serum bile acid level
30. How frequently do people with PFIC develop hepatocellular carcinoma (HCC)? Would these people follow the standard HCC treatment pathway?	
31. Does treatment for PFIC differ in the UK to that in America, Canada and Europe? If so, how?	
Key messages	

32. In up to 5 bullet points, please summarise the key messages of your statement.

- Pruritus in PFIC is an incredibly challenging symptom of chronic cholestasis for children to live with. It has a massive impact on their sleep, development, schooling, growth and a severe knock-on effect for the whole family. It cannot be overstated how awful this is to live with
- Odevixibat offers a therapy that can significantly improve quality of life by improving pruritus
- It also has the potential to improve long term outcomes for children by delaying or preventing liver injury secondary to bile acids and the slide into end stage liver disease or hepatocellular carcinoma
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Odevixibat for progressive familial intrahepatic cholestasis: A Highly Specialised Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Emma Hock, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Praveen Thokala, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Geoff Holmes, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Kate Ennis, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK Alastair Baker, Consultant Paediatric Hepatologist, King's College Hospital, London, UK
Correspondence Author	Emma Hock, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Date completed	Date completed (13/07/2021)

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Declared competing interests of the authors and clinical advisors

Alastair Baker has been recruited to be the PI of a future study of odevixibat for cholestatic itch in Alagille syndrome (ASSERT), for which he will be financially reimbursed by Alberio. He has also received financial reimbursement from Mirum Pharmaceuticals to study cholestatic itch. No other authors or clinical advisors declared competing interests.

Acknowledgements

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Hock E, Thokala P, Holmes G, Ennis K, Wong R, Baker A. Odevixibat for progressive familial intrahepatic cholestasis: A Highly Specialised Technology Appraisal. School of Health and Related Research (ScHARR), 2021.

Contributions of authors

Praveen Thokala and Kate Ennis critiqued the health economic analysis submitted by the company. Emma Hock summarised and critiqued the clinical effectiveness data reported within the company's submission. Geoff Holmes critiqued the statistical aspects of the submission. Ruth Wong critiqued the company's search strategy. Alastair Baker provided clinical advice to the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AASLD	American Association for the Study of Liver Diseases
AEs	Adverse events
AIC	Akaike's Information Criteria
ASBT	Apical sodium-dependent bile acid transporter
BIC	Bayesian Information Criteria
BNF	British National Formulary
BRIC	Benign recurrent intrahepatic cholestasis
BSEP	Bile salt export pump
CASP	Critical Appraisal Skills Programme
CEAC	Cost-Effectiveness Acceptability Curve
CFB	Change from baseline
CIC	Chronic intrahepatic cholestasis
CS	Company Submission
CSR	Clinical Study Report
DSAs	deterministic sensitivity analyses
EASL	European Association for the Study of the Liver
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D-3L	EuroQol 5 dimensions 3 level
ERG	Evidence Review Group
EU	European Union
FAS	full analysis set
FIC	Familial intrahepatic cholestasis
GEE	Generalised Estimating Equation
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HST	Highly specialised technology
IBAT	Ileal bile acid transporter
ICER	Incremental Cost Effectiveness Ratio
IHC	Intrahepatic cholestasis
IPD	Individual participant data
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
KM	Kaplan-Meier

LT	liver transplantation
LYG	Life years gained
MA	Meta-analysis
MRU	Medical Resource Use
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NORS	National Organ Retrieval Service
NR	Not Reported
ONS	Office of National Statistics
PAS	Patient Access Scheme
PEBD	Partial external biliary diversion
PedsQL	Paediatric quality of life inventory
PH	Proportional Hazards
PFIC	progressive familial intrahepatic cholestasis
PRIME	PRIority MEdicines
PSA	probabilistic sensitivity analysis
PSM	Partitioned Survival Model
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QIC	Quasi-likelihood under Independence Model Criterion
RCT	Randomised Controlled Trial
RoW	Rest of World
SAE	Serious adverse event
sBA	Serum Bile Acid
SBD	Surgical biliary diversion
SE	Standard error
SD	Standard deviation
SoC	Standard of Care
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event

TP	Transition probability
TSD	Technical Support Document
TTO	Time-trade off
UDCA	Ursodeoxycholic acid
US	United States
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Critique of the decision problem in the company's submission

The ERG considers the company's description of the underlying health problem and its impact on PFIC patients and their caregivers to be appropriate. The decision problem addressed in the CS is generally in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The evidence presented in the CS, however, does not comprehensively address the NICE scope, in that the CS presents no or limited evidence relating to rarer PFIC subtypes (3 to 6) and does not present any comparative evidence for odevixibat with partial external biliary diversion (PEBD). The outcome health-related quality of life (HRQoL) is listed in the NICE scope; the CS reports on some evidence relating to HRQoL in Appendix 8, however evidence for HRQoL is not presented in Section 9.6 of the CS, along with other clinical effectiveness evidence, as this was an exploratory outcome in the studies that provided evidence for the CS (see Section 4.2.1.4).

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical evidence relating to odevixibat for treating PFIC is based on three studies: the PEDFIC1 trial, a double-blind Phase 3 RCT, which examined the efficacy of two doses of odevixibat (40 µg/kg/day and 120 µg/kg/day) for treating PFIC1 and PFIC2; the PEDFIC2 study, a Phase 3 single-arm open-label extension of the PEDFIC1 trial plus additional patients enrolling for the first time; and the Phase 2 study, a Phase 2 single-arm, open-label dose-finding study. The majority of the evidence presented in the CS relates to the PEDFIC1 and PEDFIC2 studies, as they are more methodologically robust studies that focus specifically on PFIC and have a longer duration of treatment and follow-up.

The European Union (EU)/Rest of World (RoW) primary outcome of the PEDFIC1 trial was the proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L after 24 weeks of treatment, which the ERG considers to be an appropriate outcome for judging the effectiveness of odevixibat versus placebo in PFIC. A third of patients (33.3%) randomised to odevixibat achieved this outcome, versus none in the placebo group (0%) (p=0.0015, unadjusted); this included 43.5% and 21.1% of patients in the odevixibat 40 and 120 µg/kg/day dose groups, respectively [redacted]. The United States (US) primary outcome of the PEDFIC1 trial was the proportion of positive pruritus

assessments at the patient level over the 24-week treatment period, using the PRUCISION© ObsRO instrument developed by Albireo to assess pruritus symptoms and impact in PFIC patients and their caregivers, which is a validated measure of pruritus that is specific to this population. A greater proportion of positive pruritus assessments at the patient level over the 24-week treatment period was achieved by patients treated with odevixibat (53.5%) relative to the placebo arm (28.7%); patients treated with odevixibat achieved a response just over half of the time, on average, over all assessments made over the course of the 24-week treatment period. [redacted].

The EU/RoW primary outcome of the PEDFIC2 study was change from baseline in sBA concentration after 24 weeks of treatment (for the interim analysis), which the ERG judges to be an appropriate outcome. sBA concentrations declined in all patients across the treatment period, with [redacted]. The US primary outcome of PEDFIC2 was the proportion of positive pruritus assessments over the treatment period (from baseline to Week 24 at the interim data cut-off, 15th July 2020) using the Albireo ObsRO instrument. [redacted] No patients were listed for liver transplantation (LT) surgery or were added to the list. [redacted] (of [redacted]) patients enrolled in PEDFIC2 had discontinued.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The first key uncertainty relates to a lack of clarity around the definition of an '*adequate clinical response*', the judgement of which is required by clinicians when deciding whether or not to escalate the odevixibat dose after 3 months of continuous therapy, as reported in the draft SmPC. In response to

clarification question A9, the company stated that a precise definition is unknown at the present time, and they are currently refining this in collaboration with key clinicians in the field. Therefore, this limits the extent to which the ERG can comment on the similarity of the clinical evidence for odevixibat to the clinical context in England.

A second key uncertainty relates to an inconsistency between the dose administered in the PEDFIC2 study and the recommended dose detailed in the SmPC. Patients were started on the higher dose to begin with (although some patients received the 40 µg/kg/day dose for 3 or 6 months in PEDFIC1), and therefore it is possible that some patients will have received a higher dose than the recommended starting dose for at least three months. Additionally, patients from PEDFIC2 who achieved an adequate clinical response on the 40 µg/kg/day dose in PEDFIC1 would have received a higher dose in PEDFIC2 than they would have in clinical practice, according to the SmPC dosing instructions. The company clarified that this was to maintain blinding in PEDFIC1 (see Section 4.2.1.2). Nevertheless, the ERG believes that the trial data may not accurately reflect clinical practice and may potentially have led to the efficacy of odevixibat being potentially overestimated in a number of cases in the findings of the PEDFIC2 study.

A third key uncertainty relates to the lack of evidence for the comparative efficacy of odevixibat and PEBD. This makes it difficult to determine where in the treatment pathway odevixibat should go, relative to PEBD, and also impacts on the cost-effectiveness modelling for odevixibat. Comparative data would have improved the accuracy of the modelling assumptions, and informed clinical decision-making. The planned Odevixibat vs External Control [redacted] comparison [redacted] with external controls [redacted] (see Section 4.2.1.6) is expected to provide data on the relative efficacy of odevixibat and PEBD, which should address this uncertainty.

A fourth key uncertainty relates to the effectiveness of odevixibat among previously treated patients. Patients who had undergone PEBD surgery >6 months prior to the PEDFIC1 baseline were permitted to enrol in the study, and information presented in the company's clarification response suggests that [redacted] Therefore, the impact of prior PEBD on odevixibat treatment (and vice versa) is unknown.

A fifth key uncertainty relates to the relatively short duration of follow-up in the PEDFIC1 and PEDFIC2 studies, with comparative data only available for a 24-week time period and follow-up only

extending to 48 weeks by the point of the PEDFIC2 data cut-off, for those rolling over from PEDFIC1 to PEDFIC2. This has meant that it was difficult to assess some important outcomes that might only present over the longer-term, such as survival and transplant-free survival. In addition, the longer-term impact of odevixibat on sBA concentration and pruritus is also unknown.

A sixth key uncertainty relates to the lack of more robust, comparative evidence (and little evidence overall) for the effectiveness of odevixibat among PFIC patients with subtypes other than PFIC1 and PFIC2. The ERG recognises that the small number of patients with other PFIC subtypes presents a challenge to the collection of such data, however the point remains that odevixibat is proposed for patients with PFIC in general, whereas there is only comparative evidence relating to patients with PFIC1 and PFIC2, and some preliminary evidence among patients with PFIC3.

Another key source of uncertainty is the impact of PFIC subtype (1 or 2) on the effectiveness of odevixibat in terms of key outcomes (e.g. sBA response and pruritus response). Some data from the PEDFIC1 trial suggest there may be differential effects, however the study was not powered to detect differences in these subgroups, and statistical comparisons have not been made.

The single-arm, open-label nature of PEDFIC2, which is the only study to include patients with PFIC subtypes other than PFIC1 and PFIC2, and the only study to report longer-term follow-up, also introduces uncertainty. There is a possibility of potential biases such as attrition bias, natural recovery and regression to the mean; a double-blind RCT would have been a more rigorous study design.

1.4 Summary of cost effectiveness evidence submitted by the company

The CS presents the methods and results of a *de novo* health economic model of odevixibat versus standard of care for patients with PFIC, from a societal perspective which includes productivity costs and health effects on caregivers. The model adopts a state transition (semi-Markov) approach and includes the following health states: (i) response, (ii) loss of response, (iii) PEBD response, (iv) PEBD, loss of response, (v) LT, (vi) post-LT and (vii) death. The model uses data from PEDFIC1 and PEDFIC2 to estimate the response rates; other transitions, including those relating to mortality risk, are informed by external data such as the NAPPED study. The model includes a key assumption that none of the patients in the odevixibat arm receive PEBD. [redacted]

Based on a re-run of the probabilistic version of the company's model by the ERG, odevixibat is expected to generate an additional [redacted] QALYs at an additional cost of [redacted], with a corresponding ICER of [redacted]. The deterministic version of the model produces a slightly lower ICER of [redacted]. At willingness-to-pay thresholds (WTP) £100,000 per QALY gained and £300,000 per QALY gained, the probability that odevixibat is cost-effective is [redacted] and [redacted], respectively. Also, the company's submitted model suggests that lower the response rate of odevixibat, the lower the ICER.

Similarly, increased loss of response for odevixibat results in lower ICERs. The ERG considers this reason for this non-intuitive finding is that odevixibat seems to have high cost-benefit ratio and moving the patients off odevixibat to liver transplant, which seems to have a more favourable cost-benefit ratio results in lower ICERs.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The ERG's critical appraisal identified several issues relating to the company's original model and the evidence used to inform its parameters. These include: (1) the presence of few minor model errors/limitations, (2) deviation from the NICE reference case by including productivity costs, (3) issues regarding assumptions around PEBD surgery, (4) issues regarding the probability of liver transplant and re-transplant, (5) issues relating to utility values, (6) issues relating to post-LT mortality risk parameters, (7) counterintuitive relationship odevixibat effectiveness and cost-effectiveness, (8) uncertainty around the sBA response, (9) issues relating to treatment discontinuation, and (10) issues relating to drug costs estimation.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The clinical evidence for odevixibat for treating PFIC includes a Phase 3 RCT (PEDFIC1), which used a centralised computer-based method of allocation, all outcomes stated in the protocol were reported on, and all patients who received at least one dose of their allocated treatment were analysed in the group to which they were randomised. The main single-arm study reported on (PEDFIC2) provided longer-term follow-up from patients in the RCT, as well recruiting treatment-naïve patients from a broader set of PFIC patients, including those with rarer subtypes (PFIC3 to PFIC6).

Clinical advisors to the ERG considered that the structure of the company's health economic model was broadly appropriate and reflected the key outcomes associated with patients with PFIC. With the exception of the inclusion of productivity costs, the company's economic analysis is generally in line with the NICE scope.

1.6.2 Weaknesses and areas of uncertainty

The definition of an '*adequate clinical response*', which clinicians are required to judge when making decisions about dose escalation (as reported in the draft SmPC) lacks clarity, thus the ERG cannot accurately determine the similarity of the clinical evidence for odevixibat with the clinical context in England.

At the present time, there is a lack of evidence for the comparative efficacy of odevixibat and PEBD, which makes it difficult for the ERG to assess the appropriateness of the proposed positioning of odevixibat in the PFIC treatment pathway.

The effectiveness of odevixibat among previously treated patients, in particular patients with prior PEBD surgery, is uncertain, due to small numbers of patients and no separate subgroup analysis.

The relatively short follow-up durations of the PEDFIC1 and PEDFIC2 studies have precluded examination of the effectiveness of odevixibat on important longer-term outcomes such as survival and transplant-free survival.

There is a lack of comparative evidence (and little evidence overall) for the effectiveness of odevixibat among PFIC patients with subtypes other than PFIC1 and PFIC2.

The impact of PFIC subtype on the effectiveness of odevixibat in terms of key outcomes (e.g. sBA response and pruritus response) has not been statistically examined.

The PEDFIC2 study used an open-label design, which may have impacted on measurements taken, and introduced potential biases such as attrition bias, natural recovery and regression to the mean.

The ERG believes that there is considerable uncertainty surrounding:

- The level of HRQoL experienced by patients who receive odevixibat or SoC over time, especially HRQoL for patients receiving PEBD
- Disutility of caregivers for patients with PFIC, and the appropriateness of including caregiver disutilities in the analyses
- Dosage of odevixibat that would be realised in clinical practice

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook three broad sets of exploratory analyses using the base case version of the company's model.

The first set involved forming an ERG-preferred analysis, which includes: correction of errors/limitations identified within the ERG's critical appraisal; exclusion of productivity costs; assuming that the probability of LT in prior PEBD non-responders was the same as the probability of LT in post-PEBD non-responders; using ERG meta analyses results for post LT mortality; inclusion of costs of adverse events and amending the utility values. The ERG's preferred ICER for odevixibat versus SoC is estimated to be [redacted] using the probabilistic version of the model. The deterministic version of the model yields a lower ICER for odevixibat versus SoC of [redacted].

Additional exploratory analyses were also undertaken using the ERG's preferred version of the model to explore the impact of alternative values for parameters such as annual loss of response, mortality risks and the impact of altering assumptions regarding drug dosage, inclusion of PEBD surgery for non-responders on odevixibat, and excluding caregiver disutilities. The ERG's additional exploratory analyses using the ERG's preferred version of the model produce ICERs which are in the range of [redacted] to [redacted]. These exploratory analyses highlight the significant influence of the assumptions regarding odevixibat dose and inclusion of caregiver disutilities.

To assess the appropriateness of the proposed positioning of odevixibat in the PFIC treatment pathway, the ERG performed exploratory analyses using fully incremental comparison of possible treatment pathways to provide additional information for the appraisal committee. These analyses suggest that the "Odevixibat (including PEBD)/LT" treatment pathway, which involves patients starting with odevixibat, then receiving PEBD or LT after odevixibat loss of response, seems to accrue highest QALYs at an ICER of [redacted] versus SoC.

2 BACKGROUND

This report provides a review of the evidence submitted by the company (Albireo) in support of odevixibat (Bylvay®, A4250) for treating patients with progressive familial intrahepatic cholestasis (PFIC). It includes evidence presented within the company's submission (CS) received on 12th May 2021,[1] and the responses to clarification questions provided by the company on 16th June 2021.[2]

This chapter presents a brief summary and critique of the company's description of the disease and the current treatment pathway for PFIC in England.

2.1 Critique of company's description of underlying health problem

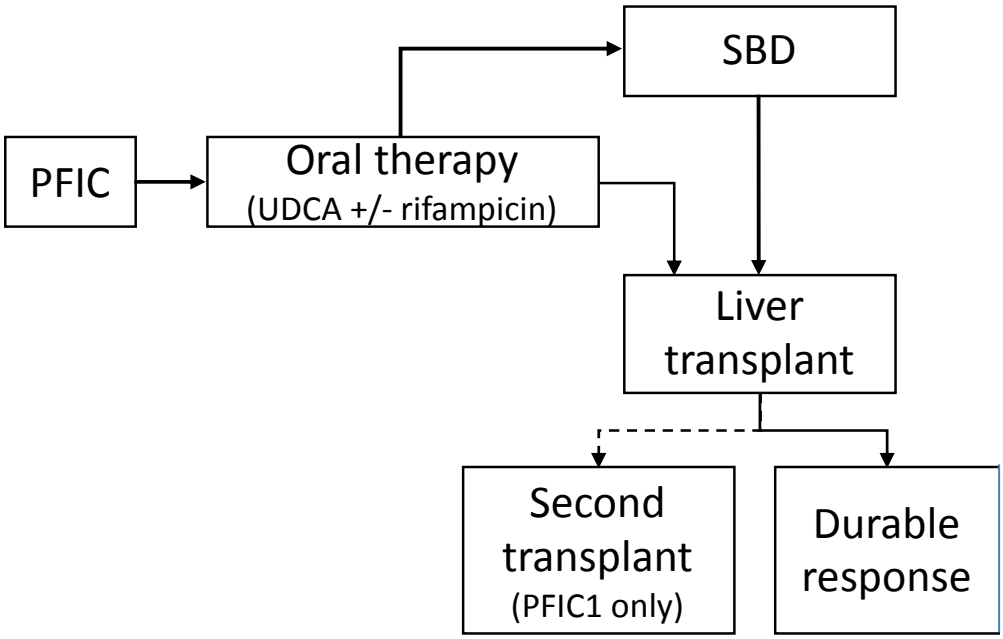
PFIC is a rare, heterogenous group of autosomal recessive liver disorders whereby bile production and excretion are impaired, and biliary substances (including serum bile acids (sBA)) cannot be eliminated from the liver and instead re-enter circulation.[3-6] PFIC and the resultant cholestatic liver disease can lead to progressive liver damage, including fibrosis, cirrhosis, portal hypertension, liver cancer, end stage liver disease and death.[3, 4, 6, 7] The main symptoms of PFIC are jaundice and pruritus,[3, 4, 6] a severe itching, which has been described as the most intolerable symptom of cholestasis.[3, 4] Pruritus is thought to be a result of increased sBAs.[4, 8] Three main subtypes of PFIC have been identified, which vary by genetic defect, clinical presentation, laboratory findings and liver histology; PFIC1 and PFIC2, in which bile acid secretion is depleted, and PFIC3, in which phospholipid secretion is impaired.[3, 4, 6] Additional subtypes have been recently discovered through genetic testing, for instance, PFIC4, PFIC5 and PFIC6.[3, 4] PFIC subtypes 1, 2 and 3 are caused by deficiencies in the FIC1 gene (*ATP8B1*), bile salt export pump (BSEP) gene (*ABCB11*), and multidrug resistance Class III (MDR3) gene (*ABCB4*), respectively.[4, 7] PFIC1 and PFIC2 typically begin in early infancy, whereas PFIC3 occurs later in childhood or young adulthood.[4, 7] PFIC2 typically presents earlier in infancy than PFIC1.[3] Worldwide incidence has been reported at 1 per 50,000 to 1 per 100,000 live births.[6] A recent systematic review reports that PFIC2 is more prevalent than PFIC1 and PFIC3 in the USA and Europe, with prevalence rates of 37.5-90.9%, 10.4-37.5%, and 28.0-37.5% among PFIC patients diagnosed via genetic testing, respectively.[3] The CS[1] contains a comprehensive account of PFIC in terms of the underlying physiology, epidemiology, prognosis and impact on patients and their caregivers.

2.2 Critique of company's overview of current service provision

The CS[1] provides a comprehensive overview of service provision. The CS states correctly that at the time of the submission, no National Institute for Health and Care Excellence (NICE), National Health Service (NHS) England or other national guidance documents on the management of PFIC were available, and that no disease-modifying medical therapy is currently approved that can impact on the long-term prognosis of the condition. Therapeutic options consist of therapy to manage the symptoms of the condition, including ursodeoxycholic acid (UDCA), rifampicin, nutritional support, vitamin

intake support, and treatment of extrahepatic features. First-line treatment typically consist of the use of off-label drugs such as UDCA and rifampicin to treat the cholestatic pruritus, followed by surgery – either surgical biliary diversion (most commonly partial external biliary diversion (PEBD)) or liver transplantation (LT) (see Figure 1).

Figure 1: Treatment pathway for PFIC (reproduced from CS, Figure 6)



SBD - surgical biliary diversion; UDCA - ursodeoxycholic acid
SBD most commonly comprises partial external biliary diversion (PEBD)

Pharmacological treatment options consist of off-label use of UDCA, rifampicin, antihistamines, cholestyramine and naltrexone, to treat cholestatic pruritus. Clinical advice received by the ERG suggests these drugs are used in clinical practice in England, but around 40% of patients do not respond, and the CS states that a minority of patients respond to these medications. Clinical literature has suggested that between 35% and 70% of PFIC patients experience a complete or partial response.[6] UDCA is typically given first-line, and is the most commonly used drug, although rifampicin may also be used.[4, 6] UDCA operates by promoting bile flow and reducing the toxicity of bile acids and is more effective in patients with less severe disease.[4, 6] Rifampicin inhibits the uptake of bile acids.[4, 6] There is limited evidence on the efficacy of these medications and the company were not able to identify any controlled trial evidence examining their effectiveness in PFIC. Antihistamines can reduce the physical sensation of pruritus, and cholestyramine prevents bile acids from entering the enterohepatic cycle.[4, 6]

Surgical options include biliary diversion and LT. Surgical biliary diversion is used to treat PFIC when pruritus persists despite first-line off-label medical treatment. Biliary diversion diverts bile from the gallbladder, decreasing the influx of bile acids to the gut and reducing the bile acid pool. PEBD involves

the creation of a permanent stoma, through the use of a 10-15 cm jejunal conduit between the fundus of the gallbladder and the abdominal skin, which diverts bile away from the liver, diminishes reuptake and decreases the pool of bile salts.[4, 6] The CS reports on a number of papers that have reported large reductions in sBA levels, leading to improvements in pruritus, sleep, fibrosis and growth following PEBD. Longer-term, PEBD may reduce the need for LT, or delay the time to LT.[4] PEBD surgery is more effective in patients who have not yet developed liver cirrhosis or advanced liver disease.[4, 6] The most common complication of PEBD surgery is stoma prolapse, and the surgery also carries a risk of postoperative cholangitis, dehydration and stoma revision.[4] In addition, the experience of having a stoma can be distressing for patients and make social interactions and usual activities more difficult.[9] Clinical advice received by the ERG has suggested that PEBD surgery is rarely conducted among PFIC patients in England, [redacted]. Other types of surgical biliary diversion are less common and include partial internal biliary diversion, for which there is little evidence on efficacy, and ileal exclusion/bypass, which is not commonly conducted in PFIC, and both can lead to pruritus recurrence in the majority of patients.[4]

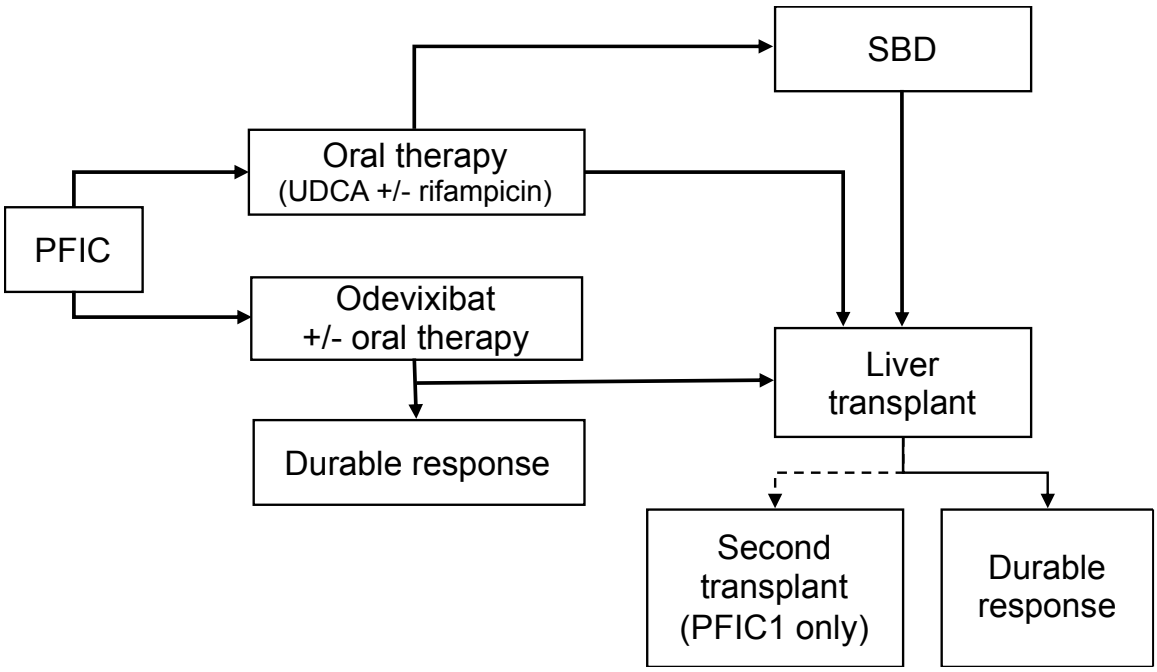
LT is eventually required by most PFIC patients, even after PEBD and off-label oral drug therapy, to enhance survival, due to the progressive and life-threatening nature of the disease. However, LT is associated with morbidity and mortality risks, as well as complications such as graft rejection and graft steatosis, and lifelong immunosuppression.[4, 6] In addition, cholestasis can recur even after LT, and patients with PFIC1 still experience extrahepatic manifestations, such as diarrhoea or liver steatosis, which may worsen.[4, 6] Clinical advice to the ERG has also suggested that PFIC1 patients tend to experience adverse effects following LT, and so clinicians are less likely to attempt transplantation in patients with the PFIC1 subtype. In addition, the availability of organ donors can be an issue. Clinical advice received by the ERG has suggested that LT surgery is technically easier once patients reach a weight of 5 kg, and from a weight of 8 kg organ availability improves.

2.3 Critique of company's proposed positioning of odevixibat in the treatment pathway

The company's proposed positioning of odevixibat is shown in Figure 2. Odevixibat is proposed as a first-line treatment for PFIC, as an alternative or adjunct to off-label oral therapy such as UDCA with or without rifampicin. The company propose that patients are treated with odevixibat in place of surgical biliary diversion such as PEBD, and that patients who do not respond to odevixibat would then go on to receive LT. This proposed positioning suggests that patients who are non-responders to odevixibat will not have the option of receiving a subsequent PEBD, and likewise that patients with a prior PEBD are not eligible to receive odevixibat. Clinical advice received by the ERG was in disagreement about whether patients would be given a PEBD following odevixibat in clinical practice, with one clinician expressing a desire to retain this treatment option and another who suggested they would not offer a

PEBD after odevixibat as the two are medically and surgically equivalent. In evidence from the PEDFIC1 trial presented in the CS, patients were eligible for the trial with prior PEBD surgery, if the surgery was ≥6 months prior to the PEDFIC1 baseline, and the company's clarification response (question A18) clarifies that [redacted] patients in total had a prior history of PEBD surgery (see Section 4.2.1.1). Therefore, whether or not odevixibat should be considered before and/or after PEBD surgery in the treatment pathway is uncertain. In addition, the Final NICE scope[10] has recommended that PEBD could be considered a comparator to odevixibat. The company's proposed positioning of odevixibat on the treatment pathway, however, does not suggest equivalency with PEBD; PEBD is positioned as a second-line treatment, following off-label oral therapy, whereas odevixibat is positioned as a first-line treatment, concurrent with any off-label oral therapy given. Thus, whether patients are treated with odevixibat first-line, or second-line following off-label oral therapy (as with PEBD), is also uncertain.

Figure 2: Position of odevixibat in the treatment pathway for PFIC (reproduced from CS, Figure 8)



SBD - surgical biliary diversion; UDCA - ursodeoxycholic acid
SBD is most commonly a partial external biliary diversion (PEBD)

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final scope issued by the National Institute for Health and Care Excellence (NICE)[10] and addressed in the CS is presented in Table 1.

Table 1: Company's statement of the decision problem (reproduced from CS, Table 1)

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with progressive familial intrahepatic cholestasis (PFIC)	None, although it should be noted that the expected indication is for patients with PFIC who are aged 6 months or older	
Intervention	Odevixibat (A 4250)	None	
Comparator(s)	Established clinical management without odevixibat (A 4250) which may include: • off-label drug treatments such as ursodeoxycholic acid (UDCA) • surgical interventions such as partial external biliary diversion or internal ileal exclusion	Although off-label drug treatments are included in the economic model they are not considered to be a direct comparator.	Off-label oral drug treatments, such as UDCA and rifampicin, have very limited symptomatic efficacy and do not alter the underlying disease or change the course of disease. No RCTs investigating off-label therapies have been identified. In clinical practice, odevixibat may be used in addition to off-label oral therapies (as was the case in the Phase 3 clinical trial). In the economic model off-label oral therapies are assumed to have no treatment effect and costs for off-label therapies are included both for patients receiving odevixibat and the comparator arm.
Outcomes	The outcome measures to be considered include: • change in serum bile acid level • change in symptoms of PFIC including reduction of pruritus • measures of faltering growth • overall survival • measures of disease progression • number of patients requiring surgical interventions • adverse effects of treatment	No variation, however as part of the assessment of health-related quality of life, sleep parameters as measured by the observer-reported outcomes (ObsRO) instrument, a validated tool for assessment of pruritus and sleep disturbance in PFIC, have been included.	Reporting of sleep parameters is of particular importance in PFIC as patients will often experience intense pruritus at night, disturbing their sleep and that of the caregiver. Poor sleep leaves patients and parents exhausted, leading to poor performance at school and work with significant impact on quality of life.

	• health-related quality of life (for patients and carers)		
Subgroups to be considered	None	None	
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options	None	
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	None	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.	None	

Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangement for the intervention under evaluation	None	

3.1 Population

The patient population in the CS[1] is consistent with the population defined in the final NICE scope,[10] which is people with PFIC. There are, however, two issues that impact on this. Firstly, the company note that the expected indication is for patients with PFIC aged ≥6 months, which is consistent with the draft Summary of Product Characteristics (SmPC),[11] which states: "*Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older*". Clinical advice received by the ERG concurs that this timeframe fits with patients who present younger but are typically older than 6 months when they commence treatment, and thus the ERG agrees that the expected indication is appropriate. Secondly, in terms of the broader PFIC patient population, the CS does not present any evidence relating to patients with the rarer PFIC subtypes PFIC4 and PFIC5, and presents limited evidence for patients with PFIC3 and PFIC6, with the majority of the clinical evidence (including all evidence from the pivotal randomised controlled trial (RCT)) relating to PFIC subtypes PFIC1 and PFIC2, which are the more prevalent PFIC subtypes in this patient population.

The clinical evidence presented in the CS[1] includes the PEDFIC1 RCT[12] (subtypes PFIC1 and PFIC2), the PEDFIC2 single-arm open-label extension study[13] (all PFIC subtypes) and the Phase 2 single-arm dose-finding study[14] (chronic cholestasis, including PFIC). All studies except the Phase 2 study included sites in the UK; the Phase 2 study also had a broader population than that defined in the final NICE scope,[10] and included patients with chronic cholestasis, a sub-sample of which had PFIC. The Phase 2 study, however, was a short duration (4-week) dose-finding study, and the clinical evidence relevant to this appraisal focuses on evidence from the two larger studies, PEDFIC1 and PEDFIC2. The ERG's clinical advisors were satisfied that the populations recruited into PEDFIC1 and PEDFIC2 broadly reflect the PFIC population who would be considered eligible for treatment with odevixibat in England.

As odevixibat has not yet received a UK marketing authorisation, it is not clear whether certain medical conditions or patient groups may be contraindicated for treatment. The draft SmPC[11] states that no data are available for the use of odevixibat in paediatric patients below the age of 6 months, or patients with severe hepatic impairment (Child Pugh C), moderate or severe renal impairment or end-stage renal disease requiring haemodialysis. Special warnings for odevixibat include diarrhoea with accompanying dehydration, and increased monitoring of liver function and fat-soluble vitamin levels is advised.

3.2 Intervention

The intervention considered in the CS[1] is odevixibat (Bylvay®, A4250) taken orally one daily in the morning, in capsule form (or opened and the contents sprinkled on food) with or without food, at a dose of 40 μg/kg/day. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be escalated to 120 μg/kg/day. The company's clarification response[2] (question A9) states that the precise definition of an '*adequate clinical response*' is not yet refined, however, the

company are collaborating with clinicians in the field to develop an appropriate definition for clinical practice. Odevixibat is produced in four strengths of hard capsules: 200 µg, 400 µg, 600 µg, and 1200 µg. The number of capsules needed to achieve the doses of 40 µg/kg/day and 120 µg/kg/day, as recommended by the company, are given in Table 2 and Table 3.

Table 2: Number of odevixibat capsules needed to achieve the nominal dose of 40 µg/kg/day (reproduced from CS, Table 2)

Body weight (kg)	Number of 200 µg capsules		Number of 400 µg capsules
4 to < 7.5	**1**	or	N/A
7.5 to < 12.5	**2**	or	1
12.5 to < 17.5	**3**	or	N/A
17.5 to < 25.5	**4**	or	2
25.5 to < 35.5	6	or	**3**
35.5 to < 45.5	8	or	**4**
45.5 to < 55.5	10	or	**5**
≥ 55.5	12	or	**6**

Capsule strength/number in bold is recommended based on predicted ease of administration.

Table 3: Number of odevixibat capsules needed to achieve the nominal dose of 120 µg/kg/day (reproduced from CS, Table 2)

Body weight (kg)	Number of 600 µg capsules		Number of 1200 µg capsules
4 to < 7.5	**1**	or	N/A
7.5 to < 12.5	**2**	or	1
12.5 to < 17.5	**3**	or	N/A
17.5 to < 25.5	**4**	or	2
25.5 to < 35.5	6	or	**3**
35.5 to < 45.5	8	or	**4**
45.5 to < 55.5	10	or	**5**
≥ 55.5	12	or	**6**

Capsule strength/number in bold is recommended based on predicted ease of administration.

Odevixibat is an inhibitor of ileal bile acid transporter/apical sodium-dependent bile acid transporter (IBAT/ASBT), which binds reversibly to IBAT in the gut to decrease the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acids (SBAs).[11] Odevixibat is manufactured by Albireo Pharma, Inc. Odevixibat was granted an orphan designation for the treatment of PFIC by the European Medicines Agency (EMA) in May 2021 (EMEA/H/C/004691), and has also been granted access to the PRIority MEdicines (PRIME) scheme for the treatment of PFIC. A marketing authorisation application to the EMA was submitted on the 9th November 2020 and is being considered under an accelerated assessment.

The list price for odevixibat is [redacted] per pack of 30 capsules containing 200 µg, 400 µg, 600 µg or 1,200 µg, respectively. This corresponds to an annual acquisition cost ranging from approximately [redacted] per year for patients aged 5 years to [redacted] per year for patients after the age of 25 years (based on the increasing weight of patients over time). The company has proposed a Patient Access Scheme (PAS), which takes the form of a simple price discount of [redacted];

the discounted cost per year of odevixibat can range from [redacted] per year for patients at the age of 5 years to [redacted] per year for patients after the age of 25 years, depending on a patient's weight.

The SmPC[11] states that: "*Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat*".

3.3 Comparators

The final NICE scope[10] includes established clinical management without odevixibat, which encompasses: (1) off-label drug treatments such as UDCA; and (2) surgical interventions such as PEBD or internal ileal exclusion. The CS differs from this as off-label drug treatments are not considered to be a direct comparator. Nevertheless, concurrent off-label drug treatments such as UDCA were permitted across the entire patient population in the studies providing clinical evidence for the CS, and thus the clinical evidence could be considered consistent with the comparator specified in the final NICE scope,[10] which the ERG agrees is appropriate. The company's assertion that these off-label oral drug treatments "*have very limited symptomatic efficacy*" (CS, Table 1) is not entirely consistent with clinical advice received by the ERG and clinical literature, which suggests that some patients achieve a complete or partial response (see Section 2.2). However, the ERG agrees that these drugs do not fundamentally modify the underlying disease or disease course.

The ERG notes that no clinical evidence has been presented comparing odevixibat against PEBD, as no clinical evidence of a direct comparison is currently available, and a planned indirect comparison has not yet been undertaken (see Section 4.2.1.6). As odevixibat is considered medically equivalent to PEBD, a comparison of odevixibat with PEBD would have more completely addressed the Final NICE scope.

The pivotal RCT (PEDFIC1[12]) compared odevixibat (at two doses; 40 µg/kg/day and 120 µg/kg/day) with placebo. Therefore, head-to-head evidence for odevixibat versus established clinical management without odevixibat (including off-label drug treatments) is available, although this evidence considers only PFIC1 and PFIC2 subtypes. The single-arm open-label extension study (PEDFIC2[13]) contained limited evidence relating to PFIC3 and PFIC6 subtypes, thus there is no comparative evidence available for subtypes 3 and 6, and no evidence available for subtypes 4 and 5.

3.4 Outcomes

Outcomes listed in the final NICE scope[10] include:

- change in serum bile acid level
- change in symptoms of PFIC including reduction of pruritus

- measures of faltering growth
- overall survival
- measures of disease progression
- number of patients requiring surgical interventions
- adverse effects of treatment
- health-related quality of life (HRQoL; for patients and carers)

All outcomes defined in the final NICE scope[10] were included in the CS.[1] The outcome HRQoL, however, was not reported as a primary or secondary outcome for either study, but was reported as an exploratory outcome in both the PEDFIC1 CSR[12] and the PEDFIC2 CSR.[13] The ERG's preference is for HRQoL to be assessed as a secondary outcome, for inclusion in the cost-effectiveness modelling.

The company's economic model includes data relating to sBA concentration and pruritus response from PEDFIC1,[12] and discontinuation rate from PEDFIC2.[13] HRQoL data (assessed using the PedsQL instrument) from the odevixibat studies are not used in the company's economic model, although HRQoL was an exploratory outcome in these studies. Furthermore, the model does not include data from the odevixibat studies on growth, overall survival/mortality, measures of disease progression, the number of patients requiring surgical intervention, nor the adverse effects of treatment (see Section 5.2).

3.5 Other relevant factors

Section 5.1 of the CS1 states that there are no equality considerations relevant for the use of odevixibat for the treatment of PFIC.

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[1] for odevixibat for the treatment of PFIC. Section 4.1 provides a critique of the company's systematic review of clinical and safety evidence. Section 4.2 provides a summary of the clinical effectiveness and safety results, together with a critique of the included studies. Sections 4.3 to 4.5 of the template (relating to indirect comparisons and additional work undertaken by the ERG) are not applicable. Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify all clinical evidence regarding the efficacy and safety of odevixibat versus other interventions for the treatment of PFIC. The methods for the company's SLR of clinical evidence are detailed in the CS,[1] and in CS Appendices 1 and 2.[15]

4.1.1 *Searches*

The company performed one clinical effectiveness search to identify all clinical effectiveness and safety studies of odevixibat or comparator treatments of people with PFIC. All peer-reviewed publications were identified though database searches and were comprehensively reported.

The company searched several electronic bibliographic databases in March 2021 (see CS Appendix 17.1 Search strategy for clinical evidence): MEDLINE [via Ovid], MEDLINE in Process [via Ovid], EMBASE [via Ovid], Cochrane Database of Systematic Reviews [via Wiley], Cochrane Central Register of Controlled Trials [via Wiley], Database of Abstracts of Reviews of Effects [via CRD], NHS Economic Evaluation Database [via CRD], and Health Technology Assessment database [via CRD].

The company searched three trials registers, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the National Institutes of Health clinical trials registry (clinicaltrials.gov) and also the EU Clinical Trials Register (clinicaltrialsregister.eu) in March 2021. Several key conference abstract websites were searched in the last five years (2017-2021): the International Society for Pharmacoeconomics (ISPOR) Presentations Database, the American Association for the Study of Liver Diseases (AASLD), the International Liver Congress, European Association for the Study of the Liver (EASL), and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting (NASPGHAN). The company also searched three UK HTA agency websites: NICE; SMC; and AWMSG.

A search strategy comprising the disease terms (PFIC) were combined with the odevixibat or comparator terms (ursodeoxycholic acid, surgery, transplant and rifampicin) and translated consistently

across the databases. Since search filters were not applied, all relevant study designs (including adverse events) would be retrieved.

Having reviewed the search strategies, there were two ERG observations:

- the company's application of proximity searching (adj#) in statements 1-6 in the MEDLINE, MEDLINE in Process, Embase and Cochrane Library database searches will inevitably result in fewer records retrieved compared to Boolean searching (AND). It is unclear whether the company have explored the impact of proximity search on the sensitivity and recall of relevant studies to support and justify the approach taken.

- the ERG recommends the inclusion of the truncation for the term "BRIC*" (for BRIC1 and BRIC2) and the addition of the free-text term "farnesoid X receptor adj4 defic*" for PFIC5 as shown in the eligibility criteria used in the clinical review (Appendix 17.1.6. of the CS).

The ERG was not able to explore the impact of above given the time and resource constraints, but concludes that the company search is reasonably comprehensive.

4.1.2 *Inclusion criteria*

The inclusion criteria are generally consistent with the final NICE scope,[10] with three main inconsistencies: (1) the company's systematic review is broader in terms of population, listing PFIC and benign recurrent intrahepatic cholestasis (BRIC), whereas the final NICE scope[10] only refers to PFIC; (2) the company's systematic review inclusion criteria are broader in terms of interventions, listing odevixibat, surgery (including partial external biliary diversion and internal ileal exclusion), LT, UDCA, and rifampicin/rifampin, with no comparators listed, whereas the final NICE scope[10] only refers to odevixibat as an intervention and as the comparator; (3) the final NICE scope[10] specifies established clinical management (including off-label drug treatments such as UDCA, and surgical interventions such as partial external biliary diversion or internal ileal exclusion) as the comparator of interest, whereas the company's systematic review does not specify a comparator in Table 9 of the CS, and the comparators were specified as "*any or no treatment*" in CS Appendix 1,[15] Table 97. The company's clarification response[2] (question A1) states that the reason for this was to ensure that evidence relating to all relevant treatments were identified, whether or not odevixibat was also used in each study, in the interests of comprehensiveness. Whilst these inconsistencies differ from the decision problem set out in the final NICE scope,[10] the ERG does not consider them to be problematic, as they would broaden rather than narrow the scope of the review, meaning that the relevant papers would still have been identified.

4.1.3 *Critique of study selection*

CS Appendix 1[15] states that two reviewers independently screened titles and abstracts of each record and then full texts, with any discrepancies adjudicated by a third reviewer. The ERG considers this to be an appropriate and high-quality reviewing method. In response to clarification question A3,[2] the company have provided a list of studies excluded at full text stage. The ERG has screened the titles of the full texts excluded by the company and agrees that nothing of potential relevance has been excluded. Neither the ERG nor their clinical advisors are aware of any additional relevant studies within the scope of this appraisal.

4.1.4 *Critique of data extraction*

CS Appendix 1[15] states that two reviewers independently extracted data. The company's clarification response[2] (question A2) states that disagreements were discussed between the first and second reviewer, and any disagreement at that point was adjudicated by a third reviewer. The ERG considers this to be an appropriate and high-quality reviewing method. Data were extracted directly into the HST submission tables, and the ERG is satisfied that the fields extracted are comprehensive.

4.1.5 *Critique of quality assessment*

The quality of the PEDFIC1 trial[12] was assessed using the checklist in the NICE HST template for assessing the methodological quality of RCTs. The company's clarification response[2] (question A4) states that this critical appraisal tool was adapted from the Centre for Reviews and Dissemination guidance[16] for appraisal of risk of bias, which is based on the Cochrane Risk of Bias tool,[17] which is widely regarded as the most robust tool for assessing bias in RCTs. The company's clarification response[2] (question A5) states that risk of bias assessments were performed by one reviewer and checked by a second, with disagreements adjudicated by a third reviewer. The ERG considers this to be a robust reviewing method. The quality of the PEDFIC2 study[13] was assessed using the checklist in the NICE HST template for assessing the methodological quality of RCTs, which the ERG judges to be a less appropriate critical appraisal measurement tool, as PEDFIC2 is not an RCT. The company's clarification response[2] (question A7) states that the quality of the Phase 2 Study has been assessed using the NICE HST template checklist for the critical appraisal of observational studies. This bears a close resemblance to the Critical Appraisal Skills Programme (CASP) Cohort Study Checklist.[18] The ERG notes that only seven of the twelve questions in the CASP checklist have been used in the HST template checklist and applied to each of the three included studies. These questions, however, look like the most appropriate and relevant ones for the appraisal of these studies, and the company's clarification response[2] (question A7) states that the answers to the remaining questions have been addressed elsewhere in the CS.

No judgement on the overall risk of bias for the PEDFIC1 trial is reported in the CS,[1] and no attempt has been made to integrate the quality assessment into the findings, or to consider the overall impact of the quality of the included study on the results.

Quality assessment of the PEDFIC1 trial,[12] PEDFIC2 study,[13] and the Phase 2 Study[14] as undertaken by the company and the ERG, is presented in Section 4.2.3.

A quality assessment for the NAPPED cohort has also been presented in the CS.[1] The company's clarification response[2] (question A6) states that the quality of the NAPPED study has been assessed using the NICE HST template checklist for the critical appraisal of observational studies. As noted above, this bears a close resemblance to the CASP Cohort Study Checklist,[18] which is an appropriate checklist for this study type, although only seven of the twelve questions in the CASP checklist have been used in the HST template checklist and applied to each of the three included studies (see above).

4.1.6 *Critique of evidence synthesis*

The CS does not include any formal evidence synthesis.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 *Studies included in/excluded from the submission*

The CS[1] includes three studies that examine the efficacy and safety of odevixibat for the treatment of PFIC: PEDFIC1 (A4250-005),[12] a pivotal RCT; PEDFIC2 (A4250-008),[13] an open-label extension of the PEDFIC1 trial; and the Phase 2 study (A4250-003),[14] an open-label dose-finding study. The study characteristics of these four studies are presented in

Table 4.

Table 4: Characteristics of the PEDFIC1, PEDFIC2 and Phase 2 studies

Study	Design	Population	Interventions	Comparator	Primary outcome
PEDFIC1	RCT	Children with PFIC1 or PFIC2, an sBA concentration ≥100 µmol/L, pruritis score ≥2 (on 0-4 scale), aged ≥6 months to ≤18 years, with no biliary diversion surgery within 6 months of screening period.	Odevixibat 40 µg/kg/day (n=23) Odevixibat 120 µg/kg/day (n=19)	Placebo (n=20)	(1) Proportion of patients with ≥70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching ≤70 µmol/L (EU and RoW). (2) Proportion of positive pruritus assessments (scratching score of ≤1 or ≥1-point drop from baseline) at the subject level over the 24-week Treatment Period (US).
PEDFIC2	Single-arm	Patients from PEDFIC1 or patients of any age ≥5kg with PFIC, an sBA concentration ≥100 µmol/L, pruritis score ≥2 (on 0-4 scale) , with no biliary diversion surgery within 6 months of screening period, and no prior non-response to an IBAT inhibitor.	Odevixibat 120 µg/kg/day (n=69)	N/a (single-arm)	(1) Change from baseline in sBA after 72 weeks of treatment (reach ≤70 µmol/L or a reduction of 70%) (EU and RoW); (2) Proportion of positive pruritus assessments (scratching score of ≤1 or ≥1-point drop from baseline) over the 72-week treatment period (US).
Phase 2 study	Single-arm	Children with cholestatic pruritus (PFIC, ALGS, BA, SC or other types of cholestasis), sBA ≥2 times ULN, VAS itch ≥3 (0-10), aged ≥12 months to <18 years (<26 years in Sweden).	Odevixibat 10, 30, 60, 100 and 200 µg/kg/day (n=24) PFIC patients: 30 µg/kg (n=3); 60 µg/kg (n=3); 100 µg/kg (n=5); 200 µg/kg (n=2)	N/a	(2) Changes in total sBA levels from baseline to 4 weeks (efficacy) (2) incidence of treatment-emergent SAEs (safety) 30 mg

ALGS - Alagille syndrome; BA - biliary atresia; EU - European Union; N - number; IBAT - ileal bile acid transporter; N/a - not applicable; PFIC - progressive familial intrahepatic cholestasis; RCT - randomised controlled trial; RoW – rest of world; SAE - serious adverse event; sBA - serum bile acid; SC - sclerosing cholangitis; ULN - upper limit of normal; US - United States.

PEDFIC1[12] was a pivotal multicentre, double-blind, randomized, placebo-controlled, Phase 3 clinical trial. The Clinical Study Report (CSR)[12] states that patients were enrolled into the PEDFIC1 trial at 33

investigational sites across 14 countries: France (4 sites), Germany (4 sites), the UK (3 sites), Italy (2 sites), the Netherlands (2 sites), Belgium (1 site), Poland (1 site), Sweden (1 site), the US (8 sites), Turkey (4 sites), Australia (1 site), Canada (1 site), Israel (1 site) and Saudi Arabia (1 site). [redacted] patients were enrolled at sites in the UK.[12]

PEDFIC2[13] is an ongoing Phase 3, multi-centre, single-arm, open-label extension study. Patients were enrolled into this study in two cohorts. Cohort 1 consists of children with PFIC1 and PFIC2 who have participated in PEDFIC1 and either rolled over after completing the PEDFIC1 treatment period or who rolled over early due to a lack of efficacy or intolerable symptoms. Cohort 2 consists of children with PFIC (any subtype) who have elevated sBA levels and cholestatic pruritis, who either did not meet the eligibility criteria for PEDFIC1, or who were eligible for enrolment after recruitment to PEDFIC1 had been completed. The Clinical Study Report (CSR)[13] states that patients were enrolled into the PEDFIC1 trial at 33 investigational sites across 14 countries in Europe (18 sites across Belgium, France, Germany, Italy, Netherlands, Poland, Spain, and the UK), the US (6 sites) and rest of world (RoW) (9 sites across Australia, Canada, Israel, and Turkey). [redacted] patients were enrolled at sites in the UK.[13]

The Phase 2 study (A4250-003) was an exploratory Phase 2 single and multiple dosing open-label dose-escalating study. The CSR[14] reports that the study was conducted across seven sites in Sweden, Denmark, France, Germany and the UK, however the EU Clinical Trials Register entry for this study (2015-001157-32)[19] states that patients were recruited from sites in Sweden, Denmark, France and Germany, [redacted] enrolled in the UK.

An additional study provides evidence from this appraisal. The NAPPED study is a natural history cohort study of patients with PFIC1 and PFIC2, and provides comparative data for the odevixibat studies in the CS,[1] in the company's economic model. No indirect comparison between data from patients treated with odevixibat and matched NAPPED data is presented in the CS, however Albireo is planning to perform an indirect comparison of clinical outcomes in odevixibat with external controls from [redacted] ([redacted] – see Section 4.2.1.6).

In summary, the PEDFIC1 and PEDFIC2 studies form the main clinical effectiveness evidence base in this appraisal, and thus the ERG's appraisal of the CS focuses on these two key studies. The evidence relating to the clinical effectiveness of odevixibat for the treatment of PFIC partially addresses the final NICE scope[10] in that odevixibat has been compared directly with off-label drug treatments such as UDCA in the PEDFIC1 trial, however no comparison (direct or indirect) has been presented between odevixibat and surgical interventions such as PEBD or internal ileal exclusion.

4.2.1.1 Patients

Eligibility criteria for PEDFIC1[12] and PEDFIC2[13] are presented in Table 5. The ERG's clinical advisors have confirmed that the eligibility criteria for both PEDFIC1 and PEDFIC2 are reasonable and representative of the patients seen in routine UK clinical practice.

Table 5: Key inclusion criteria of the PEDFIC1 and PEDFIC2 studies (adapted from CS, Tables 12 and 13)

Criteria	PEDFIC1	PEDFIC2
Inclusion criteria	• A male or female patient, with clinical diagnosis of PFIC Type 1 or 2, between the ages of ≥6 months and ≤18 years at Visit 1 with a body weight above 5 kg • A clinical genetic confirmation of PFIC1 or PFIC2 through identification of biallelic pathogenic variants in either the ATP8B1 or ABCB11 genes • Patient must have elevated sBA concentration, specifically measured to be ≥100 µmol/L, taken as the average of two samples at least 7 days apart (Visits 1 and 2) prior to randomization • Patient must have history of significant pruritus and a caregiver-reported observed scratching in the electronic diary (eDiary) average of ≥2 (on 0 to 4 scale) in the 2 weeks prior to randomization • Patient and/or legal guardian must sign informed consent (and assent) as appropriate. Patients who turn 18 years of age (or legal age per country) during the study will be required to re-consent in order to remain in the study • Patients are expected to have a consistent caregiver for the duration of the study	**Cohort 1:** • Completion of the 24-week Treatment Period of Study PEDFIC1 or withdrawn from PEDFIC1 due to patient/caregiver judgment of intolerable symptoms after completing at least 12 weeks of treatment. • Patients expected to have a consistent caregiver for the duration of the study. Caregivers (and age-appropriate patients) must be willing and able to use an electronic diary (eDiary) device as required by the study **Cohort 2:** • A male or female patient of any age, with a clinical diagnosis of PFIC and with a body weight ≥5kg at Visit S-1 • Patient must have clinical genetic confirmation of PFIC • Patient must have elevated sBA concentration, specifically measured to be ≥100 µmol/L, taken as the average of 2 samples at least 7 days apart (Visits S-1 and S-2) prior to the Screening/Inclusion Visit (Visit 1) • Patient must have history of significant pruritus and a caregiver-reported observed scratching or patient-reported itching (for patients >18 with no caregiver-reported observed scratching) in the eDiary average of ≥2 (on 0 to 4 scale) in the 2 weeks prior to the Screening/Inclusion Visit (Visit 1) • Age-appropriate patients are expected to have a consistent caregiver for the duration of the study • Caregivers and age-appropriate patients (≥8 years of age, if able) must be willing and able to use an eDiary device as required by the study
Exclusion criteria	• Patient with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein	**Cohort 1:**

	• Patient with past medical history or ongoing presence of other types of liver disease including, but not limited to, the following: • Biliary atresia of any kind • Benign recurrent intrahepatic cholestasis, indicated by any history of normal sBAs • Suspected or proven liver cancer or metastasis to the liver on imaging studies • Histopathology on liver biopsy is suggestive of alternate non-PFIC related aetiology of cholestasis • Patient with a past medical history or ongoing presence of any other disease or condition known to interfere with the absorption, distribution, metabolism (specifically bile acid metabolism), or excretion of drugs in the intestine, including but not limited to, inflammatory bowel disease. • Patient with past medical history or ongoing chronic (i.e., >3 months) diarrhoea requiring intravenous fluid or nutritional intervention for treatment of the diarrhoea and/or its sequelae • Patient has a confirmed past diagnosis of infection with human immunodeficiency virus or other present and active, clinically significant, acute, or chronic infection, or past medical history of any major episode of infection requiring hospitalization or treatment with parenteral anti-infective treatment within 4 weeks of treatment start (study Day 1) or completion of oral anti-infective treatment within 2 weeks prior to start of Screening Period • Any patient with suspected or confirmed cancers except for basal cell carcinoma, and non-liver cancers treated at least 5 years prior to screening with no evidence of recurrence • Patient with a past medical history of chronic kidney disease with an impaired renal function and a glomerular filtration rate <70 mL/min/1.73 m2 • Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period • Patient has had an LT or an LT was planned within 6 months of randomisation • Decompensated liver disease, coagulopathy, history or presence of clinically significant ascites, variceal haemorrhage, and/or encephalopathy • INR >1.4 (the patient may be treated with Vitamin K intravenously, and if INR is ≤1.4 at resampling the patient may be randomized) • Serum ALT >10 × upper limit of normal (ULN) at Screening • Serum ALT >15 × ULN at any time point during the last 6 months unless an alternate aetiology was confirmed for the elevation • Total bilirubin >10 × ULN at Screening	• Decompensated liver disease: coagulopathy, history, or presence of clinically significant ascites, variceal haemorrhage, and/or encephalopathy. • Noncompliant with treatment in Study A4250-005 (PEDFIC1). • Any other conditions or abnormalities which, in the opinion of the investigator or medical monitor, may compromise the safety of the patient, or interfere with the patient's participation in or completion of the study. **Cohort 2:** In Cohort 2 exclusion criteria were the same as for PEDFIC1, but did NOT exclude the following groups: • Patient with a past medical history of chronic kidney disease with an impaired renal function and a glomerular filtration rate <70 mL/min/1.73 m2 • Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period • Patient who has been previously treated with an IBAT inhibitor whose pruritus has not responded to treatment

	• Patient suffers from uncontrolled, recalcitrant pruritic condition other than PFIC. Examples include, but not limited to, refractory atopic dermatitis or other primary pruritic skin diseases • Patient who has been previously treated with an IBAT inhibitor whose pruritus has not responded to treatment	

ALT - alanine aminotransferase; BSEP - bile salt export pump; IBAT - ileal bile acid transporter; INR - international normalised ratio; LT - liver transplantation; PFIC - progressive familial intrahepatic cholestasis; sBA - serum bile acid; ULN - upper limit of normal

There are a few key differences between the eligibility criteria for the PEDFIC1 trial and the population as defined in the final NICE scope.[10] The final NICE scope[10] presents the population broadly as "*People with progressive familial intrahepatic cholestasis*". In contrast, the PEDFIC1 trial included only those with PFIC1 and PFIC2, and excluded patients with a "*surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period*" or those who had been "*previously treated with an IBAT inhibitor whose pruritus has not responded to treatment*" (CS,[1] Table 12, pages 75-76). These criteria narrow the potential population of people with PFIC for which there is evidence of the efficacy of odevixibat. The eligibility criteria for Cohort 2 of the PEDFIC2 trial do not contain these specifications, and are broadly consistent with the final NICE scope.[10] However, one further difference between both PEDFIC1 and PEDFIC2, and the final NICE scope,[10] is that to be eligible for both PEDFIC1 and Cohort 2 of PEDFIC2, patients were required to have sBA concentrations measured at or above 100 μmol/L (as the average of two samples taken ≥7 days apart) and an average pruritus (caregiver-observed scratching) score of ≥2 on the PRUCISION© ObsRO measure over the 2 weeks prior to randomisation. The final NICE scope,[10] however, does not specify a threshold for sBA or pruritus. Again, this narrows the potential population of people with PFIC for which there is evidence of odevixibat, although, conversely, it does mean that there is evidence for the patients with more severe symptoms. The company's clarification response[2] (question A11) states that five patients were excluded from PEDFIC1 and three patients who had a history of pruritus and a caregiver-observed scratching score of ≥2 were excluded from PEDFIC2 for having a sBA concentration <100 μmol/L during screening. Clinical advice received by the ERG suggests that a key goal of treatment is to reduce the itching and scratching inherent in severe pruritus. Thus, the populations of PEDFIC1 and PEDFIC2 may not fully represent the patients who would normally be seen and treated in clinical practice in England.

The company's clarification response[2] (question A10) gives some detail on how patients for PEDFIC1 were identified and recruited: "*The patients were identified by the site investigators participating in the studies. The patients were either identified from the investigator's patient pool or by colleagues at other institutions/hospitals who referred their patients to the study sites. Since PFIC is a rare disease no advertising in the media was used to find patients for any of the three studies. Competitive recruitment was applied and there was no cap on how many patients the sites could screen.*" Patients in the PEDFIC2 and Phase 2 studies were also recruited in the same way.

A diagram illustrating patient flow in the PEDFIC1 trial is presented in Figure 15 of the CS.[1] Initially, 107 patients were screened and of these, 62 were randomised (n=23 to the odevixibat 40 μg/kg/day arm, n=19 to the odevixibat 120 μg/kg/day arm and n=20 to the placebo arm) and received their designated treatment (odevixibat 40 μg/kg/day, 120 μg/kg/day or placebo).[1] Of these 62 patients, 49 patients (77.4%) completed the 24-week placebo-controlled treatment, and of these 48 patients 18 (78.2%) were

in the odevixibat 40 µg/kg/day arm, 16 (84.2%) were in the odevixibat 120 µg/kg/day arm and 15 (75.0%) were in the placebo arm. Patients who did not complete the treatment period due to lack of efficacy/intolerable symptoms rolled over early to the PEDFIC2 study. This applied to 11 (17.7%) trial patients (4 (17.4%) patients in the odevixibat 40 µg/kg/day arm, 2 (10.5%) patients in the odevixibat 120 µg/kg/day arm and 5 (25.0%) patients in the placebo arm). The company's clarification response[2] (question A15) states that early rollover was only permitted prior to Amendment 6 of the PEDFIC1 protocol, requiring patients to complete the 24-week treatment period in order to roll over into PEDFIC2 (although patients could still withdraw early, without the option to roll over); this was to ensure that a sufficient number of patients completed the 24-week treatment period for the data to be analysed. Other reasons for not completing the treatment period (and discontinuing treatment) were an AE of diarrhoea (1 patient; 120 µg/kg/day arm) and non-compliance/inability to travel to the site (1 patient; 40 µg/kg/day arm).[12] At the end of the 24-week placebo controlled treatment period, 56 of the 60 eligible patients had rolled over into the PEDFIC2 open-label extension study (including the 11 patients who had rolled over early, and 45 patients who rolled over at the end of the PEDFIC1 treatment period). Two patients did not complete the follow-up period (both in the 40 µg/kg/day arm; reasons included non-compliance/inability to travel to the site, and non-compliance with visits, eDiary, and dosing), and four patients completed the follow-up period but did not roll over into the PEDFIC2 open-label extension study (three in the 40 µg/kg/day arm and one in the placebo arm).[1, 12] [redacted] The company's clarification response[2] (question A16) states that the one remaining patient who did not roll over as this patient was deemed ineligible to roll over to PEDFIC2 by the investigator, due to a lack of compliance with the study drug. All enrolled patients (n=62) were included in the intention-to-treat (ITT) and safety populations.[1, 12]

Patient disposition in the PEDFIC2 open-label extension study is presented in Table 14 of the CS,[1] which was correct at the time of the data cut-off of 15th July 2020. As of the data cut-off, 71 patients were enrolled in PEDFIC2, 69 of whom had received treatment with odevixibat, and two of whom had not yet started treatment (one from each cohort). Of the 69 patients treated with odevixibat in PEDFIC2, 53 patients were in Cohort 1 and had rolled over from PEDFIC1, and 16 patients were in Cohort 2. Of the Cohort 1 patients, 34 had been previously treated with odevixibat (19 with prior odevixibat at the 40 µg/kg/day dose and 15 with prior odevixibat dosed at 120 µg/kg/day) and 19 had received placebo; thus 35 patients treated with odevixibat in PEDFIC2 were treatment-naïve, as of the data cut-off of 15th July 2020. Of the 69 treated patients, 65 patients (92%) were still receiving ongoing treatment at the data cut-off.[1] Four patients discontinued treatment early: one patient from Cohort 1 who had previously received the 40 µg/kg/day dose of odevixibat in PEDFIC1 (due to withdrawing consent); two patients in Cohort 1 who had previously received placebo in PEDFIC1 (due to an adverse event (1 patient) and

LT (1 patient)); and one patient from Cohort 2 (due to withdrawal of consent).[1] [redacted] As of the data cut-off, 37 (57%) of the 65 patients still receiving ongoing treatment had completed week 22/24 follow-up assessments. This included 21 patients from Cohort 1 previously treated with odevixibat in PEDFIC1 (12 from the 40 µg/kg/day arm and 9 from the 120 µg/kg/day arm), 11 patients from Cohort 1 previously receiving placebo in PEDFIC1, and 5 patients from Cohort 2.

In the PEDFIC1 trial, demographic and clinical characteristics were comparable between the odevixibat (both doses combined) and placebo arms at baseline (in the ITT population), with the following exceptions:

- Patients in the odevixibat arms were slightly older (mean age 4.48 years, median age 3.2 years, range 0.6-15.9) than in the placebo arm (mean age 3.75 years, median age 2.8 years, range 0.5-15.0); the CS and the PEDFIC1 CSR report that the odevixibat 120 µg/kg/day arm were older than patients in the odevixibat 40 µg/kg/day arm and placebo arm ([redacted]; median age 4.9 (range 1.0-13.2), 3.2 (range 0.6-15.9) and 2.8 (range 0.5-15.0) years, respectively. Inter-quartile ranges were not reported.)[1, 12]
- [redacted][12]
- Patients in the placebo arm were slightly more likely to be receiving UDCA (90.0%) and rifampicin (85.0%) at baseline than those in the odevixibat arms, combined (76.2% and 57.1%, respectively); [redacted]

Clinical advice received by the ERG confirmed that the baseline demographic and clinical characteristics of the patients enrolled in this study were comparable with patients usually seen in clinical practice in England, and that the baseline differences observed between the odevixibat and placebo groups would not be expected to impact on how odevixibat would work. The company's

clarification response[2] (question A18) states that [redacted] patients in total had a prior history of PEBD surgery ([redacted] in the placebo group, [redacted] in the 40 µg/kg/day odevixibat group and [redacted] in the 120 µg/kg/day odevixibat group). The ERG notes that whether and how outcomes differ between those with prior PEBD surgery and those without is unknown. In addition, the ERG notes that the inclusion of patients with prior PEBD is not consistent with the company's proposed positioning of odevixibat in the treatment pathway. The company's clarification response[2] (question A19) states that three patients in the PEDFIC1 trial had prior IBAT treatment; all three had participated in the Phase 2 study. One patient had received a dose of 30 µg/kg/day odevixibat 2.4 years prior to the start of (40 µg/kg/day odevixibat) treatment in PEDFIC1, one patient had received a dose of 60 µg/kg/day and then re-enrolled and received a dose of 30 µg/kg/day odevixibat with treatment ending 1.8 years before the start of (120 µg/kg/day odevixibat) treatment in PEDFIC1, and one patient had received a dose of 100 µg/kg/day odevixibat 2.6 years before the start of (placebo) treatment in PEDFIC1.

PEDFIC2[13] used a single-arm design; however, clinical advice received by the ERG confirmed that baseline demographic and clinical characteristics of the patients enrolled in this study (CS, Table 20, page 109) were comparable with patients usually seen in clinical practice in England. The company's clarification response[2] (question A20) states that the PEDFIC2 baseline data for Cohort 1 presented in Table 20 of the CS are from the PEDFIC2 baseline (rather than the PEDFIC1 baseline), and the PEDFIC2 baseline assessment was allowed to take place during the PEDFIC1 trial.

Eligibility criteria for the Phase 2 study are presented in CS Appendix 7,[15] Table 114, pages 34 to 35. Patients were eligible for inclusion if they had pruritis due to chronic cholestasis (including PFIC, Alagille syndrome, biliary atresia and sclerosing cholangitis), and were aged ≥12 months to <18 years (<26 years in Sweden only), with a body weight of >7kg. Patients were excluded if they had a condition that might constitute a risk to the patient or could interfere with study objectives, conduct or evaluations, had a history of LT, signs of decompensated liver disease, structural abnormality of the gastrointestinal tract, active acute or chronic infection, a history of cancer, other reason for pruritus, treatment with bile acid sequestrants, chronic kidney disease, substance misuse, a history of psychiatric disorder, pregnancy, breastfeeding or lactation, or participation in another investigational study within 30 days prior to screening.[1]

4.2.1.2 Intervention

The doses of odevixibat administered in both the PEDFIC1[12] and PEDFIC2[13] studies are outlined in the CS[1] (Table 12, page 76, and Section 9.4.1.3, page 79, respectively). In both studies, odevixibat was administered orally once per day in the morning, with or without food, in capsule form; capsules could be opened and the contents sprinkled onto food for those unable to swallow capsules.[12, 13] In PEDFIC1, patients were randomised to a dose of either 40 µg/kg/day or 120 µg/kg/day, whereas all patients in the

PEDFIC2 study were allocated the higher dose of 120 µg/kg/day. Patients who experienced a lack of efficacy or intolerable symptoms after 12 weeks in the PEDFIC1 trial could roll over to the PEDFIC2 open-label extension study and receive the 120 µg/kg/day dose of odevixibat; this is consistent with the recommended dose detailed in the draft SmPC of 40 µg/kg/day, with potential for dose escalation to 120 µg/kg/day if an adequate clinical response has not been achieved after 3 months of continuous therapy,[11] although the precise definition of an 'adequate clinical response' is unclear. The company's clarification response[2] (question A9) states that the company conducted a meeting [redacted] of the PEDFIC studies on [redacted], which was attended by 14 clinical experts, [redacted]. Clinicians were asked how they would make dose adjustments to odevixibat in clinical practice, including how they would determine a meaningful response to the drug. From the feedback received, it was not possible to determine a definition of an adequate clinical response, due to a lack of experience in administering and monitoring odevixibat in clinical practice (outside of a clinical trial setting), [redacted]. In response to clarification question A9,[2] the company stated an intention to further explore and refine potential definitions of an adequate clinical response with UK clinicians, to be able to provide more precise instructions around the administration of the drug within England.

The PEDFIC2 study is ongoing and the CS[1] does not contain details of how long patients had been in treatment at the time of the data cut-off. The company's clarification response[2] (question A17) states that the median duration of treatment with 120 µg/kg/day odevixibat in the study overall was [redacted] weeks (range [redacted]) at the time of data cut-off on the 15th July 2020. The patients in Cohort 2 had the shortest duration of 120 µg/kg/day odevixibat treatment in PEDFIC2 (see Table 6).

Table 6: Study medication exposure duration in PEDFIC2 (full analysis set) (reproduced from clarification response, question A17)

	Odevixibat 120 µg/kg, once daily dosing						
	Cohort 1[a]						
Category statistic	40 µg/kg n=19	120 µg/kg n=15	All doses n=34	Placebo n=19	Cohort 2 n=16	Cohort 2 + Placebo[b] n=35	Overall Cohort 1 + Cohort 2 n=69
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD - standard deviation
[a] For patients in Cohort 1, dose indicated is dose administered during participation in Study A4250-005
[b] Cohort 2 + Placebo = Patients enrolled in Cohort 2 and patients who were assigned to placebo during participation in PEDFIC2

The odevixibat dose administered in the PEDFIC2 study was not consistent with the recommended dose detailed in the draft SmPC, as patients were started on the higher dose to begin with (although some patients received the 40 µg/kg/day dose for 3 or 6 months in PEDFIC1). Therefore, it is possible that some patients (those in Cohort 2 of PEDFIC2, and those from the placebo arm of PEDFIC1 who rolled over into PEDFIC2) will have received a higher dose than the recommended dose for at least three months (although some patients in PEDFIC2 will not have received treatment for that duration at data cut-off). Also, patients from PEDFIC2 who previously received 40 µg/kg/day in PEDFIC1 and achieved an adequate clinical response on that dose would have received a higher dose in PEDFIC2 than they would have in clinical practice, according to the dosing instructions in the draft SmPC. The ERG believes this may have led to the efficacy of odevixibat being potentially overestimated in a number of cases in the findings of the PEDFIC2 study (although there is no evidence from the findings of the PEDFIC1 trial that the 120 µg/kg/day dose is more effective than the 40 µg/kg/day dose; see Section 4.2.4.1). The company's clarification response[2] (question A12) states that the reason for this was to maintain the blinding in PEDFIC1. Since patients were rolled over from PEDFIC1 to PEDFIC2 in an ongoing, staggered manner, and thus treatment assignment remained blinded at the time of rollover, it was not possible to roll over only those on the 40 µg/kg/day dose in PEDFIC1. Additionally, as sBA results were also blinded at the time each patient rolled over into PEDFIC2, there was no information available as to which patients were sBA responders. Therefore, all patients were rolled over to the 120 µg/kg/day dose upon entry to PEDFIC2. A subgroup analysis of the PEDFIC1 trial data for all patients who were non-responders to the 40 µg/kg/day dose was provided in the CS,[1] and included in the company's cost-effectiveness model (see CS, Section 10.1.16).

In the PEDFIC1 trial, [redacted] patients had protocol deviations that were considered to be "*important*" and led to exclusion from the per protocol analysis set;[12] [redacted] in the odevixibat 40 µg/kg/day arm, [redacted] in the odevixibat 120 µg/kg/day arm and [redacted] in the placebo arm (CSR, page 100). [redacted] in the PEDFIC2 study had a protocol deviation considered to [redacted] (CSR, page 97). Further details are provided in Section 4.2.3.4.

The doses administered in the Phase 2 study[14] are presented in the CS. Patients received odevixibat orally once daily at a dose of either 10 µg/kg/day, 30 µg/kg/day, 60 µg/kg/day, 100 µg/kg/day (n=5), or 200 µg/kg/day for four weeks. There were [redacted] protocol deviations that were considered to be "*major*" across [redacted] patients.[14]

4.2.1.3 Comparator

The comparator in the PEDFIC1 trial[12] was placebo. [redacted] The comparator in the final NICE scope[10] is established clinical management without odevixibat, including off-label drug treatments such as UDCA, and/or surgical interventions such as PEBD. However, the patients in both arms of the trial were taking UDCA and rifampicin (90% and 85% of patients in the placebo arm were taking these drugs at baseline, respectively), so for this purpose, the ERG considers evidence from PEDFIC1 to be consistent with the NICE scope.[10] As odevixibat is considered medically equivalent to PEBD, a comparison of odevixibat with PEBD would have more completely addressed the scope.

PEDFIC2 adopted a single-arm design; hence, no comparator was included. No indirect comparison was undertaken between data from PEDFIC2 and data from those who had established clinical management, including UDCA and/or PEBD (e.g. the NAPPED study), which is not consistent with the final NICE scope.[10] European Medical Agency guidance on performing clinical trials in medicines recommends that trials aiming to demonstrate/confirm efficacy are controlled, with randomised allocation to arms.[20] The PEDFIC2 study, however, is a long-term extension of the PEDFIC1 RCT, and therefore its design does not contradict these recommendations. It should be borne in mind, however, that additional patients (including patients with additional PFIC subtypes) were recruited directly into the PEDFIC2 study, and therefore the open label, uncontrolled study design of PEDFIC2 should be taken into consideration during review of data from that study (particularly of the Cohort 2 data). The Phase 2 study[14] also adopted a single-arm design and thus had no comparator.

4.2.1.4 Outcomes

The key outcomes listed in the CS for the PEDFIC1 and PEDFIC2 studies are summarised in

Table 7 and

Table 8, respectively. All outcomes presented in the CS were included in the final NICE scope,[10] although the outcome HRQoL, from the final NICE scope,[10] was not reported as a primary or secondary outcome for either study, although HRQoL (as assessed with the PedsQL instrument) is reported as an exploratory outcome in both the PEDFIC1 CSR[12] and PEDFIC2 CSR.[13]

All efficacy outcome data in PEDFIC1 were analysed using the full analysis set (FAS), defined as all randomised patients who received at least one dose of their allocated treatment, analysed according to the treatment to which they were randomised.[1, 12] All efficacy outcome data in PEDFIC2 were analysed using the FAS, defined as all randomised patients who received at least one dose of the study drug.

Table 7: Summary of PEDFIC1 key outcomes listed in the CS and their relationship to the final NICE scope and the company's economic model

Outcome	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome			
Proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L compared to placebo after 24 weeks of treatment. (EU & RoW)[a]	Yes ("*change in serum bile acid level*")	Yes	Yes
Proportion of positive pruritus assessments at the patient level over the 24-week Treatment Period (scratching score of ≤1 or ≥1-point drop from baseline on the Albireo ObsRO instrument. (US)[b]	Yes ("*change in symptoms of PFIC including reduction in pruritus*")	No	Yes
Secondary outcomes			
Change from baseline to Week 12 and to Week 24 in fasting sBA, ALT and growth	Partially – growth is included and ALT could be considered as "*measures of disease progression*"	No	Partially (protocol specifies baseline to week 24)
Proportion of responders for pruritus scores at Weeks 12 and 24 based on the Albireo PRO and ObsRO instruments	Yes ("*change in symptoms of PFIC including reduction in pruritus*")	No	No (not specified in protocol)
Change in sleep parameters measured with the Albireo PRO and ObsRO instruments from baseline over the 24-week Treatment Period	Could be considered as "*change in symptoms of PFIC including reduction in pruritus*"	No	Yes
Proportion of individual assessments meeting the definition of a positive pruritus assessment at the subject level over the 24-week Treatment Period (itch score ≤1, or ≥1-point drop from baseline on the Albireo PRO instrument in patients aged ≥8 years)	Yes ("*change in symptoms of PFIC including reduction in pruritus*")	No	Yes
Proportion of individual assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0 – 20, Weeks 0-24, respectively, and the proportion of positive pruritus assessments at each 4-week interval.	Yes ("*change in symptoms of PFIC including reduction in pruritus*")	No	No (not specified in protocol)
Proportion of individual AM and PM assessments meeting the definition of a positive pruritus assessment at the patient level from Weeks 0-4, 0-8, 0-12, 0-18, 0-24, respectively, and the proportion of positive pruritus assessments at each 4-week interval.	Yes ("*change in symptoms of PFIC including reduction in pruritus*")	No	No (not specified in protocol)
Proportion of individual PM assessments meeting the definition of a positive pruritus	Yes ("*change in symptoms of PFIC*	No	No (not specified

assessment at the subject level from Weeks 0-4, 0-8, 0-12, 0-18, 0-24, respectively, or the proportion of positive pruritus assessments at each 4-week interval.	*including reduction in pruritus*")		in protocol)
Number of patients undergoing biliary diversion surgery or LT	Yes	No	Yes
Number and percent of patients achieving positive pruritus assessment for more than 50% of the time during the 24-week treatment period.	Yes ("*change in symptoms of PFIC including reduction in pruritus*")	Yes. Scenario analysis using pruritus response as the definition of response	No (not specified in protocol)

ALT - alanine aminotransferase; EU - European Union; LT - liver transplantation ObsRO - observer reported outcome; PRO - patient-reported outcome; RoW - rest of world; sBA - serum bile acid; US - United States

[a] *This was a secondary outcome for the US*

[b] *This was a secondary outcome for the EU and RoW*

Table 8: Summary of PEDFIC2 key outcomes listed in the CS and their relationship to the final NICE scope and the company's economic model

Outcome	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome			
Change from baseline in sBA after 72 weeks of treatment (after 24 weeks for interim analysis) (EU & RoW)[a]	Yes ("*change in serum bile acid level*")	No	Yes
Proportion of positive pruritus assessments over the 72-week treatment period using the Albireo ObsRO instrument (US)[b]	Yes ("*change in symptoms of PFIC including reduction pruritus*")	No	Yes
Secondary outcomes			
All-cause mortality		No – mortality data taken from other sources	Yes
Number of patients undergoing BD	Yes	No	Yes
Number of patients listed for LT	Yes	No	Yes
Change in growth from baseline to weeks 24, 48 & 72 after initiation of treatment. Defined as linear growth deficit (height/length for age, weight for age & BMI) compared to a standard growth curve	Yes	No	Yes
Change in AST to platelet ratio index score and Fib-4 score	Could be considered "*measures of disease progression*"	No	Yes
Change to paediatric end-stage liver disease/model for end-stage liver disease	Yes ("*measures of disease progression*")	No	Yes
Change in antipruritic medication	Could be considered "*change in symptoms of PFIC including reduction in pruritus*"	No	Yes
eDiary - Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument	Yes ("*change in symptoms of PFIC including reduction in pruritus*")	No	No (not specified in protocol)

AST - aspartate aminotransferase; BD - biliary diversion; BMI - body mass index; EU - European Union; LT - liver transplantation; ObsRO - observer reported outcome; PRO - patient-reported outcome; RoW - rest of world; sBA - serum bile acid; US - United States

[a] *This was a secondary outcome for the US*

[b] *This was a secondary outcome for the EU and RoW*

Primary outcomes

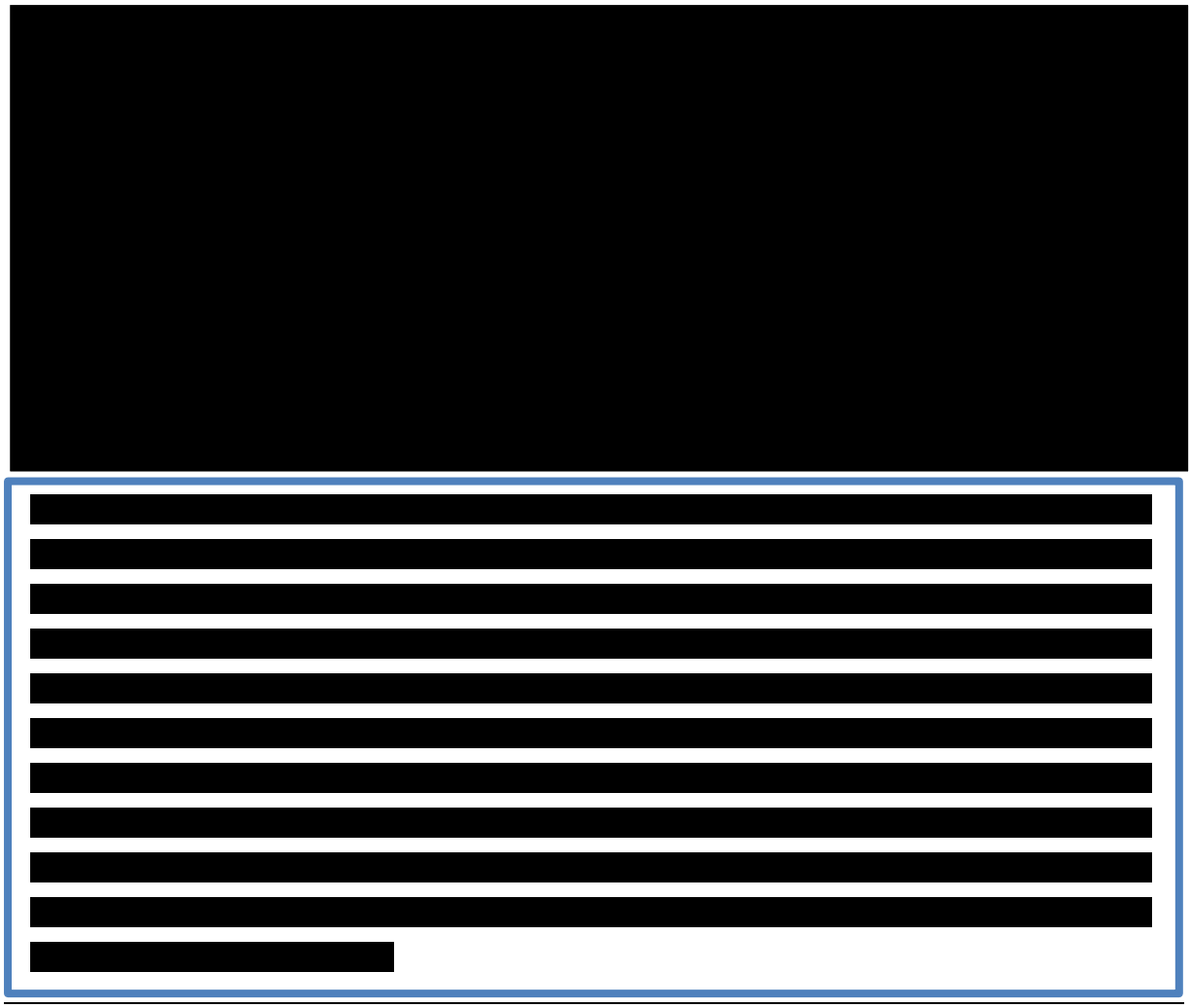
The PEDFIC1 trial had two primary outcomes, one for the US and one for the EU and RoW. The EU/RoW primary outcome was the proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 μmol/L after 24 weeks of treatment. sBAs are an indicator of cholestasis,[4] and there is evidence that PEBD surgery

decreases sBAs and pruritus among PFIC patients.[21] Clinical advice received by the ERG, however, has suggested that measured sBA levels are not always correlated with severity of pruritus among the PFIC patients seen in clinic. The threshold for sBA response is based on evidence from the NAPPED cohort,[12] whereby sBA reduction to a level <65 µmol/L following surgical biliary diversion was associated with a statistically significant improvement in native liver survival,[22] and sBA reduction by 75% or to <102 µmol/L following surgical biliary diversion was associated with prolonged native liver survival over 15 years.[21]

The US primary outcome of PEDFIC1 was the proportion of positive pruritus assessments at the patient level over the 24-week treatment period. Positive pruritus assessment defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the Albireo PRUCISION© ObsRO instrument. The PRUCISION© measure is administered twice daily via an electronic diary, and scores range from 0 ("no scratching") to 4 ("worst possible scratching"), with a reduction of 1 point from baseline considered clinically meaningful.[23] [redacted] (see

Figure 3). According to the CS, Albireo developed this measure as the company had only identified one existing instrument that adequately assesses the symptoms and impact of pruritus from the perspective of the caregiver and/or patient (the Itch Reported Outcome instrument), and that instrument is not publicly available.[1] The PRUCISION© ObsRO measure was validated by blinded psychometric analyses conducted by an independent group,[1] and found to be valid, reliable and sensitive to change.[23] The validation analyses were conducted using data from the PEDFIC1 trial, therefore the validity of this instrument was not known at the start of assessment within this trial.[1]

Figure 3: [redacted]



The PEDFIC2 study also had two primary outcomes, one for the US and one for the EU and RoW. The EU/RoW primary outcome was the change from baseline in sBA after 72 weeks of treatment (after 24 weeks for interim analysis). It is unclear why change from baseline was used, rather than a threshold, as for PEDFIC1, and no rationale has been reported in the CSR,[13] however the ERG judges this to be a reasonable outcome. The US primary outcome of PEDFIC2 was the proportion of positive pruritus assessments (defined as a scratching score of ≤1 or at least a 1 point decrease from baseline on the Albireo ObsRO instrument[13]) over the 72-week treatment period using the Albireo ObsRO instrument.

The Phase 2 study had primary efficacy and safety outcomes. The primary efficacy variable was the change in total serum bile acids from test results at Visit 1 (Study Baseline) to test results at Visit 5. The primary safety assessment was the incidence of treatment-emergent serious adverse events (SAEs), based upon information from patient reports, including the description, incidence, and severity of an SAE.

Secondary outcomes

In both the PEDFIC1 and PEDFIC2 studies, the US primary outcome was a secondary outcome for the EU and RoW, and the EU and RoW primary outcome was a secondary outcome for the US. The same considerations apply, as detailed above.

Outcomes listed in the final NICE scope[10] and reported in Table 12 of the CS[1] as key secondary outcomes for PEDFIC1 for all regions include:

- Change from baseline to Week 12 and to Week 24 in fasting sBA, ALT and growth
- Proportion of responders for pruritus scores at Weeks 12 and 24 based on the Albireo PRO and ObsRO instruments
- Change in sleep parameters measured with the Albireo PRO and ObsRO instruments from baseline over the 24-week Treatment Period
- Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level over the 24-week Treatment Period. A positive pruritus assessment includes an itch score ≤1, or at least a 1-point drop from baseline based on the Albireo PRO instrument; only patients ≥8 years of age completed the Albireo PRO instrument
- Proportion of individual assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-20, Weeks 0-24, respectively, and the proportion of positive pruritus assessments at each 4-week interval.
- Proportion of individual AM and PM assessments meeting the definition of a positive pruritus assessment at the patient level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, and the proportion of positive pruritus assessments at each 4-week interval.
- Proportion of individual PM assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, or the proportion of positive pruritus assessments at each 4-week interval.
- Number of patients undergoing biliary diversion surgery or LT
- Number and percent of patients achieving positive pruritus assessment for more than 50% of the time during the 24-week treatment period.

Of these outcomes, only the number and percent of patients achieving positive pruritus assessment for more than 50% of the time during the 24-week treatment period was used in the company's health economic model. The critical appraisal of clinical effectiveness evidence in the ERG report therefore focuses on this secondary outcome from the PEDFIC1 trial, in addition to growth, which clinical advisors to the ERG highlighted as being clinically important for patients, carers and clinicians. Clinical advisors to the ERG also stated that vitamin absorption is an important outcome, however this outcome is not reported in the CS, and does not appear to have been assessed in either PEDFIC1 or PEDFIC2.

Outcomes listed in the final NICE scope[10] and reported in Table 12 of the CS[1] as key secondary outcomes for PEDFIC2 for all regions include:

- All-cause mortality
- Number of patients undergoing BD
- Number of patients listed for LT
- Change in growth from baseline to weeks 24, 48 and 72 after initiation of A4250 treatment. Defined as linear growth deficit (height/length for age, weight for age and body mass index (BMI]) compared to a standard growth curve.
- Change in AST to platelet ratio index (APRI) score and Fib-4 score
- Change to paediatric end-stage liver disease (PELD)/model for end-stage liver disease (MELD)
- Change in antipruritic medication
- eDiary - Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument

None of these outcomes were used in the company's health economic model, although the discontinuation rate from PEDFIC2 was used in the company's model as a proxy for loss of response. The critical appraisal of clinical effectiveness evidence in the ERG report therefore focuses on the discontinuation rate from the PEDFIC2 study, plus growth, and the number of patients listed for LT surgery, which clinical advisors to the ERG highlighted as being clinically important for patients, carers and clinicians.

Outcomes listed in the final NICE scope[10] and reported in Appendix 7,[15] Table 114 of the CS as secondary efficacy outcomes for the Phase 2 study include:

- Change in patient's individual weekly mean severity of self-reported symptoms from Study Baseline to last 7 days of 4 weeks treatment were analysed for daily severity measurements from patient diary data for VAS-itch (0-10 scale), PO-SCORAD-itching (0-10 scale), Whitington scale (0-4 scale) and PO-SCORAD-Sleep Disturbance (0-10 scale)
- Change in liver biochemistry evaluations from Study Baseline to end of 4-week treatment (Visit 5) for ALT, AST, ALP, Total Bilirubin and GGT

None of these outcomes from the Phase 2 study were used in the company's health economic model. The critical appraisal of clinical effectiveness evidence in the ERG report therefore focuses on pruritus response, which clinical advisors to the ERG highlighted as being clinically important.

4.2.1.5 Study design

PEDFIC1 is a pivotal, multicentre, double-blind, placebo-controlled Phase 3 RCT, where eligible patients (n=62) were randomised to odevixibat 40 µg/kg/day, odevixibat 120 µg/kg/day or placebo at a 1:1:1 ratio using an Interactive Web Response System, by statisticians independent of the study team.[12] Randomisation was performed in a block size of 6 and was stratified by PFIC type (PFIC1 or PFIC2) and age group (6 months to 5 years, 6 to 12 years, and 13 to ≤18 years).[1] Clinical advice received by the ERG suggests that PFIC subtype is an important prognostic factor (with genetic analysis of the transporter function, particularly BSEP, also being important), and thus the ERG considers stratification by PFIC subtype to be a rigorous element of the trial procedure. [redacted] The PEDFIC1 trial consisted of a 24-week double-blind treatment period, following which patients could roll over into a single-arm, open-label long-term extension study (PEDFIC2 – see following paragraph). Patients could also roll over to PEDFIC2 early following a (blinded) treatment duration of between 12 and 18 weeks due to intolerable symptoms. Patients, investigators, study centre personnel and the sponsor were blinded to the treatment assigned at randomisation until all patients completed the study, the data were screened for completeness and accuracy, the database was locked, and important protocol deviations were identified, and serum bile acid samples were processed in a blinded fashion at a central laboratory.[12] As a double-blind, placebo-controlled Phase 3 RCT, the ERG considers the study design to be rigorous. Clinical advice received by the ERG has suggested that 24 weeks is a sufficient treatment duration, although there was conflicting opinion as to whether 24 weeks would be sufficient for an effect on growth.

PEDFIC2 is an ongoing Phase 3 prospective, multicentre, single-arm open-label extension study of patients (n=69, as of the data cut-off of 15th July 2020) who were treated with odevixibat 120 µg/kg/day. The PEDFIC2 study consists of an open-label 72-month treatment period, followed by an optional extension period, for patients who elect to continue receiving treatment with odevixibat,[13] the duration of which is not reported in the CS nor the PEDFIC2 CSR. During the optional extension period, assessments are made every 16 weeks. Interim data from the cut-off date of 15th July 2020 has been reported in the CS; the main timepoint for the interim analysis is Week 24 of treatment (which corresponds to Week 48 of treatment for patients who received odevixibat in the PEDFIC1 trial prior to entering PEDFIC2), at which the primary efficacy variables were assessed.[13] The ERG considers the design of PEDFIC2 to be open to potential biases such as attrition bias, natural recovery and regression to the mean,[24] due to being open-label and single-arm. A double-blinded placebo-controlled RCT (or a longer double-blind period within PEDFIC1) would have been more rigorous in examining the efficacy and safety of odevixibat over the longer-term.

4.2.1.6 Ongoing studies

The PEDFIC2 study is currently ongoing, with data only available at Week 24 (for 37 of the enrolled 69 patients) at the time of the cut-off date (15th July 2020), and data still outstanding from the Week 48 and Week 72 outcome assessments.[1] Full results are expected in [redacted].[1]

The [redacted] is a planned future comparison, sponsored by Albireo. [redacted] Planned comparisons include odevixibat versus external controls without prior PEBD (Part A), and odevixibat without prior PEBD versus external controls receiving PEBD. Endpoints include: [redacted]. [redacted][1] The ERG considers this comparison to be relevant to the decision problem as set out in the final NICE scope,[10] particularly as [redacted] will provide a comparison of the efficacy of odevixibat versus PEBD for the treatment of PFIC, which is a relevant comparison specified in the final NICE scope,[10] but for which there is currently no evidence available. The company's clarification response[2] (question A23) states that an indirect comparison was not undertaken for the current submission because [redacted] are not planned to take place until [redacted], based on US Food and Drug Administration recommendations.

Data are also expected in future from the ongoing Expanded Access Programme (EAP; study A4250-014), which aims to provide access to odevixibat for patients with PFIC in the US and RoW with elevated sBA concentrations, who are not able to enrol in PEDFIC2 either because they do not meet the eligibility criteria, they are not able to access a PEDFIC2 site geographically, or recruitment to PEDFIC2 had been completed. Recruitment is ongoing and data collection is ongoing and optional.[1] The CS does not specify when data from the EAP will be available.

Two studies examining the burden of illness among patients with PFIC (both sponsored by Albireo) are also currently ongoing.[1] The PICTURE (Progressive Familial Intrahepatic Cholestasis Disease Burden of Illness) study is a retrospective, cross-sectional study that aims to provide evidence on the burden of illness and medical needs relating to PFIC. This study aims to assess the impact of PFIC on patient HRQoL, caregiver HRQoL and caregiver work productivity, and provide a dataset of unit costs. Recruitment to the PICTURE study was delayed due to coronavirus disease 2019 (COVID-19), and

thus data were not available in time for the submission. Interim data from the study have, however, informed the company's health economic model. The utilities elicitation survey is currently being conducted to explore public preferences for treatment in PFIC. The results are expected to be available during the appraisal process.

4.2.2 *Details of relevant studies not included in the submission*

The ERG is confident that PEDFIC1, PEDFIC2 and the Phase 2 study are the only relevant studies in this patient population (aside from the ongoing studies – see Section 4.2.1.6), and that no relevant studies have been omitted from the CS.

4.2.3 *Summary and critique of the company's quality assessment*

4.2.3.1 Critical appraisal of study quality of PEDFIC1

The company provided a critical appraisal of the validity of PEDFIC1 using the checklist recommended by NICE (see Section 4.1.5). Table 9 presents a summary of the risk of bias in PEDFIC1 undertaken by the company alongside the ERG's independent quality assessment.

The results of the company's and the ERG's quality assessments of PEDFIC1 are similar, and there are no differences in the judgement of each criterion. The ERG concludes that PEDFIC1 has a low risk of bias; the company did not provide a summary appraisal of risk of bias.

Table 9: Company and ERG quality assessment of the PEDFIC1 trial (adapted from CS Table 15)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		ERG quality assessment (yes/no/not clear/NA)	
	Grade	Explanation	Grade	Explanation
Was randomisation carried out appropriately?	Yes	The randomisation codes were computer generated by a biostatistician at ICON and kept by an unblinded statistician at Firma, independent from the project team.	Yes	Randomisation was carried out by an Interactive Web Response System
Was the concealment of treatment allocation adequate?	Yes	An 8 digit patient identification number was assigned by the Interactive Web Response System (IWRS). The randomisation codes were computer generated and kept independent from the project team.	Yes	The randomisation codes were computer generated by an independent biostatistician and were kept by an unblinded independent statistician.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline demographic characteristics were largely similar between the treatment groups. In terms of disease characteristics, higher proportions of patients in the placebo group were concurrently using UDCA and rifampicin. These differences would not, however, be expected to favour outcomes for odevixibat	Yes	Groups were similar on most characteristics, including the proportion of patients with each PFIC subtype. There were slight differences in terms of age, growth impairment and use of UDCA and rifampicin, however these differences should not be advantageous towards either dose of odevixibat.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	The patient, investigator, study centre personnel, and the sponsor were blinded to study treatment until all patients completed the study. The authors stated that as changes in the measured serum bile acids had the potential to unblind a patient's assignment to either placebo or odevixibat, this outcome was evaluated by a central laboratory	Yes	Patients, investigators, study centre personnel and the sponsor were blinded to the treatment assigned at randomisation until all patients completed the study, and serum bile acid samples were processed in a blinded fashion at a central laboratory.[12]

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	5 (25.0%) in the placebo group, 5 (21.7%) in the odevixibat 40 µg/kg group, and 3 (15.8% on the odevixibat 120 µg/kg group did not complete the treatment period. Reasons for withdrawal were reported; higher percentages of patients withdrew from the placebo and the odevixibat 40 µg/kg groups, than in patients who received 120 µg/kg. The highest drop-out in the placebo group may not be unexpected	No	A smaller proportion of patients in the 120 µg/kg/day odevixibat group (15.8%) did not complete the treatment period compared with the 40 µg/kg/day odevixibat group (21.7%) and the placebo group (25.0%). The extent to which this might have been expected is unclear, although it does not seem surprising. The higher drop-out rates from the 40 µg/kg/day odevixibat and placebo groups were partially explained in terms of dose titration (in the form of early roll-over into PEDFIC2) due to a lack of efficacy/intolerable symptoms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes defined in the methods section of the clinical study report were reported	No	All outcomes stated in the protocol were reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy and safety analyses were primarily based on the FAS defined as all randomised patients who received at least 1 dose of study treatment. All patients were included in the analyses	Yes	The FAS was used for the efficacy analyses and this was essentially an ITT population, defined as all randomised patients who received at least one dose of their allocated treatment, analysed according to the treatment to which they were randomised.

FAS - Full Analysis Set; ITT - intention to treat; NA - not applicable

4.2.3.2 Critical appraisal of study quality of PEDFIC2

Table 10 presents the ERG's quality assessment of PEDFIC2, based on the CASP Cohort Study Checklist.[18] The quality assessment of PEDFIC2 that was presented in the CS used a checklist designed to assess the quality of RCTs, which the ERG has judged to be a less appropriate critical appraisal tool than the CASP Cohort Study Checklist, as PEDFIC2 is not an RCT (see Section 4.1.5).

The ERG has rated PEDFIC2 as moderate in terms of study quality. The main source of bias is the unblinded nature of the outcome assessment for some outcomes, which involved subjective judgement by those who would have been aware that the patient was being treated with 120 µg/kg/day odevixibat.

Despite the company's justification for the use of a single-arm design, the ERG considers that this remains an important source of potential bias for any inference of relative treatment effects.

Table 10: ERG quality assessment of the PEDFIC2 study

Quality assessment criterion question	ERG quality assessment (yes/ can't tell/no)	
	Grade	**Explanation**
Did the study address a clearly focused issue?	Yes	The primary and secondary objectives of the study are clearly focused and measurable
Was the cohort recruited in an acceptable way?	Yes	The company's clarification response[2] (question A10) states that participants were recruited through site investigators' patient pools or by colleagues at other centres who referred patients
Was the exposure accurately measured to minimise bias?	Yes	Exposure was controlled and monitored, and adherence to medication was recorded by counting capsules returned
Was the outcome accurately measured to minimise bias?	Partially	*A priori* outcomes were appropriately assessed and reported. Some outcomes were assessed in an objectively measured and blinded fashion (e.g. sBA), however some outcomes were subjectively judged by participants or their caregivers (e.g. HRQoL, pruritis).
Have the authors identified all important confounding factors?	Yes	No covariates have been used in the analysis, however subgroup analysis has been conducted on several factors, including those that clinical advice received by the ERG identified as being prognostic factors.
Have they taken account of the confounding factors in the design and/or analysis?	Yes	The potential confounders have not been used as covariates in analyses of outcomes, however, subgroup analyses have been undertaken.
Was the follow up of subjects complete enough?	Yes	At the interim data cut-off (15th July 2020), 93% patients were ongoing in the study
Was the follow-up of subjects long enough?	Yes	Clinical advice received by the ERG has suggested that 24 weeks (the follow-up time-point at the interim data cut-off) should be sufficient for changes in the outcomes.

ERG - evidence review group; sBA - serum bile acids

4.2.3.3 Critical appraisal of study quality of the Phase 2 study

The company provided a critical appraisal of the validity of the Phase 2 study in the CS, Appendix 7,[15] using the NICE HST template checklist for the critical appraisal of observational studies,[2] which bears a close resemblance to the CASP checklist for assessing the quality of cohort studies[18] (see Section 4.1.5). Table 11 presents a summary of the risk of bias in the Phase 2 study undertaken by the company alongside the ERG's independent quality assessment.

Table 11: Company and ERG quality assessment of the Phase 2 study (adapted from CS Appendix 7, Table 115)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		ERG quality assessment (yes/no/not clear/NA)	
	Response	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Aimed to evaluate paediatric patients with pruritus from cholestatic liver disease, including PFIC and other diseases. No unexpected eligibility criteria. Recruited from 6 centres.	Not clear	Little detail on recruitment has been reported. The Baumann draft manuscript states that physicians "*invited eligible patients in their care to be study participants*",[25] however there is no detail as to whether all eligible patients or only certain ones were invited. The cohort was, however, recruited from appropriate clinical centres.
Was the exposure accurately measured to minimise bias?[a]	Yes	Full details in CSR including subgroup analysis of PFIC types	Yes	Exposure was controlled and monitored, and adherence to medication was self-reported in a diary
Was the outcome accurately measured to minimise bias?	Yes	Objective measurements were evaluated	Partially	*A priori* outcomes were appropriately assessed and reported. sBA was objectively measured and analysed in a central laboratory[25] however pruritus was subjectively judged by participants or their caregivers
Have the authors identified all important confounding factors?	Yes	PFIC types grouped, baseline variation in VAS-itch score noted	No	PFIC patients were analysed as a subgroup, however PFIC subtypes were not differentiated
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Subgroup analysis of PFIC types	No	PFIC patients were analysed as a subgroup, however PFIC subtypes were not differentiated
Was the follow-up of patients complete?	Yes	All individuals were included in the analysis	Yes	There were no drop-outs
How precise (for example, in terms of confidence interval and p values) are the results?	Not clear	P values for change from baseline data were not reported	Unclear	There are multiple outcomes at several timepoints with variable precision, and thus it is difficult to make a judgement on this.

ITT - intention to treat; NA - not applicable; sBA - serum bile acids

[a] *For this review, the company interpreted this criterion in terms of how PFIC and/or mutations were described, whereas the ERG considers the drug treatment odevixibat to be the exposure*

The ERG's quality assessment differs from that of the company in that the ERG has judged that appropriate confounding factors were not identified or considered in the analyses; this relates mainly to PFIC type, which clinical advice to the ERG has indicated is an important factor in terms of treatment response. The ERG has also rated the outcome measures as being partially accurately measured to minimise bias, due to the subjective nature of some of the outcome measures (e.g. pruritis), which involved a self-reported (or carer-reported) judgement made by those who may have had treatment expectations of odevixibat. The ERG also considers the single-arm design to be an important source of potential bias for the inference of treatment effects, and the small sample size renders subgroup comparisons difficult. The ERG has rated the Phase 2 study as being of poor quality; the company did not provide a summary appraisal of risk of bias. Given the purpose of this study (i.e. as a preliminary dose-finding study), however, the methods and design chosen seem appropriate. It is also worth noting that this study does not contribute a substantial amount of evidence to the CS.

4.2.3.4 Protocol deviations

In the PEDFIC1 trial, important protocol deviations that implicated exclusion from the per protocol analysis set were reported for [redacted] of the 62 patients (CSR,[12] page 100). Numbers and proportions of patients with protocol deviations were similar across the 40 µg/kg/day odevixibat ([redacted]), 120 µg/kg/day odevixibat ([redacted]) and placebo ([redacted]) study arms. [redacted] of these patients (from the 120 µg/kg/day odevixibat arm) failed to meet the inclusion criterion of elevated sBA concentration ≥100 µmol/L, taken as the average of 2 samples at least 7 days apart prior to randomisation, and [redacted] of these patients had compliance rates of <80% for their assigned treatment, based on the case report form.[12]

In the PEDFIC2 study, an important protocol deviation was reported for [redacted] of the 69 patients dosed, as of the cut-off date (CSR,[13] page 97). [redacted]
([redacted]).

In the Phase 2 study, [redacted] major protocol deviations were reported for [redacted] patients. None of these led to the exclusion of data from the pharmacokinetic, efficacy or safety analyses, as none of these major protocol deviations affected the overall integrity or quality of the study results, in the opinion of the sponsor. These included: deviations based on inclusion criteria ([redacted]); deviations based on exclusion criteria ([redacted]); deviations based on prohibited medications ([redacted]); deviations based on incorrect assessments or assessments outside the allowed visit window ([redacted]); and deviations based on eligibility for participation in the 4-week treatment period ([redacted]).

4.2.4 *Summary and critique of results*

The PEDFIC1 trial was complete, and the cut-off date for the 24-week analyses in the PEDFIC2 study was the 15th July 2020.

4.2.4.1 PEDFIC1

The FAS (an ITT population) was used in all efficacy analyses. Table 12 summarises the efficacy results for the PEDFIC1 trial for the outcomes that are considered in this report. Other outcomes are reported in Figures 22-24, and on pages 103-109 of the CS.

Table 12: Clinical efficacy summary of outcomes focused on in the ERG report, PEDFIC1 (adapted from CS, Tables 16 and 19)

Outcome	Placebo n=20	Odevixibat 40 µg/kg/day n=23	Odevixibat 120 µg/kg/day n=19	Odevixibat all doses n=42
Primary endpoints				
Proportion of patients with an sBA response (EU & RoW)				
Responders, n (%)	0	[redacted]	[redacted]	14 (33.3)
95% CI[a]	(0.00, 16.84)	[redacted]	[redacted]	(19.57, 49.55)
Proportion difference adjusting for stratification factors (odevixibat vs. placebo)		[redacted]	[redacted]	[redacted]
95% CI[b]		[redacted]	[redacted]	[redacted]
One-sided unadjusted p-value[c]		[redacted]	[redacted]	0.0015
One-sided adjusted p-value[d]		[redacted]	[redacted]	-
Proportion of positive pruritus assessments (US)				
Mean (SE)	28.74 (5.209)	[redacted]	[redacted]	53.51 (5.006)
LS mean (SE)[e]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (SE) (odevixibat vs. placebo)[e]		[redacted]	[redacted]	[redacted]
95% CI[f]		[redacted]	[redacted]	[redacted]
One-sided p-value (unadjusted)[e]		[redacted]	[redacted]	[redacted]
Secondary endpoints				

Outcome	Placebo n=20	Odevixibat 40 µg/kg/day n=23	Odevixibat 120 µg/kg/day n=19	Odevixibat all doses n=42
Proportion of patients achieving positive pruritus assessment for more than 50% of the time				
Responders, n (%)				
95% CI[a]				
Odds Ratio (odevixibat/placebo)				
95% CI[f]				
One-Sided Unadjusted p-value[g]				
Growth				
Mean (SE) changes in height z-scores from baseline to Week 24				
Mean (SE) changes in weight z-scores from baseline to Week 24				
Mean (SE) changes in BMI z-scores from baseline to Week 24				

BMI - body mass index; CI - confidence intervals; EU - European Union; LS - least squares; RoW - rest of world; sBA - serum bile acids; SE - standard error; US - United States.
[a] Clopper-Pearson exact CI is reported
[b] Miettinen-Nurminen (score) CI is reported adjusting for stratification factors
[c] Based on the Cochran-Mantel-Haenszel test adjusting for stratification factor (PFIC type)
[d] For an individual dose, the adjusted p-value was calculated as the maximum value of the unadjusted p-value for odevixibat all doses and the unadjusted p-value for the individual dose
[e] non-parametric ANCOVA
[f] The exact CI is reported based on Vollset, Hirji, and Elashoff (1991)[26]
[g] Based on the Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors

Proportion of patients experiencing a reduction in serum bile acid concentration (EU/RoW primary outcome)

The proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L compared to placebo after 24 weeks of treatment was statistically significantly greater in the odevixibat combined treatment arms (33.3%) than

the placebo (0%) (p=0.0015, unadjusted); this included 43.5% and 21.1% of patients in the odevixibat 40 and 120 µg/kg/day dose groups, respectively (adjusted p-values compared with placebo, [redacted] and [redacted], respectively), between which a *post-hoc* 2-sided Cochran–Mantel–Haenszel test stratified by PFIC subtype found [redacted].[1] Figure 4 shows change from baseline in sBA concentration over the 24-week treatment period for odevixibat (combined and by dose) versus placebo. Although sBA concentration was reduced to a similar level in both PFIC1 and PFIC2 patients, a greater proportion of patients with PFIC2 (40.0%) than PFIC1 (16.7%) had an sBA response at week 24 (see Figure 5); the statistical significance of this difference was not tested.

These findings suggest that treatment with odevixibat can lead to a clinically meaningful reduction in sBA concentration in around a third of patients over ~6 months, with the 40 µg/kg/day dose leading to greater reductions than the 120 µg/kg/day dose [redacted], and may be more effective in patients with PFIC2 than PFIC1 at reducing sBA concentration.[1] This provides some support for the proposed starting dose of 40 µg/kg/day odevixibat.[11]

Figure 4: Mean (±SE) Change from baseline in sBA concentration (µmol/L) by visit (reproduced from CS, Figure 18)

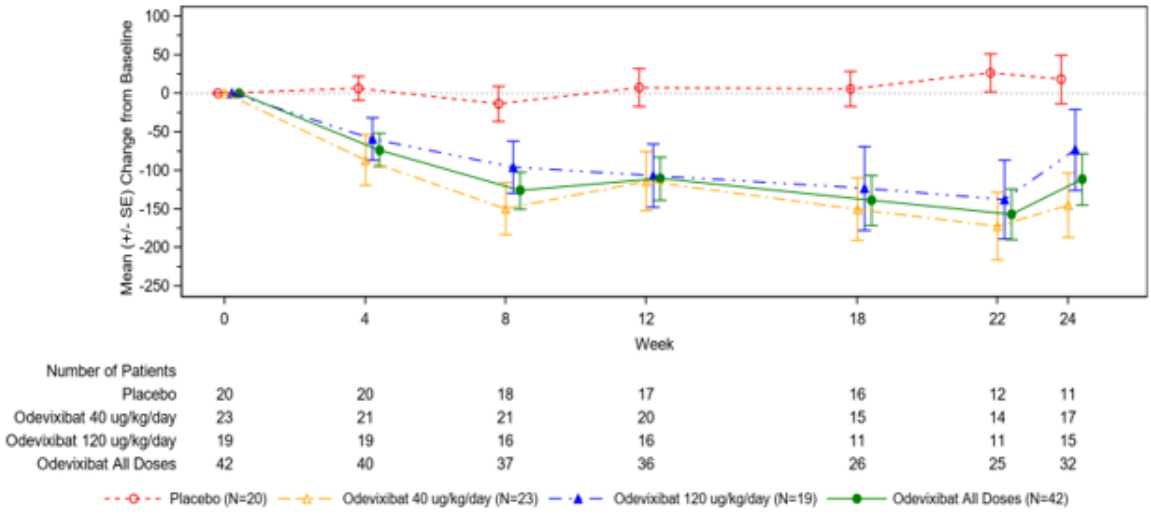
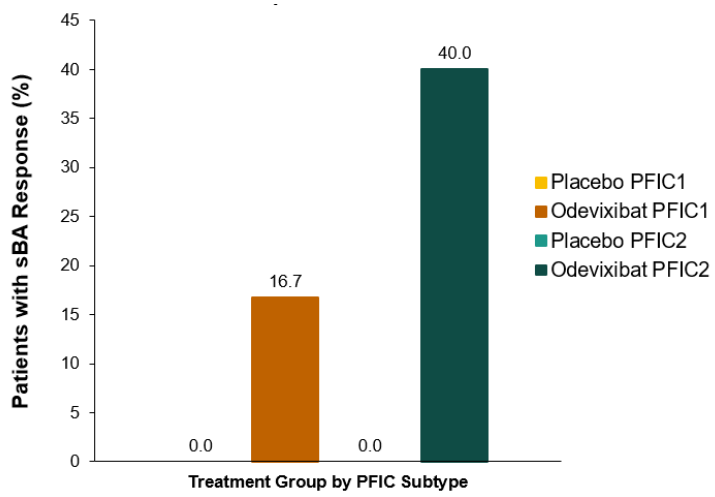


Figure 5: sBA response at Week 24 (A) and [redacted] in patients according to PFIC subtype (reproduced from CS, Figure 19)

A



[redacted]

PFIC - progressive familial intrahepatic cholestasis; sBA - serum bile acid

Proportion of positive pruritus assessments (US primary outcome)

A greater proportion of positive pruritus assessments at the patient level over the 24-week treatment period (scratching score of ≤1 or ≥1-point drop from baseline on the Albireo ObsRO instrument) was achieved by patients treated with odevixibat (all doses; 53.5%) relative to the placebo arm (28.7%).

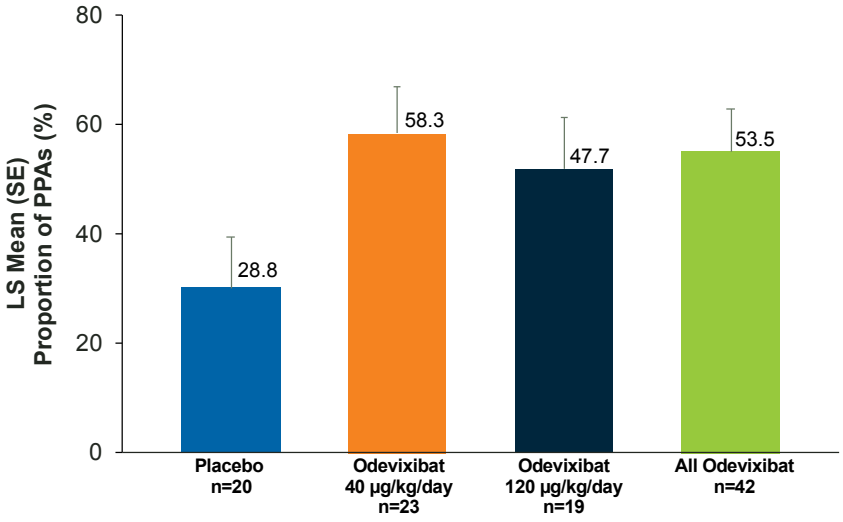
[redacted]

[redacted] Similar effects for odevixibat and placebo were achieved for patients with each PFIC subtype (see CS, Figure 21, page 102).

These findings suggest that treatment with odevixibat can lead to a clinically meaningful pruritus response around [redacted] over ~6 months of treatment. [redacted][1] [redacted]

Figure 6: Proportion of positive pruritus assessments at the patient level over 24 weeks (A) [redacted] (reproduced from CS, Figure 20)

A



[redacted]

CI - confidence interval; LS - least squares; PPA - positive pruritus assessment
Notes: PPAs defined as a scratching score of ≤1 or ≥1 point drop from baseline on an observer-reported instrument.
Source: PEDFIC1 CSR; Thompson et al, 2020[27]

Proportion of patients achieving positive pruritus assessment for more than 50% of the time

[redacted]

Consistent with the mean proportion of pruritus response findings, these findings also suggest that treatment with odevixibat can lead to a clinically meaningful pruritus response for at least [redacted] in around two thirds of patients, over ~6 months of treatment, [redacted].[1]

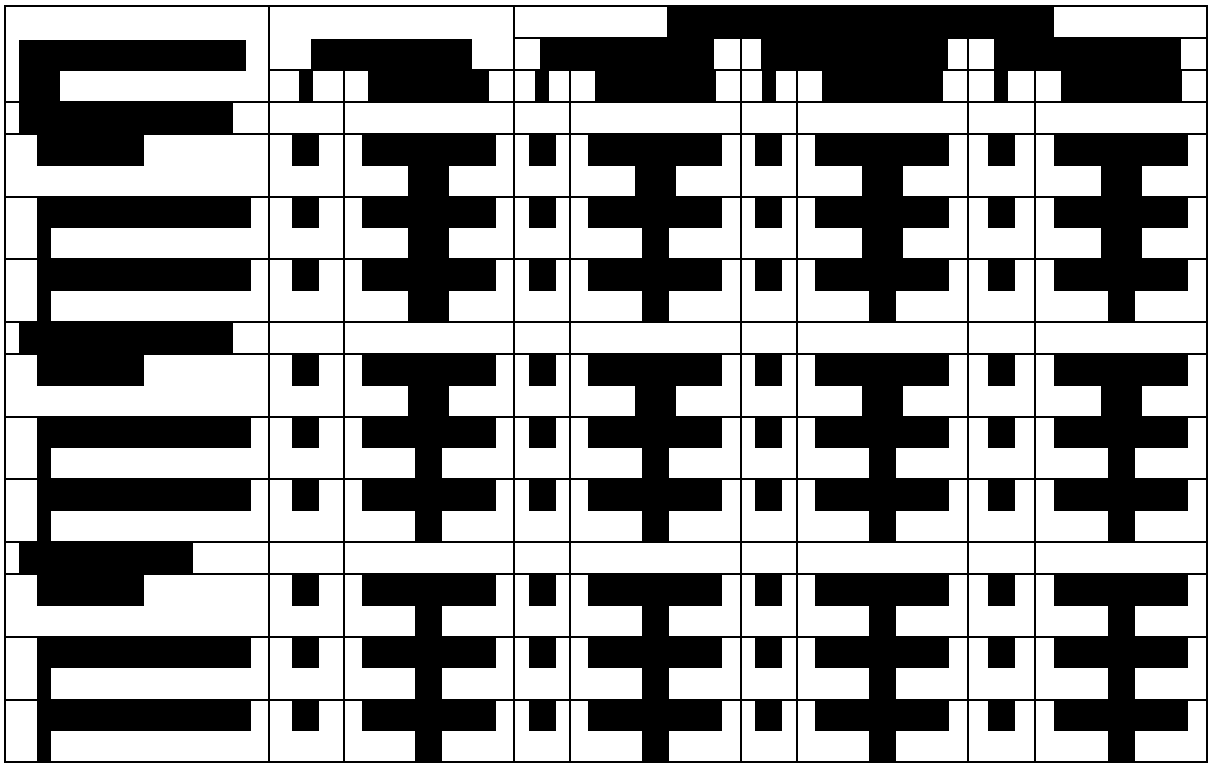
[redacted]

Growth

[redacted]

[redacted]

Table 13: [redacted]



BMI - body mass index; SE - standard error.

4.2.4.2 PEDFIC2

The FAS was used in all efficacy analyses. Table 14 summarises the efficacy results for the PEDFIC2 study for the outcomes that are considered in this report. Other outcomes are reported in Figure 27, and pages 113-114 of the CS.

Table 14: Clinical efficacy summary of outcomes focused on in the ERG report, PEDFIC2 (adapted from CS, Table 17, and PEDFIC2 CSR, Table 26)

	Odevixibat 120 µg/kg, Once Daily Dosing					
	Cohort 1[a]				Cohort 2 n=16	Cohort 2 + Placebo[b] n=35
Outcome	**40 µg/kg n=19**	**120 µg/kg n=15**	**All doses n=34**	**Placebo n=19**		
Primary endpoints						
Change in sBA (µmol/L) after 24 Weeks (EU/RoW)						
Change from baseline Mean (SE)						
% change from baseline Mean (SE)						
Proportion of positive pruritus assessments (US)						
Mean (SE)						
Secondary endpoints						
Growth						
Mean (SE) changes in height z-scores from baseline to Week 24						
Mean (SE) changes in weight z-scores from baseline to Week 24						
Mean (SE) changes in BMI z-scores from baseline to Week 24						

BMI - body mass index; CI - confidence intervals; EU - European Union; LS - least squares; LT - liver transplantation; RoW - rest of world; sBA - serum bile acids; SE - standard error; US - United States.

[a] *For patients in Cohort 1, dose indicated is dose administered during participation in PEDFIC1*

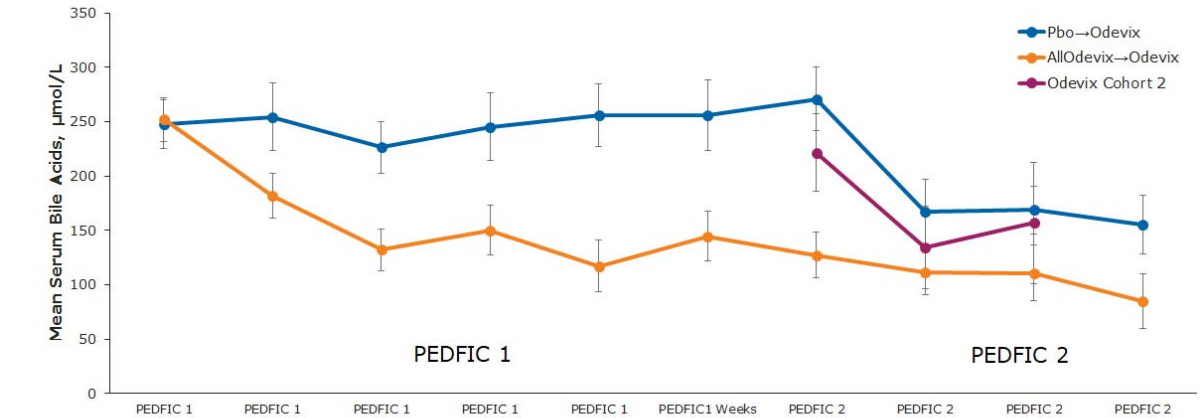
[b] *Cohort 2 + Placebo = Patients enrolled in Cohort 2 and patients who were assigned to placebo during participation in PEDFIC1*

Change from baseline in serum bile acid concentration (EU/RoW primary outcome)

Summary statistics at the interim cut-off date suggest a decline from baseline in sBA at Week 22/24 in all patients treated with 120 µg/kg/day odevixibat, including among patients with prior odevixibat (who had rolled over from PEDFIC1, and among whom the mean sBA concentration continued to decline throughout PEDFIC2) and among treatment-naïve patients (see Figure 7).[1]

[redacted]. It should be noted, however, that interim follow-up sample sizes were small (as little as [redacted] in Cohort 2), and no significance testing was undertaken between baseline and follow-up sBA concentration values. Among the 4 patients randomised to the 40 µg/kg/day dose of odevixibat who did not meet the definition of an SBA treatment response in PEDFIC1, [redacted] met the sBA responder definition at Week 24 of PEDFIC2.[1] These findings suggest that reductions in mean sBA concentrations are maintained among patients who have been taking odevixibat for almost a year, and that sBA concentrations begin to fall among those who start on the drug after having received placebo. Also, these findings suggest that dose escalation to 120 µg/kg/day may only be efficacious in [redacted] patients who did not meet the definition of treatment response on the 40 µg/kg/day dose of odevixibat, although small patient numbers may preclude generalisation of this finding.

Figure 7: Mean (±SE) serum bile acid concentration (µmol/L) during PEDFIC1 and PEDFIC2 Week 24 (reproduced from CS, Figure 25)



Source: Thompson et al, 2020[27]

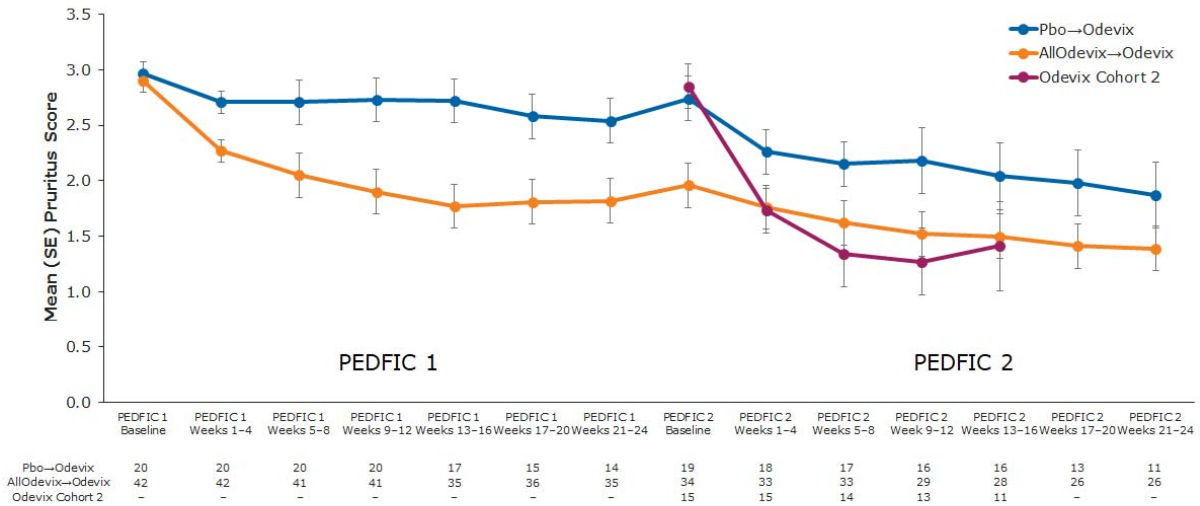
Proportion of positive pruritus assessments (US primary outcome)

[redacted]

[redacted]

Among the 8 patients randomised to the 40 µg/kg/day dose of odevixibat who did not meet the definition of a pruritus response in PEDFIC1, [redacted] met the pruritus responder definition at Week 24 of PEDFIC2 (based on a >1 point decrease from the PEDFIC1 baseline).[1] Mean pruritus scores show a downward trend throughout both PEDFIC1 and PEDFIC2 among patients in Cohort 1 (see Figure 8). These findings suggest that gains made in PEDFIC1 in terms of mean pruritus response at the level of the individual are maintained in PEDFIC2, those treated with odevixibat for the first time experience a clinically meaningful pruritus response at a similar mean proportion to those treated with odevixibat for the first time in PEDFIC1.

Figure 8: Mean (±SE) pruritus score by grouped weeks (reproduced from CS, Figure 26)



Source: Thompson et al, 2020[27]

Growth

Overall, height and weight z-scores showed [redacted]

[redacted] Mean (SE) changes in height z-scores from baseline to Week 24 were 0.34 (0.11), [redacted] and 0.40 (0.18) in patients previously treated with odevixibat in PEDFIC1 (all doses), previous 40 µg/kg/day odevixibat group from PEDFIC1, previous 120 µg/kg/day odevixibat group from PEDFIC1, and placebo group from PEDFIC1, respectively. Mean (SE) changes in weight z-scores from baseline to Week 24 were 0.23 (0.11), [redacted] and 0.47 (0.19) in patients previously treated with odevixibat in PEDFIC1 (all doses), previous 40 µg/kg/day odevixibat group from PEDFIC1, previous 120 µg/kg/day odevixibat group from PEDFIC1, and placebo group from PEDFIC1, respectively. [redacted] and all growth results should be interpreted with caution due to low patient numbers in each group.

Liver transplantation

*[redacted] enrolled in PEDFIC1 were listed for LT surgery and [redacted] were added to the list during their participation in PEDFIC1 or PEDFIC2, as of the cut-off date.[1]

[redacted] that among the 34 patients enrolled in PEDFIC2 after being [redacted] odevixibat in PEDFIC1, 1 patient had discontinued as of the data cut-off date (1 discontinuation event) (see CS,[1] Section 12.2.1.1, page 177). This data is used in the company's cost-effectiveness model.

Table 15

[redacted] [13] The data suggest that the drug is useful in terms of improving height and weight outcomes for patients, although the results for BMI are difficult to interpret.

Liver transplantation

[redacted] enrolled in PEDFIC1 were listed for LT surgery and [redacted] were added to the list during their participation in PEDFIC1 or PEDFIC2, as of the cut-off date.[1]

Discontinuation rate

The CS[1] reports that among the 34 patients enrolled in PEDFIC2 after being treated with odevixibat in PEDFIC1, 1 patient had discontinued as of the data cut-off date (1 discontinuation event) (see CS,[1] Section 12.2.1.1, page 177). This data is used in the company's cost-effectiveness model.

Table 15: [redacted]

BMI - body mass index; SE - standard error.

4.2.4.3 Phase 2 study

The FAS was used in all efficacy analyses.

Change in total serum bile acids

Mean total sBA concentrations from test results decreased for all doses of odevixibat from baseline to the end of the 4-week treatment period. The largest decrease was observed in the 60 µg/kg/day group (mean percentage change -62.8 (SD 24.4)).[1] Among PFIC patients only (10 patients, 3 of whom were re-exposed to a different dose), the mean percentage change in sBA concentration was [redacted]. sBA concentration reduced in response to odevixibat among all PFIC patients but one, whose sBA concentration was stable. The CS[1] reports that this patient had a complete absence of BSEP.

Pruritus response

There were small and not statistically significant reductions on all of the VAS-itch, PO-SCORAD-itching, Whitington scale and PO-SCORAD-Sleep Disturbance scores following the 4-week treatment period, for all doses of odevixibat. Among patients with PFIC, mean change from baseline in VAS-itch scores was −2.7 (range −5.9 to 0.4); mean change from baseline in PO-SCORAD itch score was −2.5 (range −6 to 0.3); mean change from baseline in Whitington itch score was −1.1 (range −3 to 0.1); and mean change from baseline in PO-SCORAD sleep disturbance score was −2.4 (range −5.8 to 0.4).[1]

4.2.4.4 Safety and tolerability

PEDFIC1 and PEDFIC2

Safety analyses for the PEDFIC1 trial were conducted using the safety analysis set, [redacted].[12] [redacted].[13]

An adverse event (AE) was defined in the PEDFIC1 CSR[12] (page 63) and the PEDFIC2 CSR[13] (page 64) as "*any clinically significant unfavourable and unintended sign, symptom, or disease that occurred once a patient was enrolled in the study until the patient was discharged from the study, whether or not related to the study drug*", although no definition of a treatment-emergent adverse event (TEAE) was provided in either CSR, so the ERG has been unable to determine how these differed from AEs. Drug-related AEs were those judged by the investigator to be possibly, probably or definitely caused by the study drug, based on medical judgement.[12, 13] Serious AEs were defined as those that met any one of the following six criteria:[12, 13]

- The outcome of the AE was death

- The AE was immediately life threatening (at immediate risk of death from the reaction as it occurred)
- The AE resulted in persistent or significant disability/incapacity (substantial disruption of a person's ability to conduct normal life functions)
- The AE required or prolonged hospitalisation
- The AE resulted in a congenital anomaly/birth defect
- The AE was an important medical event

Severe AEs were those judged to be incapacitating, leaving the patient unable to perform normal activities.[12, 13]

Odevixibat appears to be generally well tolerated among patients with PFIC (see Table 16). The proportion of patients experiencing at least one TEAE was [redacted] Patients in both odevixibat dose groups of PEDFIC1 and all groups in both cohorts in PEDFIC2 experienced a similar proportion of drug-related TEAEs, and this was around double that of the proportion of PEDFIC1 placebo group patients who experienced drug-related TEAEs. In the PEDFIC1 trial, the proportion of patients who experienced at least one severe TEAE and at least one serious TEAE was lower in the 40 µg/kg/day odevixibat group than the 120 µg/kg/day odevixibat and placebo groups; this may be an artifact of the small numbers of patients in each group rather than an adverse effect of the drug and no significance testing of the subgroup differences was reported. Greater proportions of treatment-naïve patients in the PEDFIC2 study experienced serious and drug-related serious TEAEs than the previously treated patients; again, the numbers are small and it is difficult to tell whether this is because these patients were receiving the drug for the first time, or was an artifact of the small sample size at the data cut-off date (see Table 16). For further details, see Sections 9.7.2.2 and 9.7.2.3 in the CS.[1]

Phase 2 study

Safety analyses of the Phase 2 study were conducted using the safety population, defined as [redacted] AEs, SAEs and drug-related AEs were defined in the same way as for the PEDFIC1 and PEDFIC2 studies, and TEAEs were similarly not defined.[14] All doses of odevixibat appear to be well-tolerated among patients with PFIC (see Table 17). The proportions of

patients with each category of AE did not appear to increase in a linear fashion with odevixibat dose, although the numbers of patients overall and in each dose group were small and the study duration was short, due to the aims and purpose of the study. Most patients experienced a TEAE, however only small numbers/proportions reported drug-related, serious and severe TEAEs, and there were no treatment discontinuations nor deaths due to AEs. For further details, see Sections 9.7.2.1 in the CS.[1]

Table 16: Overview of adverse events from PEDFIC1 and PEDFIC2 (adapted from CS Tables 25 and 28)

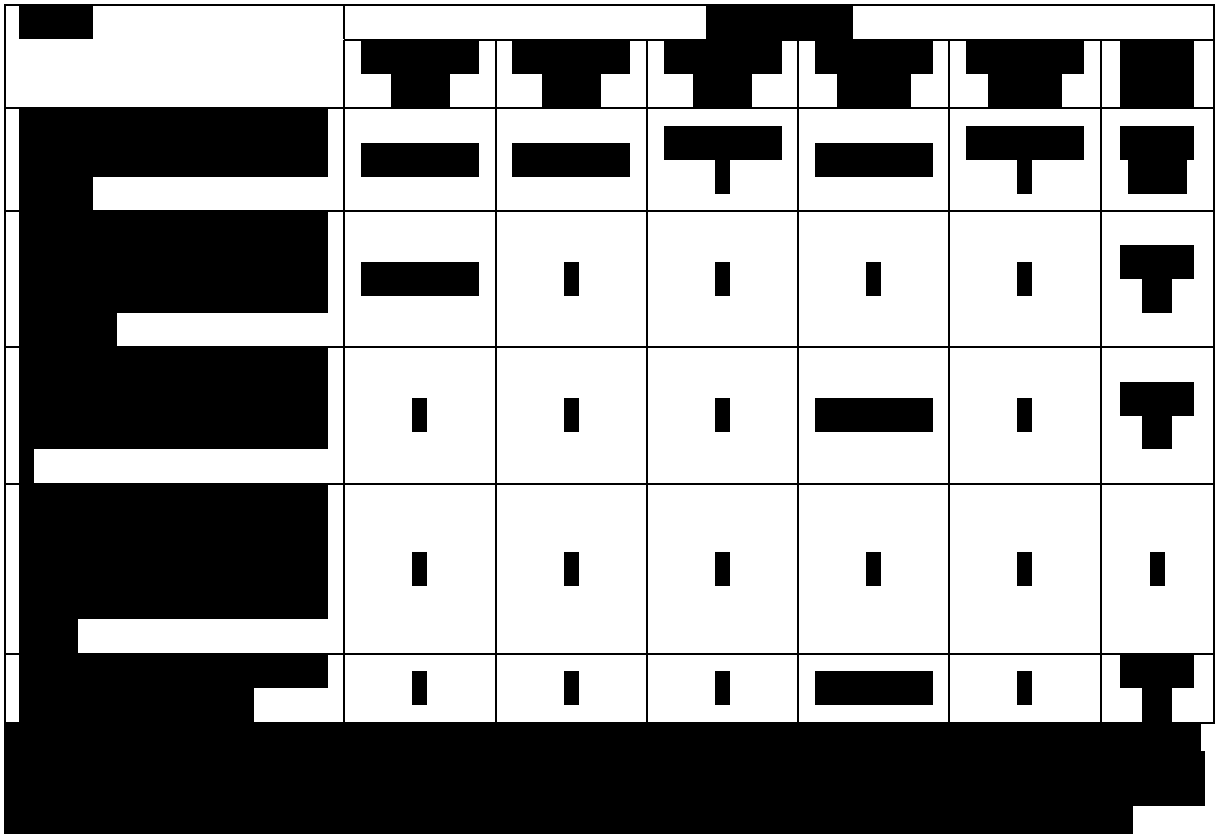
	PEDFIC1				PEDFIC2			
n (%)	**Placebo n=20**	**Odevixibat**			**Cohort 1**			**Cohort 2 n=16**
		40 µg/kg n=23	**120 µg/kg n=19**	**All doses n=42**	**Odevixibat 40 µg/kg n=19**	**Odevixibat 120 µg/kg n=15**	**Placebo n=19**	
Total number of patients with at least one TEAE	17 (85.0)	19 (82.6)	16 (84.2)	35 (83.3)	16 (84.2)	12 (80.0)	14 (73.7)	8 (50.0)
Total number of patients with at least one drug-related TEAE[a]	3 (15.0)	7 (30.4)	7 (36.8)	14 (33.3)	6 (31.6)	4 (26.7)	5 (26.3)	5 (31.3)
Total number of patients with at least one severe TEAE[b]	2 (10.0)	1 (4.3)	2 (10.5)	3 (7.1)	0	1 (6.7)	1 (5.3)	3 (18.8)
Total number of patients with at least one serious TEAE	5 (25.0)	0	3 (15.8)	3 (7.1)	0	0	3 (15.8)	1 (6.3)
Total number of patients with at least one drug-related serious TEAE	0	0	0	0	0	0	0	0
Total number of patients with at least one TEAE leading to study treatment discontinuation	0	0	1 (5.3)	1 (2.4)	0	0	1 (5.3)	2 (12.5)
Total number of patients with at least one TEAE leading to death	0	0	0	0	0	0	0	0
Total number of deaths	0	0	0	0	0	0	0	0

AE - adverse event; TEAE - treatment-emergent adverse event.

[a] *Patients reporting more than one event are counted only once at the highest relationship reported*

[b] *Patients reporting more than one event are counted only once at the maximum severity reported*

Table 17: [redacted]



4.2.4.5 Subgroups

[redacted] The company's clarification response[2] (question A13) states that these subgroup analyses were pre-planned, were not powered, and that statistical analysis was only performed when the sample size was ≥10 in each treatment group (for sample sizes of <10, summary statistics were reported). [redacted]

[redacted]

The CS[1] also reports subgroup effects of PFIC subtype and the use of rifampicin at baseline on the proportion of positive pruritus assessments in PEDFIC2, in that patients with PFIC2 [redacted] had a greater proportion of positive pruritus assessments. Among the 5 patients with PFIC3 enrolled in Cohort 2, 4 (80%) met the sBA responder definition as of the data cut-off and all had ≥94% positive pruritus assessments at the last assessment prior to data cut off.[1]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 *Completeness of the CS with regard to relevant clinical studies and relevant data within those studies*

The clinical evidence relating to odevixibat for treating PFIC is based on three studies: the PEDFIC1 trial, a double-blind Phase 3 RCT, which examined the efficacy of two doses of odevixibat (40 µg/kg/day and 120 µg/kg/day) for treating PFIC1 and PFIC2; the PEDFIC2 study, a Phase 3 single-arm open-label extension of the PEDFIC1 trial plus additional patients enrolling for the first time; and the Phase 2 study, a Phase 2 single-arm, open-label dose-finding study. The ERG is confident that no additional studies (published or unpublished) of odevixibat for treating PFIC are likely to have been missed.

4.6.2 *Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes*

The ERG is confident that the relevant population and intervention have been included in the CS. One of the relevant comparators was included (standard care, consisting of off-label drug treatments – which the majority of patients in the RCT, PEDFIC1, were taking concurrently with odevixibat or placebo), however, there is currently no evidence for a comparison of odevixibat against the other comparator listed in the final NICE scope[10] (surgical interventions, such as PEBD). The ERG notes that there is thus far no evidence of any direct or indirect comparison of odevixibat with PEBD, although a future indirect comparison of [redacted] with data from [redacted] is planned, the results of which will considerably improve the accuracy of any comparisons between odevixibat and PEBD (see Section 4.2.1.6). The CS includes evidence relating to all of the outcomes specified in the final NICE scope,[10] although HRQoL, from the final NICE scope,[10] was not reported as a primary or secondary outcome for either PEDFIC1 or PEDFIC2, although HRQoL is reported as an exploratory outcome in the CSRs of both studies.

The EU/RoW primary outcome of the PEDFIC1 trial was the proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L after 24 weeks of treatment, which the ERG considers to be an appropriate outcome for judging the effectiveness of odevixibat versus placebo in PFIC. A third of patients (33.3%) randomised to odevixibat achieved this outcome, versus none in the placebo group (0%) (p=0.0015, unadjusted); this included 43.5% and 21.1% of patients in the odevixibat 40 and 120 µg/kg/day dose groups, respectively (adjusted p-values compared with placebo, [redacted] and [redacted], respectively). The US primary outcome of the PEDFIC1 trial was the proportion of positive pruritus assessments at the patient level over the 24-week treatment period, using the PRUCISION© ObsRO instrument developed by Albireo to assess pruritus symptoms and impact in PFIC patients and their caregivers, which is a validated measure of pruritus that is specific to this population. A greater proportion of

positive pruritus assessments at the patient level over the 24-week treatment period was achieved by patients treated with odevixibat (53.5%) relative to the placebo arm (28.7%); patients treated with odevixibat achieved a response just over half of the time, on average, over all assessments made over the course of the 24-week treatment period. [redacted].

The EU/RoW primary outcome of the PEDFIC2 study was change from baseline in sBA concentration after 24 weeks of treatment (for the interim analysis), which the ERG judges to be an appropriate outcome. sBA concentrations declined in all patients across the treatment period, with [redacted]. The US primary outcome of PEDFIC2 was the proportion of positive pruritus assessments over the treatment period (from baseline to Week 24 at the interim data cut-off, 15th July 2020) using the Albireo ObsRO instrument. [redacted] No patients were listed for LT surgery or were added to the list. [redacted] (of [redacted]) patients enrolled in PEDFIC2 had discontinued.

4.6.3 *Uncertainties surrounding the reliability of the clinical effectiveness*

The first key uncertainty relates to a lack of clarity around the definition of an '*adequate clinical response*', the judgement of which is required by clinicians when deciding whether or not to escalate the odevixibat dose after 3 months of continuous therapy, as reported in the draft SmPC.[11] In response to clarification question A9,[2] the company stated that a precise definition is unknown at the present time, and they are currently refining this in collaboration with key clinicians in the field. Therefore, this

limits the extent to which the ERG can comment on the similarity of the clinical evidence for odevixibat to the clinical context in England.

A second key uncertainty relates to an inconsistency between the dose administered in the PEDFIC2 study and the recommended dose detailed in the SmPC. Patients were started on the higher dose to begin with (although some patients received the 40 µg/kg/day dose for 3 or 6 months in PEDFIC1), and therefore it is possible that some patients will have received a higher dose than the recommended starting dose for at least three months. Additionally, patients from PEDFIC2 who achieved an adequate clinical response on the 40 µg/kg/day dose in PEDFIC1 would have received a higher dose in PEDFIC2 than they would have in clinical practice, according to the SmPC dosing instructions. The company clarified that this was to maintain blinding in PEDFIC1 (see Section 4.2.1.2). Nevertheless, the ERG believes that the trial data may not accurately reflect clinical practice and may potentially have led to the efficacy of odevixibat being potentially overestimated in a number of cases in the findings of the PEDFIC2 study.

A third key uncertainty relates to the lack of evidence for the comparative efficacy of odevixibat and PEBD. This makes it difficult to determine where in the treatment pathway odevixibat should go, relative to PEBD, and also impacts on the cost-effectiveness modelling for odevixibat. Comparative data would have improved the accuracy of the modelling assumptions, and informed clinical decision-making. The planned [redacted] comparison (of [redacted]) (see Section 4.2.1.6) is expected to provide data on the relative efficacy of odevixibat and PEBD, which should address this uncertainty.

A fourth key uncertainty relates to the effectiveness of odevixibat among previously treated patients. Patients who had undergone PEBD surgery >6 months prior to the PEDFIC1 baseline were permitted to enrol in the study, and information presented in the company's clarification response suggests that [redacted] Therefore, the impact of prior PEBD on odevixibat treatment (and vice versa) is unknown.

A fifth key uncertainty relates to the relatively short duration of follow-up in the PEDFIC1 and PEDFIC2 studies, with comparative data only available for a 24-week time period and follow-up only extending to 48 weeks by the point of the PEDFIC2 data cut-off, for those rolling over from PEDFIC1 to PEDFIC2. This has meant that it was difficult to assess some important outcomes that might only

present over the longer-term, such as survival and transplant-free survival. In addition, the longer-term impact of odevixibat on sBA concentration and pruritus is also unknown.

A sixth key uncertainty relates to the lack of more robust, comparative evidence (and little evidence overall) for the effectiveness of odevixibat among PFIC patients with subtypes other than PFIC1 and PFIC2. The ERG recognises that the small number of patients with other PFIC subtypes presents a challenge to the collection of such data, however the point remains that odevixibat is proposed for patients with PFIC in general, whereas there is only comparative evidence relating to patients with PFIC1 and PFIC2, and some preliminary evidence among patients with PFIC3.

Another key source of uncertainty is the impact of PFIC subtype (1 or 2) on the effectiveness of odevixibat in terms of key outcomes (e.g. sBA response and pruritus response). Some data from the PEDFIC1 trial suggest there may be differential effects, however the study was not powered to detect differences in these subgroups, and statistical comparisons have not been made.

The single-arm, open-label nature of PEDFIC2, which is the only study to include patients with PFIC subtypes other than PFIC1 and PFIC2, and the only study to report longer-term follow-up, also introduces uncertainty. There is a possibility of potential biases such as attrition bias, natural recovery and regression to the mean; a double-blind RCT would have been a more rigorous study design.

5 COST EFFECTIVENESS

This chapter provides a summary and critique of the company's economic analyses of odevixibat for the treatment of PFIC, together with additional exploratory analyses undertaken by the ERG. Section 5.1 summarises the company's SLR of existing economic analyses of treatments for PFIC. Section 5.2 presents a detailed description of the methods and results of the company's submitted economic model. Section 5.3 presents the ERG's critical appraisal of the company's model. Section 5.4 presents the methods and results of the exploratory analyses undertaken by the ERG using the company's model. Sections 5.5 and 5.6 present a brief discussion of the company's budget impact estimates and wider impact beyond the NHS and PSS. Section 5.7 presents a discussion of the available economic evidence.

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 *Summary and critique of the company's search strategy*

The company performed two systematic literature searches for i) published cost-effectiveness studies of people with PFIC (CS Appendix 17.3) combined with the cost and resource use studies search (CS Appendix 17.4) and ii) HRQoL studies (CS Appendix 17.5). All searches were undertaken in March 2021 and were fully reported in the company submission Appendices.

The cost-effectiveness studies and cost and resource use studies search was a two-in-one search in the following databases: MEDLINE [via Ovid], MEDLINE In-Process [via Ovid], Embase [via Ovid], The Cochrane Central Register of Controlled Trials [via Wiley], The Health Technology Assessment [via CRD], Database of Abstracts of Reviews of Effects [via CRD], NHS Economic Evaluation Database [via CRD] and EconLit [via Ovid] in March 2021.

The company search strategy comprises the disease terms (PFIC) combined with the economics and the broader economic impact terms such as employment, productivity, societal impact, burden of illness, and carer burden. The origin of the search filters used are unknown. The search was consistently translated across the databases. No perceived and consequential errors were found and the ERG considers that the search is comprehensive.

For the health-related quality-of-life studies search (CS Appendix 17.5), the company used the same sources as the cost-effectiveness and cost and resource use studies search in March 2021 with the inclusion of the ScHARRHUD database. The strategy comprises the disease terms (PFIC) combined with an extensive health related quality of life and utilities search filters in MEDLINE, Embase and Cochrane Library. The ERG considers the search terms used are comprehensive, transparent, reproducible and consistently translated across all database searches.

5.1.2 *Summary of company's review findings*

The company's searches identified 840 citations through database searches. Following the removal of 85 duplicates, the titles and abstracts of 755 studies were sifted and the full texts of 72 studies were reviewed. The CS stated that no relevant full text articles on economic evaluations or costs and resource use studies were identified, however Figure 38 (page 176) of the CS shows that two studies were included. During the clarification process (additional clarification question 2, page 72[2]), the company clarified that this was an omission. One of these studies was also identified in an earlier clinical review and informed economic modelling parameters (liver transplant mortality) whilst an additional study reporting outcomes was considered inappropriate to inform the economic model due to the surgery intervention used being uncommon in the UK. The ERG believes that as this is a rare disease it is unsurprising that there were no economic evaluation studies available and that the searches conducted by the company were comprehensive.

5.2 Summary of the company's submitted economic evaluation

This section describes the methods and results of the company's submitted model. Following the clarification process, the company submitted an updated model, which fixed the errors identified by the ERG during the clarification process. The company also submitted additional data and analyses after clarification regarding health state utility values and an updated vignette study undertaken by the company, used only in scenario analyses.

The following updates were made to the company's model base-case in response to clarification:

- 3.5% discount rate used for costs and outcomes
- Final data from the PICTURE study[28] were incorporated for health state resource use and carer costs
- Utilities were correctly age-adjusted
- Drug costs are based on weight distributions
- Cholestyramine and rifampicin doses are corrected to account for varying dosage with age
- Post-liver transplant costs applied to all patients in the post liver transplant health state
- Update to the data used to estimate post-liver transplant mortality

This updated model is discussed from Section 5.2.1 onwards.

5.2.1 *Scope of the company's economic analysis*

The company submitted a fully executable health economic model of odevixibat, programmed in Microsoft Excel®. The scope of the company's model is summarised in Table 18. The company's base case analyses assess the incremental cost effectiveness of odevixibat versus standard of care, which

includes PEBD, for patients with PFIC1 and PFIC2. The CS[1]and final scope[10] state that the perspective of the National Health Service (NHS) and Personal Social Services (PSS) is used, however the model base-case uses a societal perspective which includes costs and health effects on patients' caregivers. Cost-effectiveness is assessed in terms of the incremental cost per quality-adjusted life year (QALY) gained, calculated over a 96-year (lifetime) horizon, with half-cycle correction implemented. Unit costs are valued at 2019/2020 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Table 18: Scope of company's economic analysis

Population	Patients aged 6 months and older with PFIC1/2
Time horizon	96 years (lifetime)
Intervention	Odevixibat
Comparator	Standard of care
Outcome	Incremental cost per QALY gained
Perspective	Societal
Discount rate	3.5% for health outcomes and costs
Price year	2019/2020

PFIC - progressive familial intrahepatic cholestasis; NHS – National Health Service; PSS – Personal Social Services; QALY - quality adjusted life year

Population

The population included in the company's model is patients with PFIC1/2, based on the trial population of PEDFIC1. However, the description of the population in the final scope[10] and draft SmPC[11] does not restrict the population eligible to receive odevixibat to patients with PFIC1/2 only (see Section 3.1), and the CS anticipates that patients with all PFIC subtypes will be treated with odevixibat. At model entry, patients are assumed to have a mean age of 4.25 years old and 50% of patients are assumed to be male.

Intervention

The intervention evaluated within the economic analysis is odevixibat administered orally, at a dose of 40µg/kg/day or 120µg/kg/day, daily. In the model base-case, effectiveness of the intervention for patients receiving 40µg/kg/day is based on outcome data from PEDFIC1.[12] This is based on the proportion of patients experiencing at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L compared to placebo after 24 weeks of treatment (see Section 4.2.4.1). Patients who do not achieve response by three months on 40µg/kg/day are up-titrated to 120µg/kg/day, with effectiveness data sourced from non-responders on 40µg/kg/day in PEDFIC1 who went on to receive and respond to 120µg/kg/day in PEDFIC2.[29] In addition, patients receive off-label drug treatments (described in the subsequent section).

Comparator

The CS[1] highlights that there are currently no licensed pharmacological treatments for PFIC and that the comparator in the model is PEBD, as it is part of current standard of care and the pharmacological equivalent of odevixibat. However, the company also states that not all patients under current standard of care will undergo PEBD.

The CS[1] (page 169) describes how off-label oral therapies (UDCA and/or rifampicin), are currently used but provide limited symptomatic relief. In line with PEDFIC1[12], patients in both the comparator and treatment arm of the model receive the same off-label oral therapies as each other, but they are assumed to have no treatment effect. This is based on no patients in PEDFIC1[12] placebo group showing sBA response, measured as at least a 70% reduction in fasting sBA concentration from baseline to the end of treatment or reaching a level ≤70 μmol/L after 24 weeks of treatment. Off-label therapies included in the model are UDCA, rifampicin, cholestyramine and naltrexone.

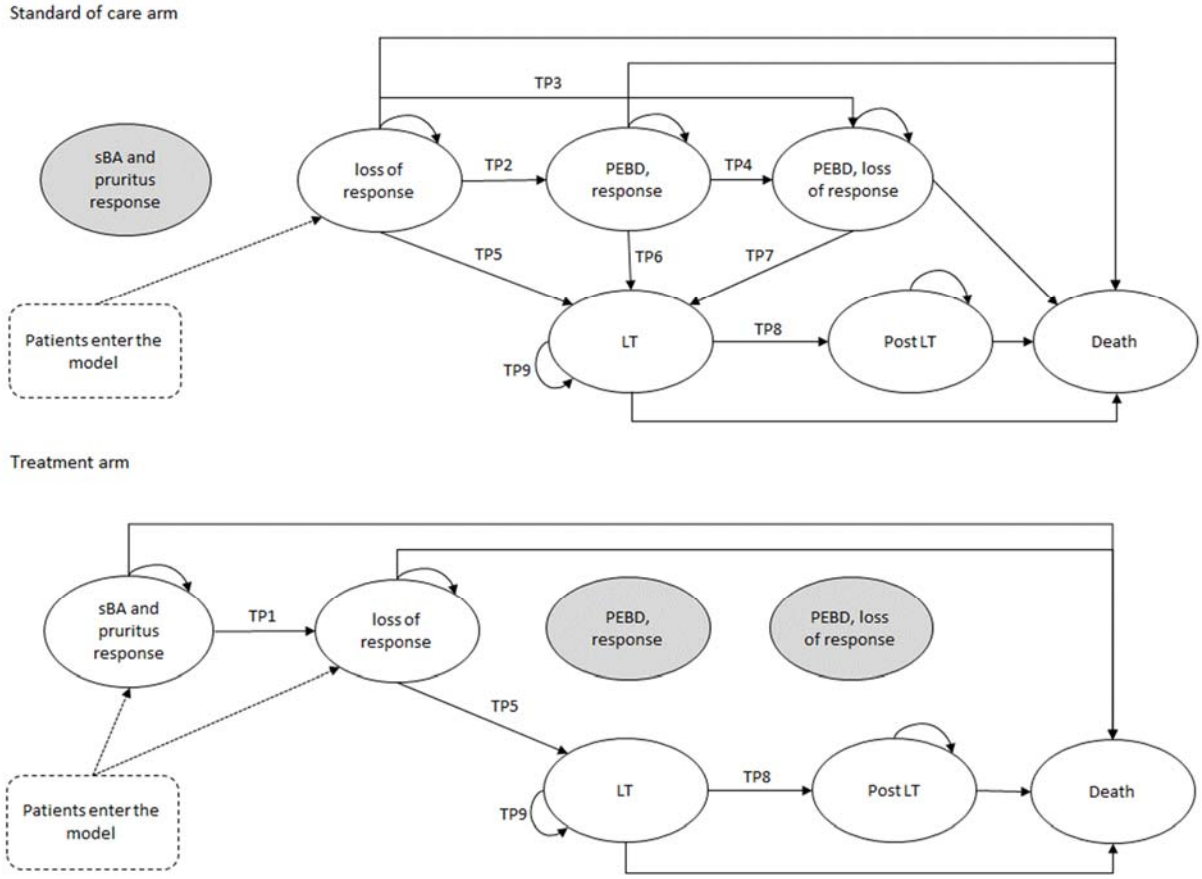
All patients in the comparator arm are assumed to start with no response to off-label therapies. Patients may then either continue to receive off-label therapies with no treatment effect or improvement on quality of life, undergo PEBD surgery or have a liver transplant.

Clinical advisors to the ERG highlighted that PEBD is not commonly used in the UK (see Section 2.2), particularly in comparison with other parts of Europe, and may be less common than the figures used in the model. Also, clinical advice received by the ERG suggested that standard care in the UK is to try to manage the disease conservatively (i.e. without PEBD), and then go on to LT if necessary. Two ERG clinical advisors further commented that patients with PFIC3 subtype are more likely to respond to UDCA and less likely to require surgery. This is not captured in the economic model which is based on PFIC1 and PFIC2 subtypes only.

5.2.2 *Model structure and logic*

The company's economic analysis uses a cohort-level state transition model, comprising of seven health states, including an absorbing health state for death. The model health states are based on patient's response (defined as both pruritus response and sBA response in the base-case) which then drives progression to PEBD or LT. Although the same health states are used in both arms of the model, the permitted transitions between health states differ, dependent on the treatment group (see Figure 9). It is assumed that patients in the treatment arm receiving odevixibat will not undergo PEBD after loss of response to treatment. The company stated that the model structure and treatment pathway were validated by a clinical expert.

Figure 9: Company's model structure, reproduced by the ERG



Health states shaded in grey are not used in that arm of the model. Labelled transition probabilities correspond with those noted in the company's model diagram.
LT - liver transplant; PEBD - partial external biliary diversion; sBA - serum bile acid; TP- transition probability

The model logic operates as follows. In the SoC arm, all patients enter the model in the 'loss of response' state and receive off-label treatment therapies. These are assumed to have no treatment effect in the model and are included in both treatment arms. In the treatment arm, patients enter the model in either the 'pruritus and sBA response' health state and receive odevixibat until response is lost, at which point they move to the 'loss of response' state. In a scenario analysis, an additional health state is used in which patient's response to treatment with odevixibat is measured as either 'pruritus and sBA response' or 'pruritus response only'. Patients enter the model split between these two health states in the treatment arm in the scenario analysis only.

The following health states transitions are permitted during each 1-year model cycle:
Comparator arm:

- Patients in the loss of response state can either remain in this state, transition to PEBD with response, transition to PEBD loss of response, transition to LT or die

- Patients in PEBD with response can remain in this state, transition to PEBD loss of response or die.
- Patients in PEBD loss of response can remain in this state, transition to LT or die
- Patients in LT can remain in this state (representing re-transplant), transition to post-LT or die.
- Patients in the post-LT state can remain in this state, or die.

Treatment arm:

- Patients in the pruritus and sBA response state can either remain in this state, transition to loss of response or die.
- Patients in the loss of response state can either remain in this state, transition to LT or die
- Patients in LT can remain in this state (representing re-transplant), transition to post-LT or die.
- Patients in the post-LT state can remain in this state, or die.

The model separately calculates the percentage of 'new in state patients' for both PEBD and LT in order to apply one-off costs related to PEBD surgery and LT surgery, respectively. Rather than having a separate health state for re-transplantation, a fixed proportion of patients remain in the LT state each cycle to represent those patients who require a re-transplant, with data used from an external study.[30]

The probability of dying for patients responding to either odevixibat or PEBD is modelled using age- and sex-matched general population life tables.[31] Therefore, patients remaining in these states are assumed to have zero disease-related excess risk of death. Patients not responding to treatment have an increased risk of death prior to liver transplant compared to the general population, based on data from the NAPPED[32, 33] study, and the annual probability of death for non-responders for PFIC1 and PFIC2 was estimated using calibration. The probability of death in the first year post-LT was sourced from a meta-analysis undertaken by the company. The annual probability of death for all remaining years post-LT are sourced from a pooled analysis of digitised Kaplan Meier (KM) curves from published studies, undertaken by the company.

Utility values are dependent on response to treatment and were sourced from an external study of children with Alagille syndrome and other liver diseases, including chronic intrahepatic cholestasis (CIC), versus healthy children.[34] This study collected data using PedsQL which the company mapped to the EQ-5D-3L using a mapping algorithm from Khan et al.[35] Responders to treatment are assumed to have the same quality of life as healthy children whilst non-responders have quality of life equal to children with CIC. All patients who undergo PEBD have a multiplier applied to represent the disutility of a stoma bag. An additional multiplier is applied to all non-responding patients to represent lower utility associated with short stature. Separate utility values were used for LT and post-LT health states,

sourced from external studies. The model also includes disutilities for carers of children who have loss of response to treatment, PEBD surgery and post-LT, up to 18 years of age. There are no QALY losses associated with adverse events included in the model. Health state utilities are adjusted for increasing age.

The model includes costs associated with: (i) drug acquisition, (ii) medical resource use conditional on model health state (no surgery, post-PEBD, post-LT), (iii) surgery costs (one-off costs for PEBD and LT), (iv) LT follow up costs, including LT complications and post-LT immunosuppression costs, and (v) carer productivity losses.

5.2.3 *Key assumptions employed in the company's model*

The company's base-case model employs the following key assumptions:

- Patients who receive odevixibat do not undergo PEBD surgery at any point in the future
- All patients with a sBA response, defined as either reaching a level of < 70μmol/L or at least a 70% reduction in sBA concentration from baseline in PEDFIC1[12], are assumed to have a corresponding pruritus response
- The discontinuation rate from PEDFIC1 was used as a proxy for the loss of response to odevixibat, which is modelled at a constant rate using an exponential function
- In the company's model, patients undergoing PEBD surgery have a 5% annual probability of losing response to surgery.
- Probability of progression to liver transplant for non-responders to treatment with odevixibat is equal to that of non-responders to PEBD
- Patients in odevixibat response or PEBD response health states will not progress to LT until response is lost
- Patients in the PEBD no-response health state progress to LT at a different rate (probability) to patients in response states
- Patients who require re-transplantation after initial LT have the same risk of death and outcomes as patients following initial transplant
- There is no risk of progression to/death from hepatocellular carcinoma included in the model
- Additional monitoring costs for odevixibat are assumed to be zero
- Off-label therapies used a part of current standard practice are assumed to have no treatment effect and are associated with no effect on pruritus/sBA response
- 67% of patients require re-operation following PEBD, due to complications. These re-operations incur the same costs as initial PEBD surgery.
- 100% treatment adherence and no wastage of odevixibat is assumed in the model

- No treatment related disutilities are applied in the model. AE costs are explored in a scenario analysis but were not applied in the base case.
- HRQoL for patients responding to odevixibat is assumed to be equal to that of healthy children, whilst non-responders are assumed to have equivalent HRQoL of children with CIC, as reported in Kamath *et al*[34]
- All patients who do not respond/lose response to treatment are assumed to have a disutility associated with short stature.
- Caregiver disutilities and costs are applied to all patients who lose response to treatment or have PEBD or liver transplant due to increased care required, up until the age of 18

5.2.4 *Evidence used to inform the company's model parameters*

The evidence sources used to inform the parameters in the company's base case model are summarised in

Table 19 and discussed further in subsequent sections.

Table 19: Summary of evidence used to inform the company's model

Parameter group	Source
Patient characteristics	Mean age and proportion of patients who are male taken from PEDFIC1[12]
Odevixibat sBA and pruritus response rates	Response to 40 µg/kg/day dose taken from PEDFIC1[12] treatment arm. Response for patients titrating to 120 µg/kg/day following 40 µg/kg/day based on those not responding to 40 µg/kg/day in PEDFIC1 and receiving 120 µg/kg/day in PEDFIC2.[29] The response to the 120 µg/kg/day dose and the pooled doses from PEDIFIC1 are not used in the company's base-case
Annual loss of response to odevixibat (TP1)	Assumed to be equal to the proportion of patients discontinuing treatment in PEDFIC1[12], validated by the company's clinical advisor
PEBD response rates (TP2, TP3)	NAPPED study
Annual loss of response to PEBD (TP4)	Company assumption, validated by the company's clinical advisor
Probability of LT (TP5, TP6, TP7)	LT following loss of response, without PEBD (TP5): NAPPED study LT following PEBD response (TP6): Company assumption (set to zero) LT following loss of response to PEBD (TP7): NAPPED study
Mortality, odevixibat and PEBD responders	Assumed to equal general population mortality, estimated using ONS life tables[31]
Mortality, loss of response (PEBD or no PEBD)	Model calibration using data from NAPPED study for PFIC1 and PFIC2 patients, pre-LT surgery
Mortality, post LT, 1st year	Meta-analysis conducted by the company, with sources identified in an SLR.
Mortality, post LT (long-term)	Pooled data analysis of digitised Kaplan Meier curves from Hori *et al* (2011)[36] and Wanty *et al* (2004)[37] and fitted exponential curve, with sources identified in an SLR.
Health state utility values	'Pruritus and sBA response', 'loss of response' and PEBD responder and non-responder health states: Kamath *et al* (2015)[34] mapped to EQ-5D-3L. Disutility associated with PEBD stoma bag: Arseneau *et al* (2006).[38] Disutility associated with growth impairment: Al-Uzri *et al.* (2013)[39] mapped to EQ-5D-3L. Liver transplant: Kini *et al.* (2011)[40] Post-liver transplant: Parmar *et al* (2016),[41] mapped to EQ-5D-3L Carer disutilities: NICE TA534[42] and NICE TA588[43]
Odevixibat acquisition costs	Manufacturer
Standard of care therapies costs	BNF 2021[44]
PEBD surgery costs	NHS Reference Costs 2018/19.[45] Proportion requiring re-operation taken from Bjournland *et al* (2020)[46]
LT surgery costs	NICE TA443,[47] uplifted to 2019/20 prices; NHS Blood and Transplant (NHSBT)[48] and National Organ Retrieval Service (NORS)[49]
LT follow up costs	Follow up costs and immunosuppression drugs: NICE TA443,[47] uplifted to 2019/20 prices; NICE TA348[50] and BNF 2020.[44] LT complications: Crossan *et al.* (2015);[51] NICE guideline NG98[52] uplifted to 2019/20 prices; and NHS Reference Costs 2018/19[45]
Medical resource use	PICTURE burden of illness study.[53] Unit costs taken from various sources including NHS Reference Costs 2018/19;[45] PSSRU;[54] Buchanan *et al.* (2011);[55] Akhtar and Chung (2014);[56] NICE PH56[57] and NICE clinical guideline 45[58]
Productivity costs	PICTURE burden of illness study[53] and ONS[59]

BNF - British National Formulary; LT - liver transplant; ; NHS - national health service; ONS - Office of National Statistics; PEBD - partial external biliary diversion; PSSRU - personal social services resource unit; sBA - serum bile acid; TA - technology appraisal; TP - transition probability

5.2.4.1 Patient characteristics

Patient characteristics are based on those for the overall population of the PEDFIC1 trial.[12] At model entry, patients are assumed to have a mean age of 4.25 years and 50% of patients are assumed to be female. These characteristics are used to estimate drug acquisition costs, general population mortality risks and to perform age adjustment of utilities.

5.2.4.2 Treatment effectiveness

The treatment effectiveness of odevixibat was informed by response rates reported in PEDFIC1.[12] In the model, base-case response is defined as the proportion of patients with at least a 70% reduction in sBA concentration from baseline or reaching a level ≤70µmol/L in PEDFIC1.[12] The company's model assumes that if patients have an sBA response they will also have a pruritus response and therefore response in the model base-case is reported as 'sBA and pruritus response'. In response to clarification question B7, regarding justification for this assumption, the company stated that this is based on a data review performed by the company, showing that all patients with an sBA response also had a pruritus response.

Response rates for both 40µg/kg/day and 120µg/kg/day dosages are taken from PEDFIC1[12] whilst the proportion of patients responding after titration to 120µg/kg/day is informed by the proportion of patients who did not respond to 40µg/kg/day in PEDFIC1[12] and responded to 120µg/kg/day in PEDFIC2[29]. The response rates on the 120µg/kg/day dose and the pooled doses from PEDIFIC1 are not used in the company's base-case The response rates for patients titrating to 120µg/kg/day in PEDFIC2[29] are based on very small patient numbers, as only four patients did not meet sBA response in PEDFIC1 (assessed at 6 months of continuous treatment with odevixibat) and were titrated to 120µg/kg/day in PEDFIC2[29] with just [redacted] then achieving response.

In the model base-case, the proportion of patients entering the model in the 'sBA and pruritus response' arm is estimated as the proportion of patients responding to 40µg/kg/day in PEDFIC1[12] ([redacted]) plus the proportion of responders who were titrated to 120µg/kg/day in PEDFIC2[29] ([redacted]). This corresponds to a total of [redacted] of patients starting in the 'sBA and pruritus response' health states in the treatment arm, with the remaining patients entering in the 'loss of response' arm.

The company also ran a scenario analysis whereby response to odevixibat is defined as either 'sBA and pruritus response', using the same data as the base-case, or 'pruritus response only', measured as the proportion of patients achieving a positive pruritus assessment for >50% of the 24-week treatment period in PEDFIC1.[12] In this scenario, [redacted] of patients enter the model in the 'sBA and pruritus response' health state whilst an additional [redacted] enter the model in the 'pruritus only' health state.

In this scenario, the response rate to standard of care is [redacted] based on the results from PEDFIC1[12] and these patients enter the model in the 'pruritus only' health state.

5.2.4.3 Transition probabilities

Transition probabilities were informed by a range of sources and these are described in detail below. It should be noted that these transition probabilities are estimated for patients with PFIC1 and PFIC2 separately, and a weighted average of these is used in the model based on the proportions of patients with PFIC1 and PFIC2 in PEDFIC1. Also, the data used to estimate the transition probabilities are based on SBD, which is assumed to be equivalent to PEBD.

The annual loss of response to odevixibat (TP1) is assumed to be equal to the proportion of patients discontinuing treatment in PEDFIC2[13] following receiving odevixibat in PEDFIC1. No further loss of response other than discontinuations observed in PEDFIC2 are assumed to occur. This resulted in an annual probability of discontinuation of [redacted] and the company's model assumes a constant rate of discontinuation through the model.

The company developed six survival models to inform four of the transition probabilities as detailed in

Table 20 (TP2, TP3, TP5 and TP7). The models were fitted to data from NAPPED[21, 22] due to immaturity of the PEDFIC1 and PEDFIC2 studies. The model fitting methods are not described in detail and it is unclear how censoring and competing events are accounted for. In each case, standard exponential models were used with the exception of modelling SBD by age in PFIC2, where a piecewise (two piece) exponential model was used. The main reason given for choosing exponential models was to simplify the economic modelling by excluding the need for tunnel states. With the exception of SBD by age in PFIC2 where a piecewise model was fitted, the CS[1] did not discuss whether there was a risk of any biases arising from assumption of constant hazards. The CS[1], page 178, stated that other survival distributions were considered, and in response to clarification question B14,[2] the company presented Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics for the fitting of six standard parametric models to the survival data. In all but one case (LT in PFIC1 with SBD and no response), models more complex than the exponential had a significantly better statistical fit to the data. However, the company argued for exponential models given the complexity that would be introduced to the economic model through potentially having multiple time dependent transitions. The ERG was not able to assess whether choosing exponential models for all transitions resulted in any bias in the results of the economic model.

Table 20: Survival models developed by the company to inform transition probabilities in the economic model

ID	Dataset	Survival distribution	Model rate parameter (natural scale)	Annual probability	Transition probabilities informed (see Figure 9)
1	NAPPED SBD by age in PFIC1[22]	2-piece exponential	0.201 (0-3 yrs) 0.0487 (3+ yrs)	18.18% 4.75%	TP2,TP3 (PFIC1, control arm)
2	NAPPED SBD by age in PFIC2[21]	Exponential	0.0487	4.75%	TP2,TP3 (PFIC2, control arm)
3	NAPPED LT in PFIC1 with no prior SBD[22]	Exponential	0.0519	5.07%	TP5 (PFIC1, both arms)
4	NAPPED LT in PFIC2 with no prior SBD[21]	Exponential	0.0782	7.52%	TP5 (PFIC2, both arms)
5	NAPPED LT in PFIC1 with SBD and no response (i.e. sBA not below 65µmol/L) [22,c]	Exponential	0.0655	6.34%	TP7 (PFIC1, control arm)
6	NAPPED LT in PFIC2 with SBD and no response (i.e. sBA not reduced by 75%)[21,c]	Exponential	0.01193	11.24%	TP7 (PFIC2, control arm)

LT - liver transplantation; sBA - serum bile acids; SBD - surgical biliary diversion; TP - transition probability
[a] The annual probability of 18.18% from survival model 1 for patients aged up to 3 isn't used in the economic analysis since patients enter the economic model at 4.5 years.
[b] The Company confirmed in response to clarification question B17[2] that it was coincidental that an annual probability of 4.75% was obtained for two different transitions modelled from different datasets.
[c] The difference in definition of response arises from the studies reported.

Probability of PEBD

The probability of moving to a PEBD (TP2 and TP3) state in the control arm (from initial state ‘sBA and pruritus response’) was derived from survival models fitted to the NAPPED data.[21, 22] Separate models were fitted to the data for PFIC1 and PFIC2 patients (

Table 20, IDs 1 and 2,). It was not clear from the CS whether individual participant data (IPD) was available from the NAPPED study. In response to clarification question A23[2], the company explained that they do not yet have access to the NAPPED data. From the description in the CS Section 12.2.1.5, it is unclear exactly what method was used to derive the exponential model. The ERG assumed that as described for other transitions in the CS, data was extracted by digitising the relevant published figures for incidence by age of SBD in PFIC1 and PFIC2[21, 22] as presented in Figure 10 (adapted by the Company from Van Wessel *et al.* 2021[22]) and Figure 11 (reproduced from Van Wessel *et al.* 2020[21]). In response to clarification question B16, [2] the Company provided Figure 12 which shows a single survival function derived by pooling the three incidence functions from Figure 11. Incidence of SBD in PFIC1 suggests a marked change in incidence rate at around two years (see Figure 10). A piecewise exponential was used for this transition with a cut point at 3 years of age. It is unclear to the ERG why 3 years was chosen instead of 2 years. The exponential rates were converted to annual probabilities and a single annual probability of PEBD in the economic model was calculated by weighted average over PFIC1 and PFIC2 according to the proportions of each in PEDFIC1.

The Company noted that due to a lack of long-term data on the durability of PEBD surgery, the annual loss of response to PEBD (TP4) is assumed to be 5%. In response to clarification question B13,[2] the company confirmed that this figure was suggested by the company based on clinical input stating that they expect it to be similar to the loss of response to odevixibat. The company stated that a slightly higher value was used compared to loss of response to odevixibat to allow for ongoing complications due to PEBD that may result in loss of response or liver transplant.

Figure 10: **Incidence of SBD by age in PFIC1 patients from the NAPPED data, as adapted by the Company from Van Wessel *et al.* 2021[22] (reproduced from CS, Figure 42[1])**

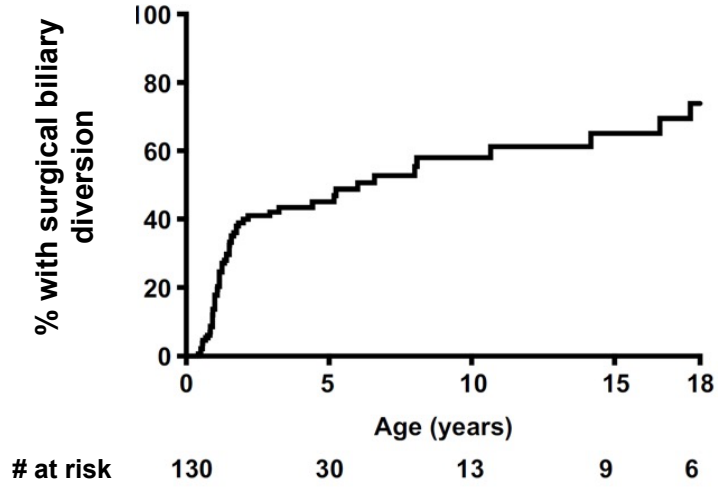
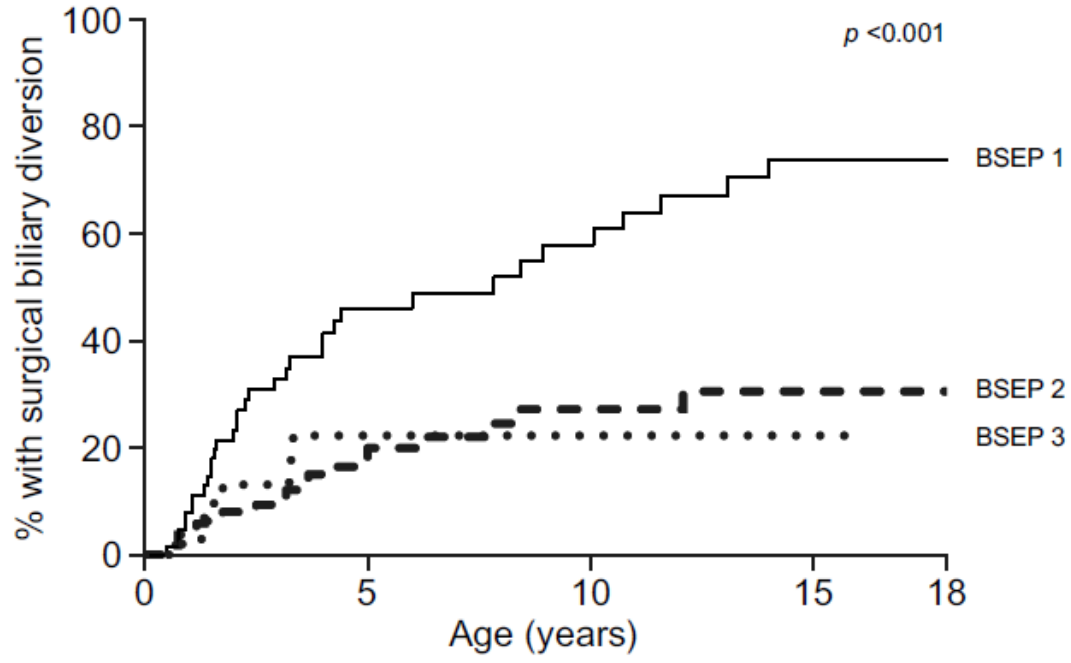
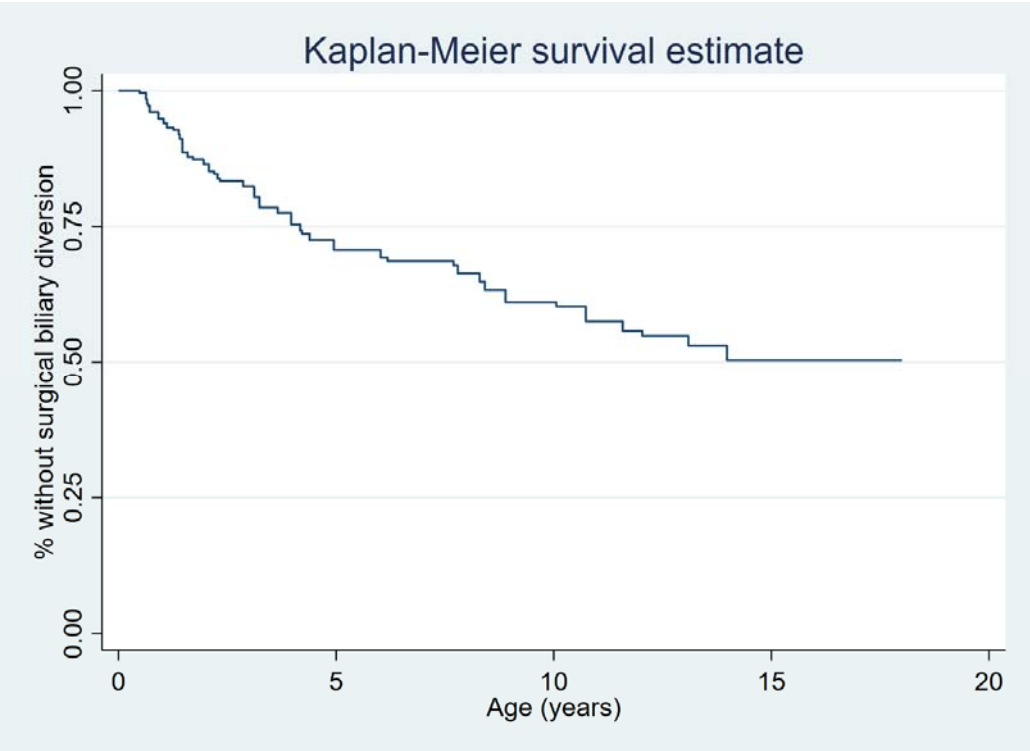


Figure 11: **Incidence of SBD in PFIC2 by subtype from the NAPPED data. Reproduced from Van Wessel *et al.* 2020[21] (reproduced from CS, Figure 41[1])**



N° at risk					
BSEP 1	72	20	14	8	5
BSEP 2	136	43	22	16	11
BSEP 3	56	12	9	3	0

Figure 12: Combined survival function for PFIC2 patients remaining free of SBD by age from the NAPPED data presented in Figure 11 (reproduced from clarification response, question B16, Figure 5)



Probability of liver transplant (LT)

The NAPPED data[21, 22] was used to derive annual probabilities of LT from the states 'No PEBD, no response' (TP5) and 'PEBD, no response' (TP7). Separate exponential survival models were created for patients with PFIC1 and PFIC2. The company assumed that while patients have a sBA response to PEBD, they cannot transition to LT and therefore this is set to zero in the model base case (TP6). This is also similar for odevixibat patients with sBA response, who are also assumed not to transition to LT.

The model for PFIC1 patients with no SBD (

Table 20, ID 3) was created by fitting an exponential model to the relevant Kaplan-Meier data for native liver survival. These data were obtained by digitising the 'No surgical diversion' curve in Figure 13 (adapted by the Company from Van Wessel *et al*. 2021[22]). Likewise, the model for PFIC2 patients with no SBD (

Table 20, ID 4) was created by fitting an exponential model to the relevant Kaplan-Meier data that was obtained by digitising the 'Patients without surgical diversion' curve from Figure 14 (adapted by the Company from Van Wessel et al 2020[21]). The ERG notes that these data appear to be for LT in non-SBD patients regardless of whether they had sBA response or not, which suggests that the LT rates for non-responders may have been underestimated. The method used to identify the exponential coefficients is not stated. The exponential rates were converted to annual probabilities and a single annual probability of PEBD in the Company's model was calculated by weighted average over PFIC1 and PFIC2 according to the proportions of each in PEDFIC1.

The Company also derived a rate ratio for LT in patients without PEBD which was used in the scenario analysis where response in the model is defined as pruritus response. It was not clear to the ERG how this was derived. In response to clarification question B19, the Company provided a corrected version of the rate ratios but it was still not clear to the ERG how they were derived.

Figure 13: Observed native liver survival in PFIC1 patients by SBD status, as adapted by the Company from Van Wessel *et al.* 2021[22] (reproduced from CS, Figure 34[1])

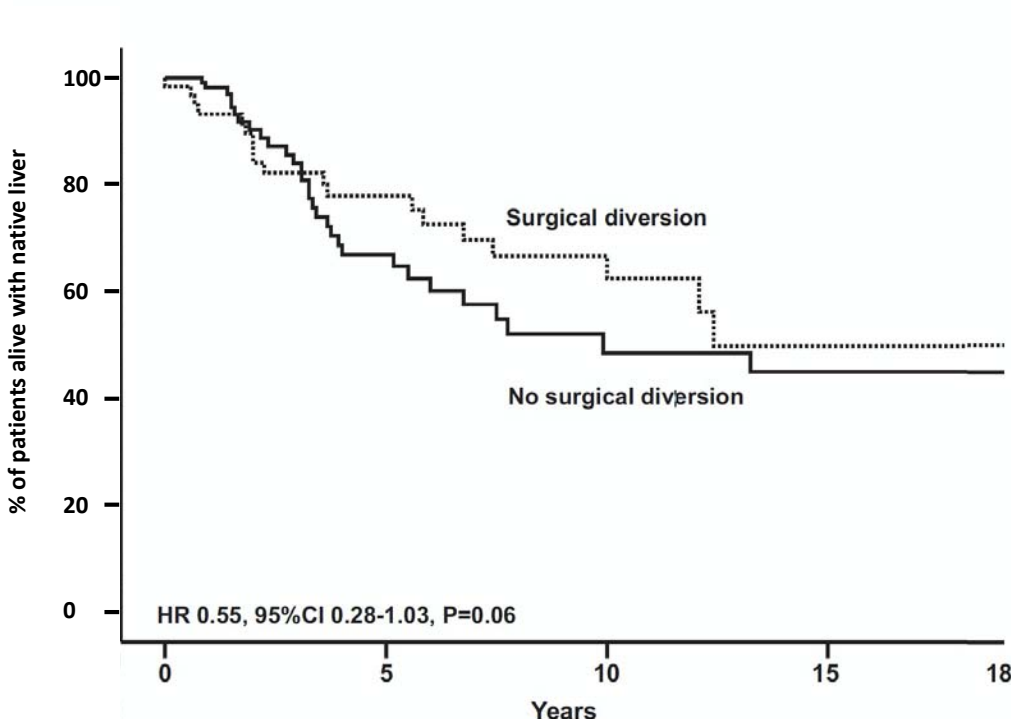
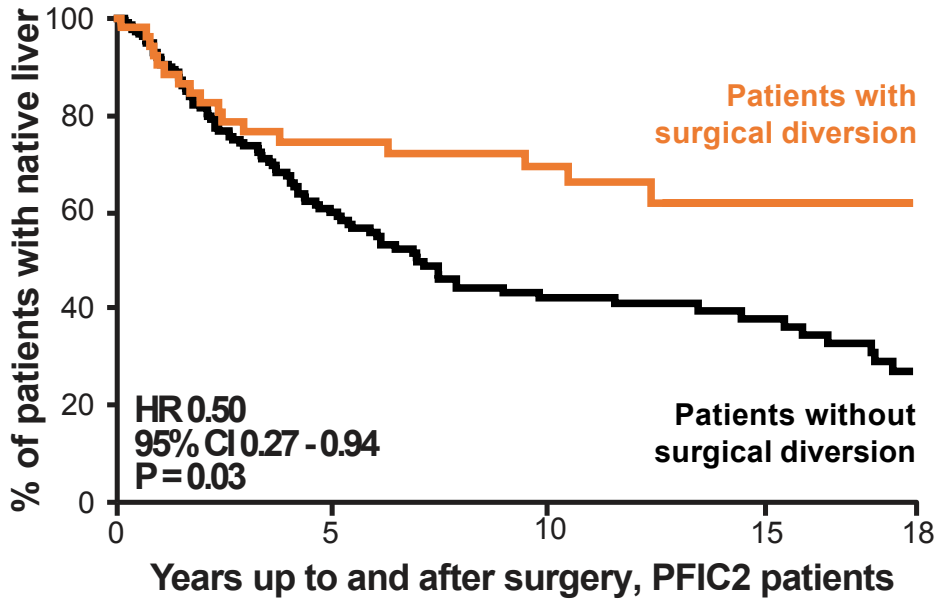


Figure 14: Observed native liver survival in PFIC2 patients by SBD status, as adapted by the Company from Van Wessel *et al.* 2020[21] (reproduced from CS, Figure 32[1])



The model for PFIC1 patients with SBD and no response (

Table 20, ID 5) was created by fitting an exponential model to the relevant Kaplan-Meier data for native liver survival. The ERG presumes these data were obtained by digitising the 'Post-SBD sBA≥65µmol/L' curve from Figure 15 (adapted by the Company from Van Wessel et al 2021[22]). Likewise, the model for PFIC2 patients with no SBD (

Table 20, ID 6) was created by fitting an exponential model to the relevant Kaplan-Meier data that the ERG presumes was obtained by digitising the 'Patients with serum bile acids reduced by <75%' curve from

Figure 16 (adapted by the Company from Van Wessel et al 2020[21]). The method used to identify the exponential coefficients is not stated. The exponential rates were converted to annual probabilities and a single annual probability of PEBD in the economic model was calculated by weighted average over PFIC1 and PFIC2 according to the proportions of each in PEDFIC1. The ERG notes the use of different sBA cut-offs used for patients with PFIC1 and PFIC2 in the two papers by Van Wessel *et al.*[21, 22]

Figure 15: Observed native liver survival after surgical biliary diversion, stratified for post-surgical sBA cut-offs (PFIC1 patients), as adapted by the Company from Van Wessel *et al.* 2021[22] (reproduced from CS, Figure 35[1])

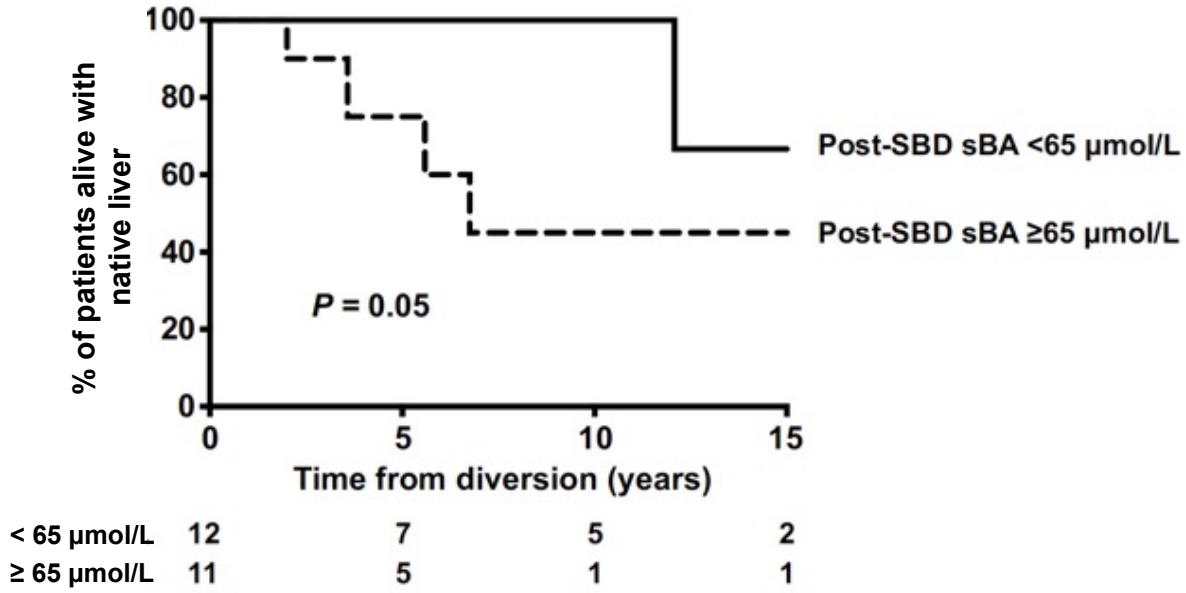
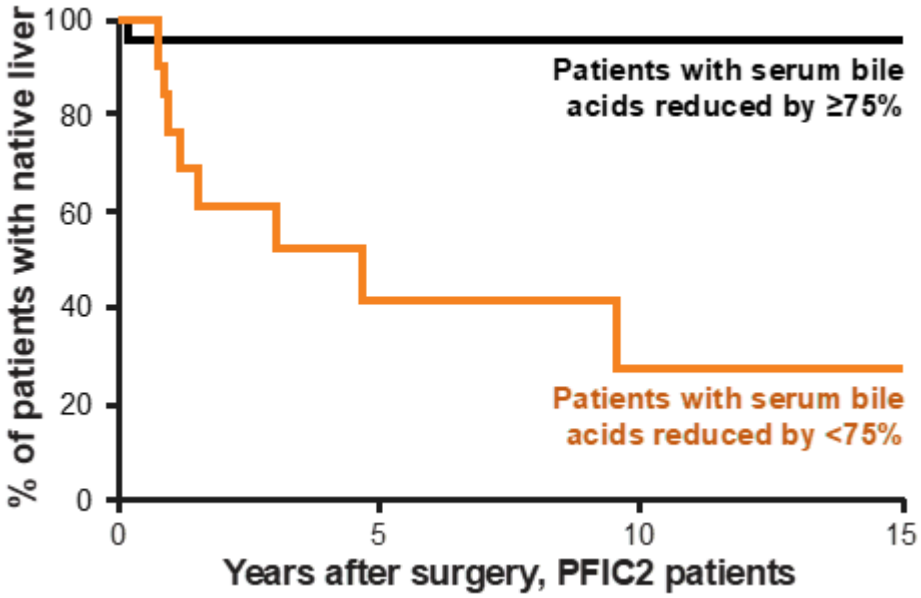


Figure 16: Observed native liver survival after surgical biliary diversion, stratified for post-surgical sBA cut-offs (PFIC2 patients), as adapted by the Company from Van Wessel *et al.* 2021[22] (reproduced from CS, Figure 33B[1])



Mortality risk for Odevixibat and PEBD responders

The model assumes that patients who are responding to either treatment (sBA and pruritus response; PEBD, response) have the same mortality risk as the general population, estimated using ONS life tables.[31]

Mortality risk for patients in loss of response health states

The annual mortality probability for patients in loss of response health states ('loss of response', 'PEBD, no response') is informed by data from the NAPPED study.[21, 22] The CS states that model calibration was used in order to obtain the appropriate annual probability of death for patients prior to LT with PFIC1 and PFIC2 separately, and in response to a request for clarification (see clarification response, question B24), the company outlined the details of the 'goal seek' calibration separately for patients with PFIC1 and PFIC2. The Company states that "*This approach assumes that all pre-LT mortality above that captured in lifetables is experienced at a constant rate, regardless of age and is only applicable to patients that have not responded to odevixibat or SoC."*

Post liver transplant mortality

The company adopted two transition probabilities for post liver transplant mortality. An annual probability of acute mortality was applied in the first year to account for the increased risk from complications and organ rejection, and a long-term annual probability was used from one year and onwards after transplant. Relevant data to inform these probabilities were sought from the published literature. Due to variability in the evidence found, two meta-analyses were conducted. There was, however, no discussion of possible reasons for the heterogeneity. In response to clarification question B25(b), the company stated that the original four studies[36, 37, 60, 61] identified to inform post-LT mortality were from a systematic review performed in 2019 and that heterogeneity was likely due to differences in study design, including breakdown of patients by subtype, and geography as well as the variability in mortality rates arising from low patient numbers. The company also updated their evidence base, adding six new studies[32, 62-67] making 10 studies in total (

Table 21). It is not clear to the ERG how the additional studies were identified by the company. The company's post-clarification analysis is reported and critiqued by the ERG in this report.

The ERG notes that among the 10 studies, there were differences in proportions of patients by PFIC types with some studies not specifying the proportions. There were also differences in geography which were wider than the study locations suggesting that patients may have travelled from their country of residence for treatment. The time periods covered by the studies varied considerably and the nature of the procedures varied with some LT being living related and split-liver which may affect the probability of mortality. The evidence that the company derived from the 10 studies and the result of their meta-analysis is presented in Figure 23. The company implemented fixed effect and random effects model but did not provide further details of how the meta-analysis was carried out. The company's preferred result was from the random effects model and was presented as a rate of acute post-LT mortality of 0.13, which was converted to an annual probability of 11.31% in the post-clarification base-case model.

Table 21: Studies identified by the company to inform the rates post-liver transplant mortality

Study, Country, Dates	Details	Results presented
Wanty 2004[37] Belgium 1989-2004	38 patients No breakdown by type reported PFIC1&2 30 (61%), PFIC3 19 (39%)	KM function (To derive a probability for long-term post-LT mortality, the Company digitised the KM functions from the four studies that reported long term mortality outcomes36, [37, 63, 64] (Figure 17, Figure 18, Figure 19, Figure 20) and created pseudo individual participant data. This data was pooled and used to estimate an exponential survival distribution for survival from 1 year after LT, conditional on survival to that point. The resulting exponential survival function had a rate parameter of 0.0196 (0.0116, 0.0320). This corresponds to a yearly probability of 1.94% in the post-clarification base-case model. In their clarification response2 (question B25(e)), the Company presented a KM function created from the pooled pseudo individual participant data (Figure 22). Figure 17) Five year survival 92%
Hori 2011[36] Japan 1990-2011	14 patients PFIC1 3 (21%), PFIC2 11 (79%)	KM function (Figure 18) PFIC1 3 deaths PFIC2 0 deaths
Valamprampil 2019 [61] India 2010-2018	34 patients PFIC1 8 (24%), PFIC2,3,4 26 (76%)	One year mortality: 3/8 in PFIC1 4/26 in FPIC2,3,4
Aydogdu 2007[60] Turkey 1997-2002	12 patients PFIC1,2,3 No breakdown by type reported	One year survival 75%
Cutillo 2006[62] Belgium 1993-2001	7 patients No breakdown by type reported Living-related LT	1 death in year 1
Gridelli 2002[63] Italy 1997-2001	8 patients No breakdown by type reported Some multiple procedures and some re-transplantations	KM function (Figure 21) 1 year survival 88%

Okamoto 2020[64] Japan 1990-2019	12 patients All PFIC1 (100%) 1 had retransplantation	KM function (Figure 22) 1 years survival 100%
Polat 2017[65] Turkey 2009-2016	62 patients 12 PFIC1 (20%), 38 PFIC2 (62%), 11 PFIC3 (18%) (sic – totals 61)	1 year survival 95% Corresponding to 3 deaths
Torri 2005[66] Italy 1997-2004	12 patients No breakdown by type reported	1 year survival 83.3% Corresponding to 2 deaths
Vuong 2019[67] USA 2005-2018	12 patients 2 PFIC1 (17%), 10 PFIC2 (83%)	Survival 100%, follow-up period not stated but presumed to be >1 year.

Patients may come from countries other than where the study was conducted

To derive a probability for long-term post-LT mortality, the Company digitised the KM functions from the four studies that reported long term mortality outcomes[36, 37, 63, 64] (Figure 17, Figure 18, Figure 19, Figure 20) and created pseudo individual participant data. This data was pooled and used to estimate an exponential survival distribution for survival from 1 year after LT, conditional on survival to that point. The resulting exponential survival function had a rate parameter of 0.0196 (0.0116, 0.0320). This corresponds to a yearly probability of 1.94% in the post-clarification base-case model. In their clarification response[2] (question B25(e)), the Company presented a KM function created from the pooled pseudo individual participant data (Figure 22).

Figure 17: Kaplan Meier survival function post liver transplant reproduced from Wanty 2004[37]

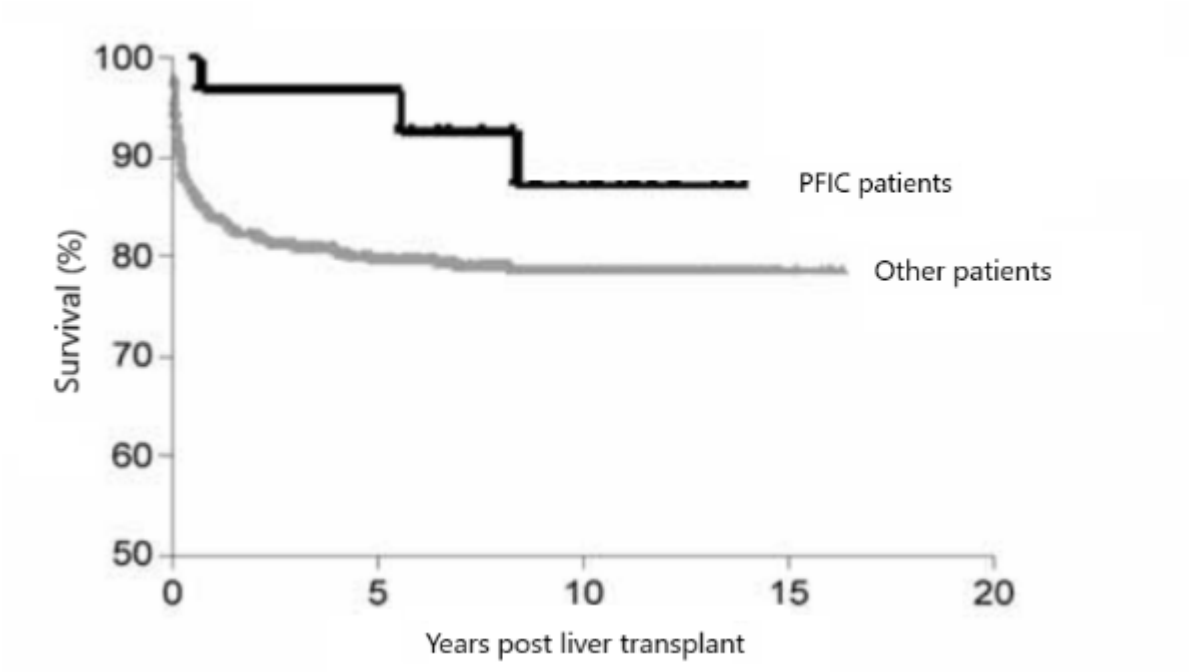


Figure 18: Kaplan-Meier survival function post liver transplant adapted the the ERG from Hori 2011[36]

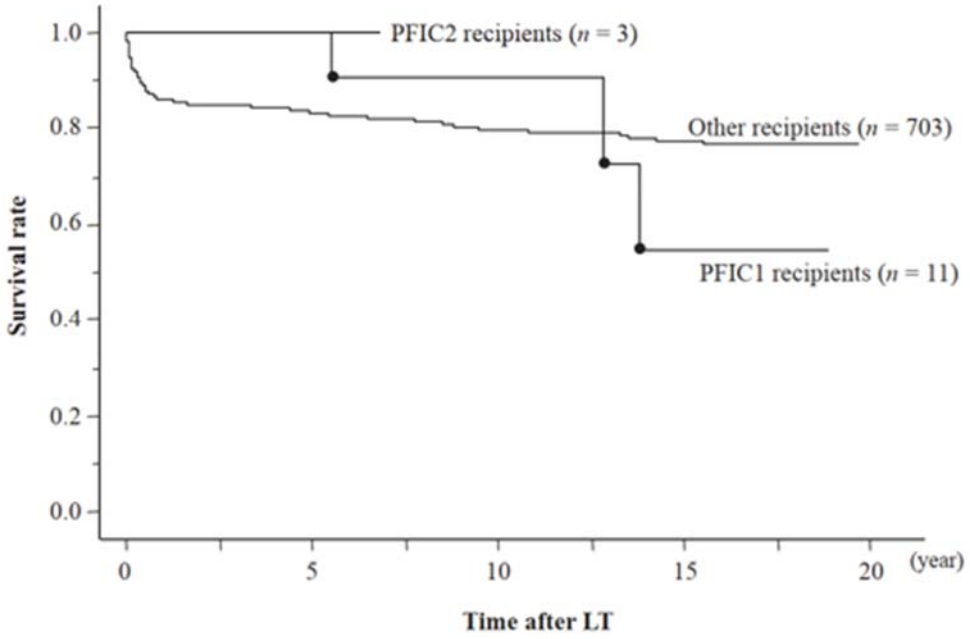


Figure 19: Kaplan-Meier survival function post liver transplant reproduced from Gridelli 2002.[63] The triangles represent PFIC patients with one death occurring (at 0.13 months)

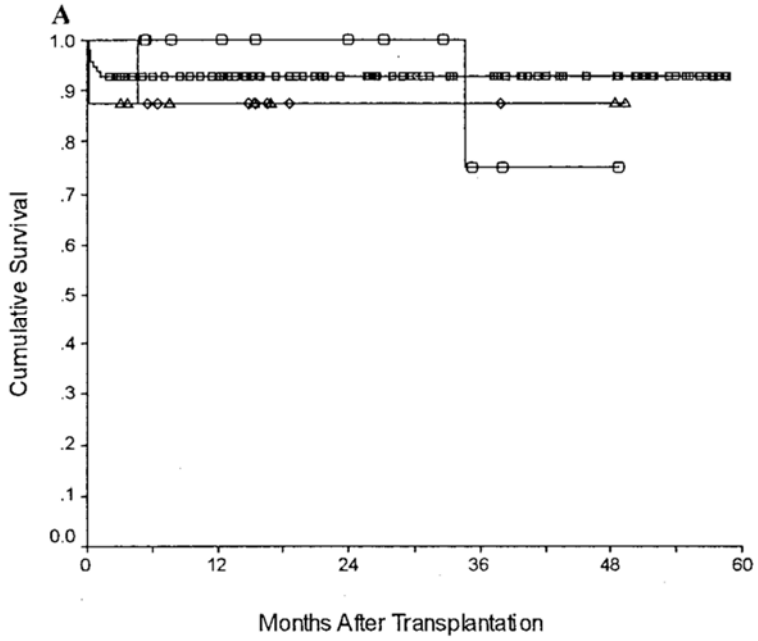


Figure 20: Kaplan-Meier survival function post liver transplant reproduced from Okamoto 2020.[64] The blue curve represents patient survival

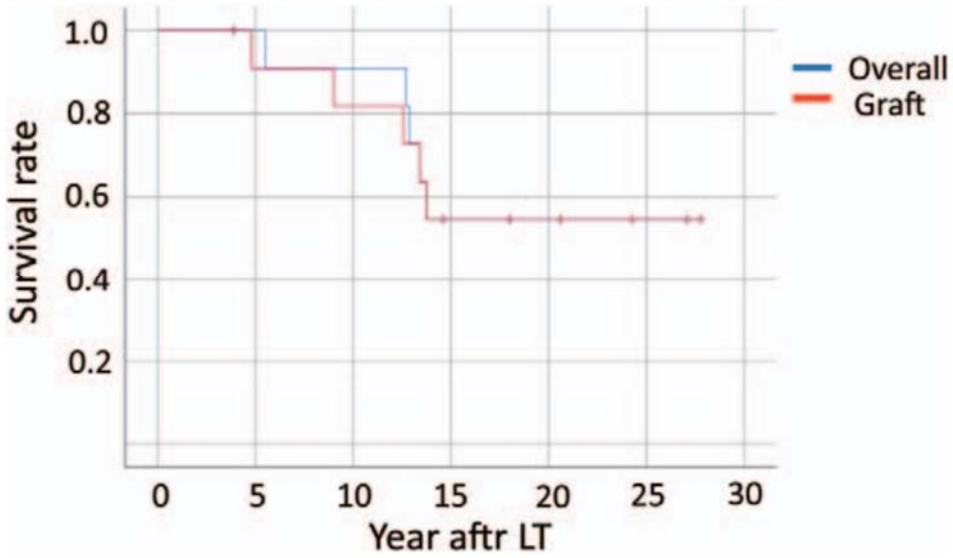


Figure 21: Evidence used in and results obtained from the post-clarification Company meta-analysis for acute post-LT mortality, reproduced from the CS. The Time column represent person-years at risk

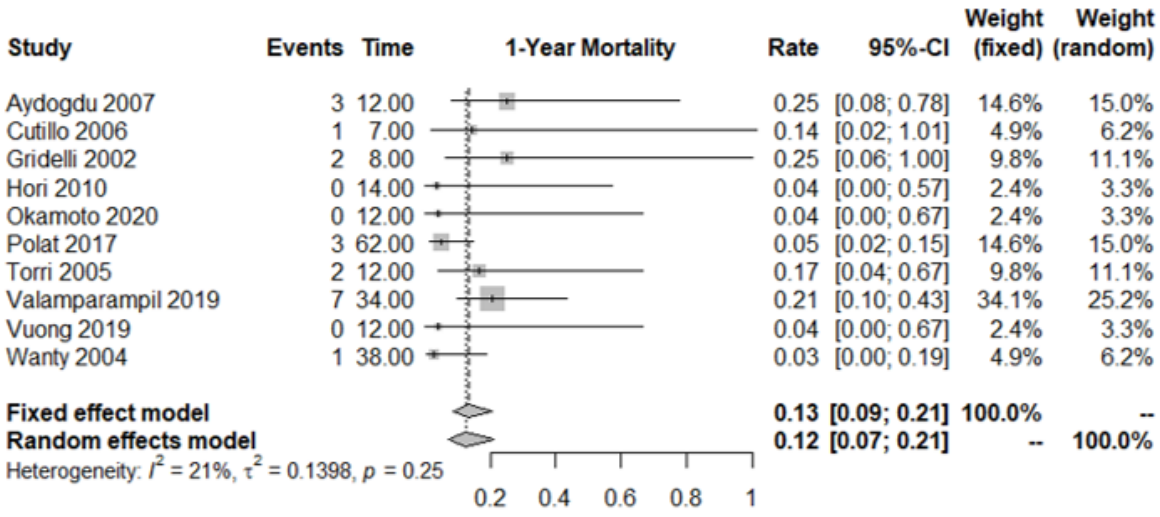
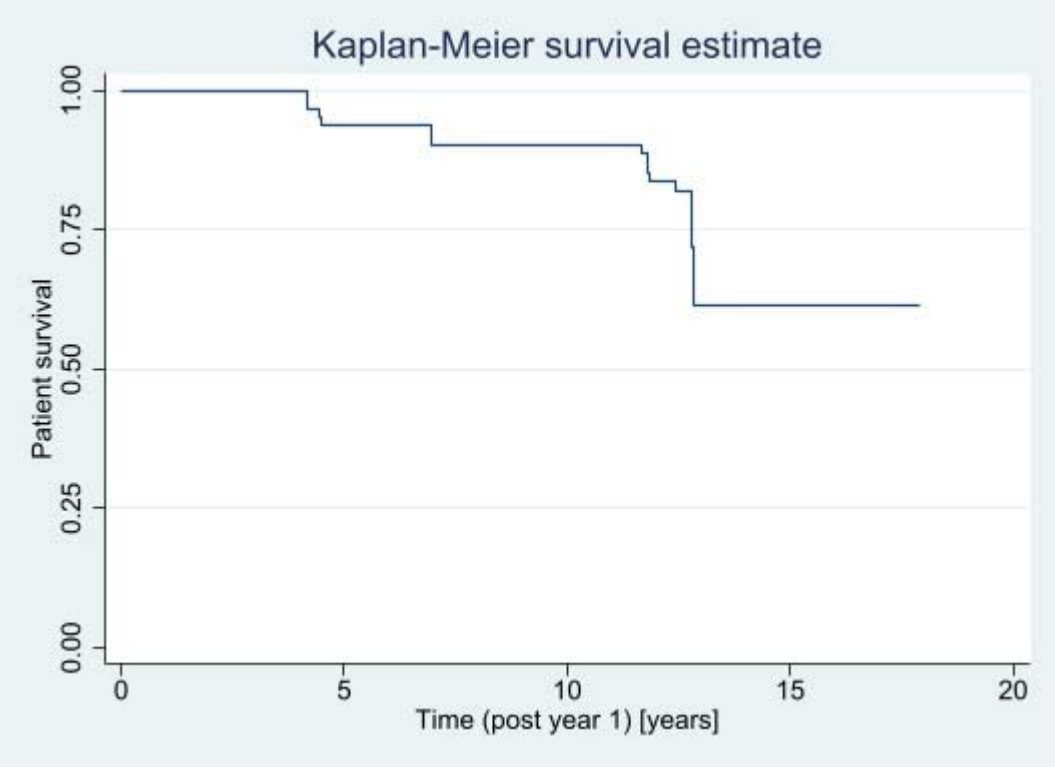


Figure 22: Kaplan-Meier survival function from the Company's post-clarification pooled analysis of long-term post-LT mortality (reproduced from clarification response, question B25(e), Figure 10[2]).



5.2.4.4 Health related quality of life

The PEDFIC1 trial[12] collected HRQoL from patients and parent proxies using the paediatric quality of life inventory (PedsQL), which the company mapped to EQ-5D-3L using the Khan *et al.* (2014)[35] mapping algorithm. However, the company report that due to small patient numbers and low statistical power, these utility values were not used in the model base-case. The company state that the results showed marginal differences in absolute scores of responders and non-responders causing results to seem counter-intuitive, which is likely due to the differences between the two groups at baseline. Following a request from the ERG, the company submitted an updated sensitivity analysis at clarification using a common baseline utility for all patients and applying observed change from baseline.

An SLR was conducted by the company for HRQoL which identified 11 studies, seven of which were related to the PEDFIC1/2 trials, and therefore not used by the company as they had full data available. Of the remaining four studies, the company state that only one study by Wassman *et al.* (2018)[68] provided data that could be used in the model, which compared quality of life of PFIC patients following PEBD (0.873) to those following LT (0.887). The ERG notes that data from this study is not used in

the company's model base-case either. The company did not provide any justification as to why these values were not used in the base-case.

During the clarification stage, the company submitted the results of a vignette study undertaken with 95 members of the general public using time trade-off (TTO) valuation exercises, describing PFIC health states based on treatment response and PEBD status (see Addendum A[69]). The health state descriptions were largely based on the PedsQL items, making use of data collected during the PEDIFIC1 trial using PedsQL for responder and non-responder health state descriptions. The vignette descriptions for PEBD health states included a description of a patient having a stoma drain and bag as a result of PEBD surgery. The company received feedback from four clinical experts on the initial descriptions of the health state vignettes and amended were necessary. The company provided the results when assessed using TTO or EQ-5D weights. Despite the company having the vignette descriptions checked and amended by clinical experts with experience of treating patients with PFIC, the company state that they do not feel the burden of PEBD was accurately reflected in the vignettes in order for survey participants to capture the full impact on quality of life of PEBD surgery. Therefore, these results are only used in the company's scenario analyses.

Health state utilities used in the model

Utility values from Kamath *et al.* (2015)[34] are used in the model for 'pruritus and sBA response' and 'loss of response'. This study was not identified in the company's SLR so it is unclear to the ERG how this study was selected. The study collected PedsQL scores of children or parent proxies of children with Alagille syndrome and other liver diseases compared to healthy children. Of the 'other liver disease cohort', 49 children and 82 parents of children with intrahepatic cholestasis (IHC) were included. Patients with PFIC1, 2 and 3 were included within this cohort and data from the entire IHC cohort were used in the company's model to represent HRQoL in the 'loss of response' health state. As data was not available based on response to treatment versus no response, the company assumed that patients responding to odevixibat (pruritus and sBA response health state) would have the same HRQoL as healthy children reported in the Kamath *et al*.(2015)[34] study. The company used the mapping algorithm by Khan *et al*.[35] to map both the patient reported and parent proxy reported PedsQL scores to the EQ-5D-3L. Only the patient-reported scores were used in the model base-case, with no reasoning provided as to why parent-proxy scores were not also used.

For the PEBD responder and non-responder health states, a disutility multiplier to represent disutility associated with a stoma bag following PEBD surgery was applied to utility values in 'pruritus and sBA responders' and 'loss of response' states, respectively. Data for the disutility related to a stoma bag was taken from a study of patients with ulcerative colitis by Arseneau *et al.*(2006)[38], applied in the model base-case (multiplier of 0.72). An alternative source from adult patients with colorectal cancer

(multiplier of 0.945)[70] is applied in the company's scenario analyses. At clarification stage (Question B37), the company confirmed that the multiplier was selected by a clinical expert, but was considered conservative as the value was likely to decrease as patients get older and become more aware of the stoma bag. After the clarification stage, the company also submitted the results of a further follow-up vignette study (see Addendum C[71]) with 3 carers of patients with PFIC and one clinical expert, in order to obtain a disutility multiplier value specifically associated with PEBD stoma bags. A disutility multiplier value of [redacted] was obtained and used in company scenario analyses.

The company also assumed that all patients in 'loss of response' and 'PEBD, loss of response' health states will experience growth impairment and therefore an additional disutility is applied to all patients in these health states to represent short stature. This was taken from a HRQoL study of 483 children with chronic kidney disease, designed to assess the impact of short stature using PedsQL.[39] The company mapped data to EQ-5D using the Khan *et al.*[35] mapping algorithm in order to calculate a multiplier to be applied in the model.

Utilities for the LT health state were sourced from a study of adult patients with pruritus and chronic pain the United States.[40] The company used a value of 0.71, reported for those patients with severe pruritus, to reflect patients who will undergo LT in the first year in the model. The study used a time-trade off method to obtain health state utility values, however no further data is provided in the study on the valuation set used and therefore the ERG could not assess the applicability of the score for the UK population. Utility values for the 'post-LT' health state were taken from a systematic review of studies reporting HRQoL following paediatric liver transplant.[41] Ten studies included in the systematic review included HRQoL data collected using the PedsQL score. The company calculate the weighted average score of each domain based on the number of patients included in each study and then mapped this average to the EQ-5D-3L using the Khan *et al.*[35] mapping algorithm. This results in a utility value of 0.85 applied to all patients in the post LT health state.

A summary of the health state values applied in the company's model is provide in Table 35 of the CS.[1] All health state utility values were adjusted for age using Ara and Brazier,[72] by applying a year on year multiplier.

Carer disutilities

The company's model applies a disutility to patient caregivers (1.78 caregivers per patient) in all health states other than 'sBA and pruritus response', up until the age of 18 to represent QALY losses to parents/carers. A disutility of -0.1 is applied to patients in 'PEBD, loss of response' health state, taken from NICE TA588[43] for spinal muscular atrophy, whilst a value of -0.05 is applied to the other states.

The CS[1] states that this value is a midpoint of the values in NICE TA588[43] and is also consistent with disutilities applied in NICE TA534 (treating moderate to severe atopic dermatitis).[42]

5.2.4.5 Resources use and costs

The model includes costs associated with: (i) drug acquisition, (ii) surgery costs (one-off costs for PEBD and LT) (iii) LT follow up costs, including LT complications and post-LT immunosuppression costs, (iv) medical resource use conditional on model health state (no surgery, post-PEBD, post-LT) and (v) carer productivity costs. The costs applied in the model base-case are discussed in more detail in the following sections

Drug acquisition costs

Odevixibat is given in capsule form and is available in four different quantities; 200 µg, 400 µg, 600 µg and 1,200 µg. The corresponding list prices are [redacted]; [redacted]; [redacted] and [redacted], respectively for pack sizes of 30 capsules. The company has proposed a PAS which takes the form of a simple price discount equal to [redacted]. The corresponding costs when incorporating the PAS discount are [redacted]; [redacted]; [redacted] and [redacted]. Patients will either take a low dose (40 µg/kg/day) or high dose (120 µg/kg/day) of odevixibat, with patients who do not respond to treatment by 3 months on the lower dose being titrated up to the higher dose. The proportion of patients in the model base-case receiving the high dose is [redacted]. The number of capsules required per day, and therefore the annual acquisition cost, is dependent on: patient's weight, dosage and the mode of administration (sprinkled on food or swallowed). At model entry age, patients are assumed to be at the 25th percentile of weight of the UK general population in the first year of treatment and the 33rd percentile in the second year. All remaining years of the model assumes that patient weight is equal to the 50th percentile of the UK population as patients responding to treatment with odevixibat are assumed to catch up in weight. Data on weight for patients aged 0-18 years is taken from UK growth charts whilst data for patients ages over 18 years is based on Health Survey data from the Health and Social Care Information Centre (HSCIC), and taking the weighted average for male and females. The proportion of patients in each different weight category is estimated using a normal distribution applied to the mean weight from growth curve charts and a calculated standard deviation. Maximum recommended dose in the draft SmPC[11] means that all patients with a weight of 55.5kg or greater received the same dose.

Table 22 shows the daily costs for odevixibat applied for each weight group. During clarification response the company also provided the mean dosage from the PEDFIC1[12] trial. The ERG estimated the drug acquisition costs based on the mean dose observed in the trial and compared this to costs estimated by the company using the approach outlined above, and found minimal difference in the drug acquisition costs.

Table 22: Daily odevixibat acquisition costs for each weight group in the company's model, PAS discount applied (adapted by the ERG based on Table 61 of the CS and company's model)

Weight (kg)	Daily dose (µg)		Capsules/day†		Daily cost	
	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 required for sprinkled administration are based on lower dosage 200 µg capsule strength whereas those swallowed are based on higher dose using 1200 µg capsules strength

Patients in both treatment arms receive off-label therapies in the 'loss of response' health states; UDCA, cholestyramine, rifampicin and naltrexone. Cholestyramine is given at a fixed dose in the model (4000 mg/per day for pediatric patients, 6000 mg/per day for adults), whilst UDCA and naltrexone are weight-based (12 mg/kg and 2 mg/kg respectively). Rifampicin is weight-based for paediatric patients (10 mg/kg) and a fixed dose for adults (450 mg/day). Drug costs were sourced from the most recent version of British National Formulary (BNF).[44] The proportion of patients receiving UDCA and rifampicin was based on data from PEDFIC1,[12] whilst proportion receiving cholestyramine and naltrexone was taken from a burden of illness study[53] conducted by the company and previous a technical appraisal, TA443.[47]

No wastage costs were included in the model for odevixibat and 100% treatment adherence is assumed. In response to clarification question B30[2], the company state that they do not anticipate capsule splitting and therefore no wastage costs are included. In addition, 100% treatment adherence is expected based on the 99% median overall compliance in the PEDFIC1[12] trial and 97% in the PEDFIC2[13] trial, calculated from the case report forms. These numbers were slightly lower when calculated from the eDiary (93% in PEDFIC1, 96% in PEDFIC2). No drug administration costs such as the cost of pharmacy preparation and dispensing are included and odevixibat is assumed to require no further monitoring above standard care. In addition, no adverse event costs for odevixibat are included in the model base-case, despite adverse events being experienced in the trial.

Surgery costs- PEBD and liver transplant

PEBD surgery is assumed to only apply to a proportion of patients in the standard care arm, based on data from NAPPED.[73, 74] The cost of surgery is based on NHS Reference costs for 'Very complex hepatobiliary or pancreatic procedure, CC score 2-3', at a cost of £12,634. Based on a study of 33 patients with intrahepatic cholestasis liver diseases by Bjornland *et al*. (2020)[46], it is assumed that 67%

of patients require re-operations due to complications. These are costed at the same cost of initial surgery. In addition, 43% of patients undergoing PEBD are assumed to require treatment for infection, at a cost of £1,847 (Paediatric intermediate infection, CC score 2-4) and 7% require surgery for bowel prolapse (£2,986- Paediatric other gastrointestinal disorders). The costs of PEBD surgery are applied as a one-off cost of £22,119 to all patients new in state to PEBD.

The total cost of liver transplant was taken from numerous sources. Pre-transplant and transplant phase costs were sourced from a previous NICE technology appraisal (TA443[47] for primary biliary cirrhosis), and inflated from 2014 to 2019/20 costs. The costs used in TA443[47] were taken from a study of patients of patients diagnosed with hepatitis C and B.[75] The ERG is uncertain how accurately these costs will reflect that of patients with PFIC, particularly those patients undergoing LT as children, and is unsure why NHS reference costs were not used to estimate LT costs, which are lower than the costs used. In response to clarification question B33[2], the company stated that NHS costs were not used as it was not clear how accurately a micro-costing approach would capture all resources needed and the cost from TA443[47] had been used in previous appraisals. Additional cost for organ and organ retrieval were calculated based on data from NHS Blood and Transplant (NHSBT)[76] and National Organ Retrieval Service (NORS).[49] The total costs incurred in the first year of LT are £133,986 and are applied to all patients in the LT health state. These are summarised in Table 65 of the CS.[1]

LT follow up costs

LT follow up costs are included in the model and taken from the same study as pre-transplant and transplant costs[75] and inflated to 2019/20 prices (£39,287). This cost is divided by 2 to give an annual cost (£19,644), which the CS states is applied for the first 2 years post LT only.

Immunosuppression drug costs post-LT transplant (azathioprine, tacrolimus and prednisolone) are applied to all patients in the 'post-LT' state, with separate costs applied for first years following LT and all subsequent years. Both azathioprine and tacrolimus are costed based on weight, whereas prednisolone is given at a fixed dose. Resource use for immunosuppression costs is informed by NICE technology appraisal TA348[50] and costs are sourced from BNF.[44] These are summarised in Table 67 of the CS.[1] It is unclear to the ERG if the costs of immunosuppression drugs will already be captured in the first 2 years from the estimate used for LT follow up costs. Removal of these costs only leads to a small increase in the ICER.

The company report that complications related to LT are commonly reported in PFIC1 patients and are therefore included in the model. These include diarrhoea, liver steatosis, deafness and pancreatitis. Diarrhoea was also included for PFIC2 patients. Costs of diarrhoea and pancreatitis were sourced from NHS reference costs 2019/20.[77] The cost of liver steatosis was sourced from a published study by

Crossan *et al.* (2015)[51] and the cost of hearing loss was sourced from NICE guideline for hearing loss in adults.[52] These costs are reported in CS Table 72[1] and are applied to all patients in the LT health state. The ERG is uncertain if applying these costs to all patients may slightly overestimate the costs associated with LT. However, the ERG notes that if these costs are removed it has very minimal impact on the ICER.

Medical resource use

Medical resource use costs are applied conditional on model health state, based on if a patient has had no surgery (responders and non-responders to odevixbat/standard care), is post-PEBD or post-LT. Data on the proportion of patients requiring each resource use and the average number of visits per year is sourced from a burden of illness study (PICTURE study) conducted by the company.[53] Interim results of this study were updated during the clarification stage and incorporated into the updated model (see Addendum B for final results[78]) All costs applied to each resource use are taken from PSSRU[79] apart from the cost of stoma care which was taken from a study by Buchanan *et* al (2011)[55] and inflated to 2019/20 prices. A summary of the costs applied in the model health states in shown in Table 23. Additional costs of £69.50 are also applied to all pre-LT health states to account for regular annual monitoring tests. Data on the proportion of patients requiring each test was taken from the burden of illness study[53] whilst costs came from a variety of sources, including NHS Reference costs 2019/20[77] when available or previous literature and NICE reports/clinical guidelines,[52, 56-58] inflated to 2019/20 prices.

Table 23: Health state resource use and costs, reproduced by the ERG from the company's model

Health state	Annual costs
Pre surgery states*	[redacted]
Post PEBD	[redacted]
Post-LT	[redacted]

LT- liver transplant; PEBD - partial external bilary diversion
**Includes sBA and pruritus response; loss of response; PEBD response; PEBD loss of response health states*

Carer productivity costs

The company's model base case includes costs related to lost carer productivity, applied in the model up to patient age 18, and travel costs of [redacted] annual visits to specialist centres (applied continuously in the model regardless of age to all patients in 'no response' health states). Productivity costs are assumed to apply to patients in all health states other than response to odevixibat and death. Table 74 of the CS[1] implies that productivity losses are also applied to those patients having a response to odevixibat (sBA/pruritus response), however the ERG notes that this is not applied in the model. Carers of patients

in the 'PEBD, no response' health state are assumed to have a productivity loss of [redacted] based on the proportion of carers reporting work impairment in the BOI study[53], with figures updated during the clarification stage as final results became available (see Addendum B, Table 5[78]). The company assumes that patients in the 'PEBD, response' and LT health states will experience half of this productivity loss ([redacted]), however no justification is provided for this assumption or why carers of patients responding to odevixibat experience no productivity loss. Data on the number of carers per household and average hourly wage are both taken from the Office of National Statistics(ONS).[59] The number of visits to specialist centres per year in the original model and CS was informed by a clinical expert (2 visits per year). Following final results of the PICTURE study[28], made available to the ERG during clarification (Addendum B[78]), this was changed to [redacted] per year based on the average of [redacted] carer's responses.

5.2.5 *Company validation methods*

The company stated that the model was validated by undertaking face validation, internal validation, cross validation and external validation. However, only the methods used for face validity and external validity were described in the CS.[1] Face validity was conducted through interviews with clinicians and experts and external validity was conducted by comparing clinical trial outcomes with model outputs.

5.2.6 *Model evaluation methods*

The CS[1] presents a deterministic base case incremental cost-effectiveness ratio (ICER) for odevixibat versus standard care. The company also presents results of a probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSAs) presented with a tornado diagram and additional scenario analyses. The results of the PSA are based on 1,000 Monte Carlo simulations and presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). The PSA results are presented separately for when the model used the list price for odevixibat and with a PAS applied. The distributions applied in the company's PSA are summarised in

Table 24. The company undertook scenario analyses to explore the impact of alternative assumptions regarding: model perspective; discount rates; mortality associated with LT; alternative health state utilities; stopping rules for odevixibat; treatment pathway following odevixibat; measure of response; annual probability of loss of response to treatment; proportion of PFIC1 patients; inclusion of AE costs and projected growth curves for weight-based dosing.

The ERG notes that there were negative QALYs in around 5-10% of PSA runs. The model uses VBA macros to update the parameter values during the PSA runs and the samples of the input parameters are not stored elsewhere in the model. As such, the ERG is unable to identify the reasons for these implausible results.

Table 24: Summary of distributions used in company's PSA

Parameter group	Parameter(s)	Distribution	ERG comment
Patient characteristics	Proportion male	Beta	-
	Start age	Normal	-
	Weight	Fixed	This parameter is subject to uncertainty
Adverse events	Treatment adverse event frequency, SoC and odevixibat	Fixed	This parameter is subject to uncertainty
	Post-LT complications	Beta	Beta distribution used assuming a SE of 15% of the mean
Health state transitions	Odevixibat loss of response to (TP1)	Beta	Beta distribution used assuming a SE of 15% of the mean
	PEBD response rates (TP2, TP3)	Beta	-
	Annual loss of response to PEBD (TP4)	Beta	Beta distribution used assuming a SE of 15% of the mean
	Probability of LT (TP5, TP6, TP7)	Normal	-
Efficacy	Response to odevixibat	Beta	-
	Response to PEBD	Beta	-
Mortality	Pre-LT	Beta	Beta distribution used assuming a SE of 15% of the mean
	Post LT (first year)	Beta	-
	Post LT (long term)	Beta	-
HRQoL	Health state utilities	Normal	Scores from PedsQL domains varied prior to mapping to EQ-5D
	Disutilities (stoma bag and caregiver	Beta	-
Costs	SoC drug acquisition costs	Fixed	Drug costs not varied however uncertainty around dosage and proportion receiving is modelled
	Disease management costs	Gamma	-
	PEBD surgery costs	Gamma	-
	LT surgery and complications costs	Gamma	-
	Adverse events	Gamma	-
	Productivity and out-of-pocket costs	Gamma	-
Resource Use	Proportion receiving each SoC treatment (drug share)	Beta	Beta distribution used assuming a SE of 15% of the mean
	SoC treatment dosage	Gamma	-
	Disease management resource use	Beta	Beta distribution used assuming a SE of 15% of the mean
	Proportion with PEBD re-operations and complications	Beta	Beta distribution used assuming a SE of 15% of the mean

EQ-5D - EuroQol 5 dimension; HRQoL - health related quality of life; LT - liver transplant; PEBD - partial external biliary diversion; SE - standard error; SoC - standard of care; TP - transition probability

5.2.7 *Company's model results*

This section presents the company's results from the company's model. The CS[1] presents separate results using the list price for odevixibat and the PAS price. The results presented in this section are based on the PAS price only.

Central estimates of cost-effectiveness

Table 25 presents the results of cost-effectiveness for odevixibat versus standard care based on the company's model with a PAS applied. Based on a re-run of the probabilistic version of the model by the ERG, odevixibat is expected to generate an additional [redacted] QALYs at an additional cost of [redacted], with a corresponding ICER of £[redacted]. The deterministic version of the model produces a slightly lower ICER of [redacted]. The deterministic analysis suggests that odevixibat generates 7.02 additional undiscounted LYs and [redacted] additional undiscounted QALYs compared with SoC.

Table 25: Company's cost-effectiveness results, odevixibat versus standard care

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Probabilistic model**							
Odevixibat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Odevixibat	55.67	[redacted]	[redacted]	7.02	[redacted]	[redacted]	[redacted]
Standard care	48.65	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; NR - not reported; QALY - quality-adjusted life years
**Undiscounted*
***Probabilistic results based on a re-run of the company's model by the ERG*

Company's PSA results

The results of the PSA, re-run in the company's model by the ERG, are presented in the CEAC in Figure 24 and the cost-effectiveness plane in Figure 24. At willingness-to-pay thresholds (WTP) £100,000 per QALY gained and £300,000 per QALY gained, the probability that odevixibat is cost-effective is [redacted] and [redacted], respectively. As previously noted in Section 5.2.6, the ERG notes that there were negative QALYs in around 5-10% of PSA runs and due to the nature of the programming of the PSA in the model, the ERG is unable to identify the reasons for these implausible results.

Figure 23: Cost-effectiveness acceptability curve, odevixibat versus standard care (generated by the ERG using the company's model)

Figure 24: Cost-effectiveness plane, odevixibat versus standard care (generated by the ERG using the company's model)

Company's deterministic sensitivity analysis results

Figure 25 presents the results of the company's DSA in the form of a tornado diagram, showing change in the ICER from baseline. The size of the PAS discount had the greatest impact on the ICER, however the ERG is unclear why the company included the PAS discount in the sensitivity analyses as this is not an uncertain parameter. The most influential parameters are the proportion of patients who have an sBA and pruritus response following titration from 40 µg/kg/day to 120 µg/kg/day, [redacted], and the stoma bag disutility multiplier applied to patients undergoing PEBD.

Figure 25: DSA tornado diagram - odevixibat versus standard of care, includes PAS (re-produced by the ERG using the company's model)

Company's scenario analyses

The company presented the results of 17 scenario analyses, which have been reproduced by the ERG in

Table 26. The ICERs ranged from [redacted] (SA10: [redacted] annual loss of response to odevixibat) to [redacted] (SA7: patients treated with odevixibat until LT surgery). In SA7, the company assume that all patients receive the costs of odevixibat until they transition to LT, regardless of if they are responding or not. The results of the scenario analyses show that the ICER is highly sensitive to the utility/disutility values used in the model (SA3-8), with all of these scenarios resulting in substantial increases in the ICER, as did the use of NHS transplant data to model LT mortality (SA2).

In scenario analysis 10, where treatment with PEBD is included following loss of response to odevixibat, there is an increase in incremental LYGs but a decrease in incremental QALYs. The ERG believe this is due to patients who do not respond to odevixibat who go on to have PEBD response have a lower risk of mortality compared to if they were non-responders to odevixibat (as in the base-case). This results in patients not dying as quickly, resulting in higher LYGs. The lower QALYs is a result of the low utility values applied in PEBD states compared to odevixibat non-responders and post-LT patients.

Table 26: Results of company's scenario analyses, odevixibat versus standard care (PAS included) produced by the ERG using the company's model

Scenario	Odevixibat versus standard of care			
	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case (deterministic)	7.02	[redacted]	[redacted]	[redacted]
SA1: NHS and PSS perspective only (removal of carer costs and disutilities)	7.02	[redacted]	[redacted]	[redacted]
SA2: LT transplant mortality from NHS transplant data	3.38	[redacted]	[redacted]	[redacted]
SA3: Utility values using EQ-5D valued results from company vignette study	7.02	[redacted]	[redacted]	[redacted]
SA4: Utility values using TTO valued results from company vignette study	7.02	[redacted]	[redacted]	[redacted]
SA5: Utility values using PEDIFIC trial values with change from baseline analysis	7.02	[redacted]	[redacted]	[redacted]
SA6: Utility values using EQ-5D valued results from company vignette study plus stoma bag disutility multiplier	7.02	[redacted]	[redacted]	[redacted]
SA7: Utility values using TTO valued results from company vignette study plus stoma bag disutility multiplier	7.02	[redacted]	[redacted]	[redacted]
SA8: Disutility multiplier for stoma bag following PEBD from a colorectal cancer study (0.945)[70]	7.02	[redacted]	[redacted]	[redacted]
SA9: Patients treated with odevixibat until surgery	7.02	[redacted]	[redacted]	[redacted]
S10: Treatment with PEBD following loss of response to odevixibat included	8.34	[redacted]	[redacted]	[redacted]
SA11: Response includes pruritus only response rates	6.89	[redacted]	[redacted]	[redacted]
SA12: 5% annual loss of response to odevixibat (equal to PEBD loss of response)	5.27	[redacted]	[redacted]	[redacted]
SA13: [redacted] annual loss of response to PEBD (equal to odevixibat loss of response)	6.38	[redacted]	[redacted]	[redacted]
SA14: 10% annual loss of response to PEBD	8.16	[redacted]	[redacted]	[redacted]
SA15: Proportion of PFIC1 patients 50%	6.93	[redacted]	[redacted]	[redacted]
SA16: Adverse event costs included	7.02	[redacted]	[redacted]	[redacted]
SA17: Patients growth curve based on 25% percentile of general population	7.02	[redacted]	[redacted]	[redacted]

**Undiscounted*

EQ-5D - EuroQol 5 dimension; ICER - incremental cost-effectiveness ratio; LT - liver transplant; LYG - life year gained; NHS - national health service; PEBD - partial external biliary diversion; PSS - personal social services; QALY - quality-adjusted life year; SA - scenario analysis; TTO - time-trade off

5.3 Critique of company's submitted economic evaluation by the ERG

This critique relates to the updated economic model and addendum submitted by the company at the clarification response.

5.3.1 *Methods for reviewing the company's economic evaluation and health economic model*

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's economic analysis and the underlying health economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[80, 81]
- Scrutiny of the company's model and discussion of issues identified amongst the members of the ERG.
- Double-programming the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the company's executable model and its description in the CS.
- Replication of the results of the company's base case analysis, PSA, DSAs and scenario analyses reported in the CS.
- Where possible, checking key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2 *Adherence of the company's model to the NICE Reference Case*

The extent to which the company's economic analyses adhere to the NICE Reference Case[82] is summarised in

Table 27.

Table 27: Adherence of the company's economic models to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is in line with the final NICE scope.[10]
Comparator(s)	As listed in the scope developed by NICE	The company's model includes standard of care as the sole comparator, in which all patients start with off-label treatment and some go on to receive PEBD.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The analysis includes health effects on patients and carers. Health gains accrued by patients are valued in terms of QALYs gained. The company's model also includes additional disutility for caregivers of patients.
Perspective on costs	NHS and PSS	Costs include those borne by the NHS and PSS, as well as productivity losses and out-of-pocket costs for the caregivers. The ERG considers this inclusion of productivity costs as being inconsistent with the NICE methods guide.[83]
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained for odevixibat versus standard of care.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 96-year (lifetime) time horizon.
Synthesis of evidence on health effects	Based on systematic review	sBA response outcomes are based on the PEDFIC1 trial, which is the pivotal trial of odevixibat identified from the company's systematic review. Longer-term outcomes are based on published sources such as the NAPPED study. The ERG considers both of these data sources to be relevant to the decision problem.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health state utility values in the model are based on data from published literature, however, the utility values used in the model lack face validity. The ERG notes that the company has conducted a mapping study and a vignette study but did not use these utility values in the model.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	

Element	Reference case	ERG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Drug costs are valued at current prices. Other resource costs are valued using estimates from the NHS Reference Costs[77] and British National Formulary[44]
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects in the original submission are discounted at a rate of 3.5% per annum.

EQ-5D - Euroqol 5 Dimensions; ERG - Evidence Review Group; HRQoL - health-related quality of life; NHS - National Health Service; NICE - National Institute for Health and Care Excellence; PSS - Personal Social Services; PSSRU - Personal Social Services Research Unit; QALY - quality-adjusted life year; TA - Technology Appraisal

5.3.3 *Key issues identified from the ERG's critical appraisal*

This section presents a discussion of the main issues identified from the ERG's critical appraisal of the company's economic analysis which are summarised in Box 1, with a detailed discussion presented in the subsequent sections.

Box 1: Main issues identified from ERG's critical appraisal

(1) Presence of model errors
(2) Inappropriate inclusion of productivity costs
(3) Issues regarding assumptions around PEBD surgery
(4) Issues regarding probability of liver transplant and re-transplant
(5) Issues relating to utility values
(6) Issues relating to mortality risk parameters
(7) Counterintuitive relationship between odevixibat effectiveness and cost-effectiveness
(8) Uncertainty around the sBA response rates
(9) Issues relating to treatment discontinuation
(10) Concerns regarding the estimation of drug acquisition costs

(1) Presence of model errors/limitations

The ERG identified a few errors/limitations in the company's original submitted model: these are summarised in

Table 28.

Table 28: Summary of errors identified in the company's original submitted model

Item no.	Description of error/limitation
Model trace calculations	
1	PEBD surgery costs are not included in the first model cycle.
2	Error in the estimation of the post-PEBD costs for the PEBD non-responders.
3	Inconsistency in the discount rates between costs and QALYs. For the QALYs, the half-cycle corrected discount rates are used while the discount rates for costs are not half-cycle corrected.
Costs	
4	The company's model applies the acquisition costs of UCDA and rifampicin from the BNF;[44] however a lower price for both drugs is available from eMIT[84] (UCDA: BNF price = £14.49, eMIT price = £7.97; rifampicin: BNF price = £18.32, eMIT price = £8.68)

BNF - British national formulary; eMIT - electronic market information tool; PEBD - partial external biliary diversion; QALY - quality-adjusted life year; UCDA - Ursodeoxycholic acid

The ERG amended the company's revised model to address the errors/limitations outlined in the table above. Overall, the impact of these errors on the ICER is minimal, resulting in increasing the company's original deterministic ICER from [redacted] to [redacted] (see Section 5.4.3).

(2) Inappropriate inclusion of productivity costs

The company's base case analysis includes productivity costs and out-of-pocket costs related to travel to specialist centres (see CS Table 83, page 222). The CS (section 12.3.9, page 210) mentions that "*Societal costs are included in the model base case to capture the financial burden for parents and caregivers of children with PFIC".*

There is no specific guidance reported in NICE interim Methods Guide for HSTs[85] regarding the inclusion of productivity costs and the NICE guide to the methods of technology appraisal[83] suggests that *"Productivity costs are not included in either the reference-case or non-reference-case analyses"* (NICE Guide to the methods of technology appraisal[83]). Furthermore, there is no estimate of the opportunity costs of productivity losses in England (i.e. there is no guidance on the appropriate valuation of productivity costs).

Based on these issues, the ERG considers that the company's inclusion of productivity costs and out-of-pocket costs not appropriate for NICE decision-making.

(3) Issues regarding the assumptions around PEBD surgery

The ERG has concerns regarding the assumptions around PEBD surgery in the model. These can be summarised as follows:

(i) Issues with assuming no PEBD surgery in odevixibat arm

(ii) Issues around the costs of PEBD surgery

(i) Issues with assuming no PEBD surgery in odevixibat arm

The CS (section 12.2.1.5, page 179) states that while patients without response in the standard of care arm can progress to PEBD, this transition is assumed to be zero in the treatment arm in the company's base case analysis (though explored in a scenario analysis – see SA10 in

Table 26). That is, the base-case model assumes that the probability of receiving PEBD in the odevixibat arm is zero. As such, this results in different treatment pathways for the SoC arm and odevixibat arm.

The ERG considers assuming no PEBD surgery for patients treated with odevixibat to be quite a strong assumption. In response to clarification question A18, the company confirmed that "*8 patients who had previously received PEBD surgery were enrolled in the PEDFIC1 trial (2 in placebo, 2 in 40 ug/kg/day group, 4 in the odevixibat 120 ug/kg/day group)*". This suggests that sequential treatment with PEBD and odevixibat is possible. Indeed, the expert clinical advice to the ERG suggested that PEBD surgery could be offered to those who did not respond on odevixibat. Also, the ERG understands that there may be a waiting list for liver transplant surgery (e.g. due to scarcity of livers) which also makes it likely that patients not responding on odevixibat would be offered PEBD surgery. Of note, the company's model does not explicitly account for possibility of long waiting lists for LT surgery due to lack of available livers, however, this may be accounted for implicitly by using transition probabilities to LT.

The ERG considers the use of different treatment pathways for the SoC arm and odevixibat arm inappropriate as it seems to offer additional benefits in odevixibat arm. The utility values for PEBD health states in the company's model are lower than that of the liver transplant health states, resulting in odevixibat arm gaining more QALYs due to the fact the patients in odevixibat arm only receive LT while patients in the SoC arm also receive PEBD. Indeed, in the model submitted by the company, when the response rate for odevixibat is assumed to be 0% (thus making it theoretically identical to the standard care), the odevixibat arm has [redacted] compared to SoC, resulting in an ICER of [redacted]. This suggests that cost-effectiveness of odevixibat is calculated as a combination of the costs and benefits associated with LT (and avoidance of PEBD surgery) along with the costs and benefits of odevixibat itself. Furthermore, the ERG considers that this also contributes to the relationship between odevixibat efficacy and cost-effectiveness outlined in point (7) below.
The ERG performed analyses where it was assumed that the annual probability of PEBD in non-responders in odevixibat arm is the same as that for the non-responders in SoC arm (see Section 5.4.1 for more details).

(ii) Issues around the costs of PEBD surgery

The CS (Table 64, page 203) suggests that the 67% of the patients receiving PEBD surgery have re-operations and thus accrue a further £12,643 (i.e. the cost of the initial PEBD surgery). The ERG believes that this assumption might lead to an overestimate of the cost of PEBD surgery. In addition, the company's model applies treatment for infections due to PEBD at a cost of £1,847 to 43% of patients based on 14 patients in Bjornland *et al.*[46] reporting post-operative complications within the first 30 days of PEBD surgery and treatment for bowel prolapse at a cost of £2,987 to 7% of patients based on 1

patient in Bjornland *et al*.[46] The ERG notes that the 14 patients experiencing post-operative complications includes the bowel prolapse and so including this as a separate proportion is double-counting these patients. In addition, the cost applied to patients with an infection ("paediatric intermediate infections with CC score 2-4": £1,846) may be an overestimate for some patients who only experienced minor complications.

The company's clarification response (question B32) comments that "*As noted, the proportion of patients with complications following PEBD was informed by Bjornland et al., 2020. Due to lack of data from other sources including UK-specific studies, this study, which reported on a population of PFIC patients treated at four Nordic centres was considered appropriate, since clinical practice in the Nordics is not expected to vary significantly from the UK. The study was carried out at 4 centres seeing few patients and it is possible that they are less experienced than key UK centres in this type of surgery. Secondary surgeries were performed mainly due to variety of stoma problems (leakage, prolapse, stricture, and bleeding), patient's wish for removal of the external stoma, or inadequate bile drainage with persistent sever itching. In several cases the surgery was a conversion to another form biliary diversion. The high rate of the re-operations reflects the significant complications and inadequacies related to this type of surgery.*"

The ERG believes that the costs of PEBD surgery used in the model might be an overestimate, and as such, performed scenario analyses using lower costs of PEBD surgery (see Section 5.4.2 for more details).

(4) Issues regarding the probability of liver transplant

The ERG has concerns regarding the assumptions and methods used for the probability of liver transplant in the company's model. These can be summarised as follows:

(i) Assuming 0% probability of liver transplant in responders

(ii) Issues with the methods used to estimate liver transplant probability for patients without prior PEBD

(i) Assuming 0% probability of liver transplant in responders

In the company's economic analysis, the probability of liver transplant in responders is assumed to be 0%. However, the CS (Figures 33 and 35, pages 134 and 137, respectively) seems to suggest that patients achieving response do go on to have liver transplant (i.e. the probability of liver transplant in responders is not 0%). The ERG believes that the assumption of 0% probability of liver transplant in responders may result in an overestimation of the benefit of achieving response.

The company's clarification response (question B20) comments that "*The data presented in Section 12.2.1.7 suggests a 0% probability of LT in PEBD responders, however, this does not account for the annual 5% of patients who lose response (see Section 12.2.1.3). When patients have lost response to PEBD, they are subjected to the same probability of LTx as those presented in Table 48 of the CS (i.e. 6.34% in PFIC1, 11.24% in PFIC2). It is assumed that patients who later receive transplants have lost response to PEBD. This was confirmed by a UK clinical expert, in the same manner odvixibat responders should assume having a 0% probability for LTx.*"

The ERG acknowledges the argument made by the company; however, it is not clear whether the rate of liver transplant among responders estimated in the model (indirectly, using the probability of LT among 5% of patients who lose response) is higher or lower than the rate of LT that would have been estimated from the NAPPED data presented in the CS (CS, Figures 33 and 35, pages 134 and 137, respectively).

(ii) Issues with methods used to estimate liver transplant probability for patients without prior PEBD

The ERG noticed (after clarification stage) that the probability for transition from the 'No PEBD, no response' state to the LT state appears to have been informed by data for LT from SBD regardless of response and it seems likely that the probability of LT for non-responders is underestimated.

The annual probability of LT without PEBD is estimated as 6.85% per annum (see CS, Section 12.2.1.6, Table 44, page 181). The probability of LT without PEBD in PFIC1 and PFIC2 patients is derived from the 'no surgical biliary diversion' curves adapted from Van Wessel *et al*. (CS, Figure 32, page 133 and CS, Figure 34, page 136 respectively). However, these curves represent data for non-PEBD patients regardless of whether they have had a sBA response or not. Thus, the ERG believes that LT rates for non-responders without prior PEBD to be underestimated in the company's model.

In the ERG-preferred base-case analyses, it was assumed that the annual probability of LT for non-responders without prior PEBD to be the same as LT probability in PEBD non-responders (i.e. 9.90%, see CS, Section 12.2.1.7, Table 48, page 182).

(5) Issues relating to utility values

The ERG has a number of issues relating to the utilities applied in the company's model, which were sourced from published literature. These can be summarised as follows:

(i) Issues with the face validity of the utility values used in the model

(ii) Not using the utility values from the mapping study

(iii) Issues with the methods used to estimate the utility values for PEBD health states

(iv) Issues with face validity of post-LT utility value

Table 29 presents the utility values used in the model sourced from published literature as well as the utility values estimated from the company's mapping study and company's vignette study, but not used in the company's analysis.

Table 29: Utility values in the company's submitted model and the utilities estimated from company's mapping study and vignette study (reproduced from the company's model)

Health state	Utilities used in the company's model	Utilities from company's mapping study	Utilities from 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]

LT - liver transplant; PEBD - partial external biliary diversion

(i) Issues with the face validity of the utility values for odevixibat responders and non-responders used in the model

The CS (Table 35, page 158) assumes that the patients achieving response have the same utility as healthy children. However, the expert clinical advice to the ERG suggested that patients who have a response to treatment would not have the same quality of life as a healthy child due to ongoing problems and symptoms of disease. The ERG believes that the assumption used in the model would result in overestimation of the QALYs associated with achieving response on odevixibat. In response to a request for clarification (see clarification response,[2] question B35), the company suggested "*While it is accepted that patients that have responded to treatment will not experience the same quality of life as a healthy child, this simplifying assumption was applied due to a lack of available data on quality of life in children with PFIC generally and split by sBA response specifically. The data applied for non-responders in the model has been taken from a general PFIC cohort and the exact response and surgical status of these patients remains unknown. As such, the difference in quality of life between the PFIC cohort and healthy children was judged to be an appropriate estimate of the impact of response on quality of life.*"

Similarly, the ERG also believes that a utility of 0.83 for non-responders (Table 35, page 158) may be an overestimate, due to the ongoing problems and symptoms of disease outlined (see CS, executive summary). The ERG notes that there were utility data available from the company's mapping study, see point *(ii)* below, which would have been more appropriate than using simplifying assumptions. The ERG also believes that these assumptions used in the model would result in overestimation of the QALYs associated with achieving response on odevixibat as well losing response on odevixibat.

(ii) Not using the utility values from the mapping study

The CS reports that "*Mapping of the PEdsQL in PEDFIC1 was carried out but was not used in the base case analysis*" (Section 10.1.4, page 151). Further details of the mapping study were presented in the CS, Appendix 17.8, which states that "*While this analysis shows the benefit of response in improving quality of life for patients with PFIC, due to the small sample size and marginal differences in absolute scores, it was decided not to apply these values in the economic model"* (Table 117, CS, Appendix 17.8). The ERG did not believe this to be an adequate reason for not using the utility data from mapping study and requested further clarification on the differences in HRQoL at baseline in responders and non-responders (CS, Appendix 17.8, Tables 116 and 117), and whether the company considered using a common baseline value for responders and non-responders, and using the CFB (change from baseline) observed in the trial (e.g. as reported in Table 117) to estimate the utility values for responders and non-responders.

The company's clarification response (question B36) comments that *"Mapped EQ-5D utilities from the trial were not applied in the model - PedsQL data were included as an exploratory endpoint in the PEDFIC1 as there was a lack of consistency in the results. Patient numbers were small, especially among self-reporting patients, and the mapping analysis was applied to aggregate data rather than patient-level data.*

A sensitivity analysis assuming a common baseline EQ-5D utility for all patients and applying observed change from baseline is presented. The combined baseline utility observed in the mapping analysis was 0.633. Patients with an sBA response to treatment experienced a 0.244 increase from baseline, compared to 0.064 in non-responders."

The use of common baseline utility resulted in utility values for responders and non-responders of 0.858 and 0.697, respectively. The ERG considers these values to be more appropriate than the utility values used in the company's analyses and performed analysis using these utility values (see Section 5.4.1).

(iii) Issues with the methods used to estimate the utility values for PEBD health states

In the model, there is the option to select two separate studies to calculate a multiplier for the disutility associated with a stoma bag. It was not clear how the value used for the base-case was chosen, and whether was this based on clinical opinion on the appropriateness of the two studies. In response to a request for clarification (see clarification response,[2] question B37), the company suggested "*The disutility multiplier for colorectal cancer (0.945) seemed inappropriate for the base case, because colorectal cancer patients are far older (mean age 72 years) and likely at end of life, compared to the target population. An ulcerative colitis multiplier was used in lieu of this as the base case (0.722). This study represented younger patients with a stoma bag. Clinical opinion confirmed that a multiplier of 0.722 more accurately reflected the discomfort of carrying a stoma bag, and that this value was likely to decrease (i.e., worse quality of life) as children get older and become more aware of it. Our current base case therefore represents a conservative scenario, where a constant multiplier is applied for all age groups."*

The company performed an initial vignette study to estimate the impact of PEBD on the utilities (see Table 29) but these utilities were not used in the model. The ERG notes that the utilities from the vignette study seem higher than those used in the company's model, especially for the PEBD response health state. An additional vignette study undertaken by the company was presented to the ERG post clarification stage, which aimed to specifically calculate a disutility multiplier associated with a stoma bag as a result of PEBD surgery. This used results from just two parents to calculate a mean disutility multiplier of [redacted], applied only in a scenario analysis.

The ERG believes that utility multiplier used in the company's model for PEBD health states seems low and would result in underestimation of the QALYs associated with achieving response on PEBD as well losing response on PEBD. The ERG believes that a more appropriate disutility multiplier would be 0.833, which is the average of two values in the studies identified by the company (i.e. 0.722 and 0.945). This disutility multiplier is also similar to the ratio of the utility values for PEBD loss of response health state identified in the vignette study and odevixibat loss of response health state identified in the mapping study, respectively. As such, the ERG performed analysis using this disutility multiplier utility value of 0.833 for PEBD health states (see Section 5.4.1).

(iv) Issues with the face validity of the utility values for post-LT in the model

The ERG considers that utility value of 0.850 used for post-LT health state in the model to be lacking in face validity as it seems high compared to the estimates of utilities reported in published studies (which typically are around 0.70 to 0.78). Given all LT patients require immunosuppression and at risk of complications, the utility value used in the model seems high. The CS highlights that "*many individuals with PFIC and their caregivers tend to be anxious about LT because of the extreme nature of the procedure and associated risks*" (CS, section 7.1.1) and *"many individuals with PFIC and their*

caregivers tend to be anxious about LTx, feeling that it is extreme and will lead to complications in daily life" (CS, section 8.2.6).

Furthermore, patients in the post-LT health state in the model also include patients who received liver re-transplant and it is assumed that these patients who receive re-transplantation have the same outcomes (i.e. quality of life) as those patients having a first liver transplant. In the company's clarification response (question B23), the company reported "*the company made a pragmatic assumption and applied the same assumption for both acute and long-term liver transplant.*"

As such, the ERG considers that the utility value used for post-LT health state to be an overestimate and performed analysis using alternative utility value (see Section 5.4.1). This value was estimated by applying the ratio of utility in post-LT health state (0.850) and utility in odevixibat response health state (0.914) in the company's model, and applying it to the utility of odevixibat response health state (0.858) estimated from the mapping study. This resulted in a utility value of 0.798 (i.e. 0.858*0.850/0.914) and the ERG performed analysis using this utility value for post-LT health state (see Section 5.4.1). The ERG notes that this utility value is still higher than the utility values for the post-LT health state in published studies.[86]

(6) Issues relating to post liver transplant mortality risk parameters

The ERG has concerns regarding the assumptions around the mortality risk parameters used in the model. These include

(i) Ambiguity around methods to estimate acute LT mortality

(ii) Ambiguity around methods to estimate long-term post LT mortality

(i) Ambiguity around methods to estimate acute LT mortality

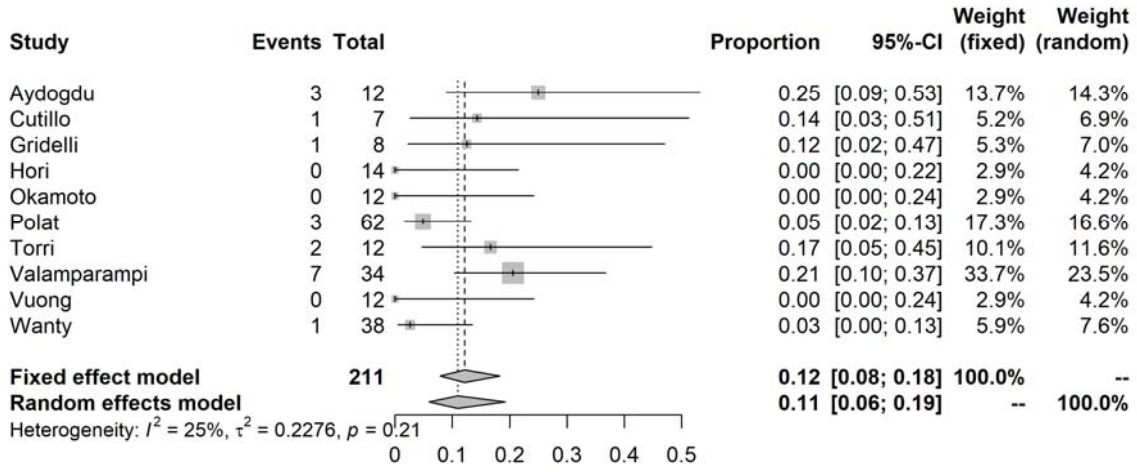
The company did not describe in detail how they identified the studies that provided their evidence for post-LT mortality, as such, it is unclear whether all relevant studies were included. The company did not describe in detail the statistical model and implementation used for the synthesis of acute (up to 1 year) post-LT mortality probabilities. The ERG identified some discrepancies between the source data in the published studies and the data used by the company. Also, the company adjusted the estimates from the meta-analysis using the rate-to-probability conversion which the ERG believes may have been an error by the company. The ERG notes that, as the inputs to the meta-analysis are proportions of deaths in one year, the output is also proportion of deaths per year (i.e. annual probability). There is thus no need to adjust the meta-analysis results and doing so will bias the probability downwards.

The ERG repeated the meta-analysis using the 10 studies identified by the company in their clarification response. The ERG notes that the company wrongly assumed two events in the study by Gridelli *et al.*[63]

study when only one event occurred (as 12% of 8 is 1). Also, the ERG noticed an inconsistency in the reporting in Polat *et al.*[65] where N=62 is stated but the breakdown of PFIC types gives a total of 61 patients. In the ERG analysis, N=62 was retained. The ERG recreated the meta-analysis using R version 4.0.3[87] and the 'meta' package version 4.18-2.[88] Fixed and random effects models were used to pool the proportions on the logit scale using the 'metaprop' function implementing the inverse variance method and the Wilson Score interval for CIs. A standard continuity correction of 0.5 was used when no events had occurred. The ERG meta-analysis results are presented in

Figure 26. The ERG estimated acute post-LT mortality using the random effects model resulted in a yearly mortality probability of 10.92%.

Figure 26: Results of ERG MA for acute post-LT mortality



(ii) Ambiguity around methods to estimate long-term post-LT mortality

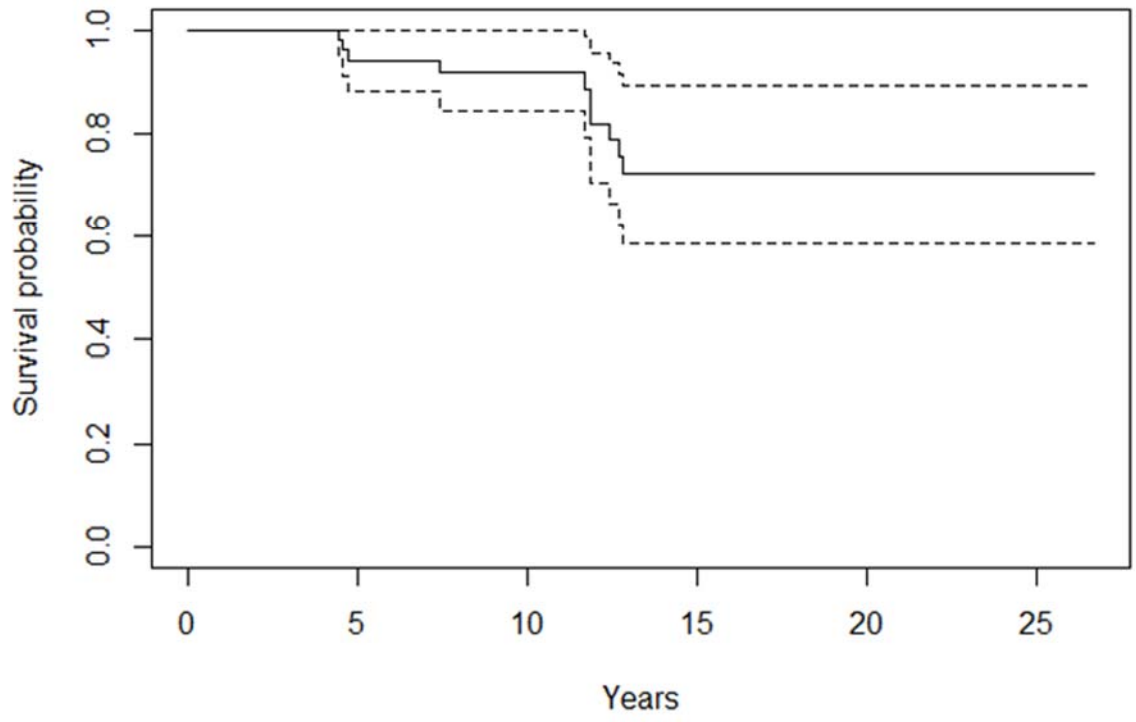
For the probability of long-term post-LT mortality (i.e. from the end of the first year onwards), the company drew evidence from the 4 (of the 10) identified studies which provided long term survival data[36, 37, 63, 64] (see Table 21). In each case, the published KM function (To derive a probability for long-term post-LT mortality, the Company digitised the KM functions from the four studies that reported long term mortality outcomes[36, 37, 63, 64] (Figure 17, Figure 18, Figure 19, Figure 20) and created pseudo individual participant data. This data was pooled and used to estimate an exponential survival distribution for survival from 1 year after LT, conditional on survival to that point. The resulting exponential survival function had a rate parameter of 0.0196 (0.0116, 0.0320). This corresponds to a yearly probability of 1.94% in the post-clarification base-case model. In their clarification response[2] (question B25(e)), the Company presented a KM function created from the pooled pseudo individual participant data (Figure 22).

Figure 17 to Figure 20) was digitised and pseudo IPD was created. These IPD were pooled and an exponential survival model fitted to give a constant rate of mortality.

The ERG examined the four studies and found some ambiguities and some apparent discrepancies with the evidence used by the company. In Wanty 2004[37], it was stated that 3 deaths occurred within 5 years among the 38 patients. However, it is apparent from the KM function and descriptive text that these 3 deaths occurred over 15 not 5 years. It is not known how the company interpreted this. From Gridelli 2003[63], the company deduced that two deaths occurred among 8 patients during follow up. However, the survival probability dropped to 88% which can only represent one death from 8 patients. For completeness, the ERG found 5 deaths among the 12 patients reported in Okamoto 2021[64] corresponding to the 58% 25 year survival and 3 deaths among the 15 patients in Hori 2011,[36] as directly reported there.

Using this information and data from digitising the four KM curves, the ERG created pseudo IPD using the Guyot method[89] implemented in R[87] using the survivalnma package. This IPD had two deaths and one censoring within the first year after LT. These were removed from the IPD dataset and the survival times were reduced by one, in order to analyse survival from one year after LT, conditional on survival of that first year. This dataset contained pseudo IPD for 69 individuals and among these 10 deaths were observed all occurring at different times. The ERG notes that when all deaths occur at different times, the downward steps in a KM function can never get smaller as time increases. The KM function for the company's pseudo IPD contradicts this fact as seen in Figure 22 which also truncates the maximum follow up time which should be 26.7 years. It is not clear if this truncation was used in the company's analysis. The KM function summarising the ERG's pseudo IPD is shown in Figure 27. The ERG fitted an exponential model to this IPD data and the resulting exponential rate was 0.01426 which equates to a yearly long term mortality probability of 1.42% which is less than the company's value of 1.94%.

Figure 27: Kaplan Meier survival function and 95% confidence intervals summarising the ERG's pseudo IPD derived from the evidence for long-term post LT mortality



(7) Counterintuitive relationship between odevixibat efficacy and cost-effectiveness

The ERG has concerns regarding the relationship between the odevixibat efficacy and cost-effectiveness in the company's base case model. In particular, these relate to

(i) Lower odevixibat response rates resulting in lower ICERs

(ii) Increased loss of response for odevixibat resulting in lower ICERs

The company's submitted model suggests that assuming a lower odevixibat response rate, results in the ICER decreasing. In the base case analysis using the PAS price, using a response rate of [redacted] the ICER is [redacted] Keeping the proportion of patients on high dose the same but amending the response rate to [redacted] results in a lower ICER of [redacted] and at a response rate of [redacted] the ICER is [redacted]. These results seem to suggest that the lower the response rate on odevixibat treatment, the more favourable the cost-effectiveness.

The company's model also suggests that the ICER decreases with the increase of the odevixibat discontinuation rate (note that the model uses the discontinuation rate as a proxy for the annual loss of response). In the base case analysis, assuming an annual loss of response of [redacted] the ICER is [redacted] using the PAS price. When the annual loss of response is increased to [redacted] the ICER decreases to [redacted] and at an annual loss of response of [redacted] the ICER is

[redacted]These results seem to suggest that sooner the patients discontinue odevixibat treatment, the more favourable the cost-effectiveness.

[redacted]The reason for this non-intuitive finding is that odevixibat seems to have a high cost-benefit ratio and moving the patients off odevixibat to LT, which has a more favourable cost-benefit ratio, results in lower ICERs. In the FAC response (Issue 5), the company suggested that "*As discontinuation rates increase, the average age of a patients still on treatment is decreased. The cost-effectiveness in younger patients is expected to be higher for two reasons: 1) younger patients fall into lower weight categories and the cost of treatment is lower, and 2) patient utilities in the model are age adjusted and thus QALY gains are higher for younger patients. Thus, any scenario which involves a higher proportion of the time on treatment being at a younger age is likely to lead to more favourable results."* The ERG agrees with these points, however in an exploratory analyses conducted by the ERG which kept the weights and utilities of patients constant over time, the finding that the ICER became more favourable to odevixibat with lower response rate or higher discontinuation rate, was maintained.

The ERG performed exploratory analyses using a fully incremental comparison of all possible treatment pathways to explore this issue further (see 5.4.3).

(8) Uncertainty around the sBA response rates

The ERG identified notes that the data on sBA response with 120 µg/kg/day dose in those not responding to 40 µg/kg/day is based on small numbers of patients. The CS (page 163) states that "*In the clinical development programme, patients completing PEDFIC1 were allowed to enrol directly into PEDFIC2 in which all patients receive 120 µg/kg/day. This allows for an evaluation of the responses in patients as they transition from 40 µg/kg/day during PEDFIC1 to 120 µg/kg/day in PEDFIC2.*" The CS (page 163) also states that *"Data are available at Week 24 of PEDFIC2 for 4 patients who did not meet the sBA responder definition during PEDFIC1*[redacted]*met the sBA responder definition.*"

In the model, the response rate of odevixibat is [redacted], which is estimated as [redacted] plus the [redacted] who are assumed to have met the sBA responder definition at the higher dose. The ERG believes that there is likely to be substantial uncertainty in this parameter, given the small numbers of patients used to estimate this parameter.

(9) Issues relating to treatment discontinuation

The ERG has concerns regarding the company's assumptions around treatment discontinuation. These are described below:

(i) Use of discontinuation rate as a proxy for loss of response

(ii) Ambiguity around the estimation of discontinuation data

(i) Use of discontinuation rate as a proxy for loss of response

In the company's economic analysis, odevixibat is assumed to be given until loss of response; however, discontinuation rate is used as a proxy to model this loss of response - see point (ii) below. The ERG considers this to be an optimistic assumption as the loss of response itself (i.e. the response not sustained in the long-term for patients on treatment) is not modelled, but rather that loss of response is only due to the patients stopping treatment due to adverse events or withdrawal of trial consent.

(ii) Ambiguity around the estimation of discontinuation data

In the CS, the rate of discontinuation for odevixibat is taken from patients enrolled in PEDFIC2 after receiving odevixibat in PEDFIC1. The CS states that "*this data was judged to be most representative of patients continuing treatment after the initial 6-month period used to assess response. There was* [redacted]*, with a mean exposure time of* [redacted] *weeks, giving a discontinuation rate of* [redacted] *per patient year, which results in an annual probability of discontinuing odevixibat of* [redacted]"

The ERG is unclear about the source of these data as the CS (Table 25, page 121) suggests that there is one TEAE leading to study treatment discontinuation in the 120 µg/kg odevixibat group. However, the CS (Table 28, page 123) also suggests that in PEDFIC2 there are [redacted] leading to study treatment discontinuation in the placebo and cohort 2, respectively.

(10) Concerns regarding the estimation of drug acquisition costs

Odevixibat is dosed based on weight at either 40 µg/kg/day or 120 µg/kg/day and is available in capsules containing 200 µg, 400 µg, 600 µg or 1,200 µg; which have a list price of [redacted] respectively per pack of 30 capsules. A patient access scheme has been proposed at simple discount [redacted]. The ERG believes there is uncertainty around the proportion of patients receiving high and low doses and the corresponding drug acquisition costs applied in the model.

The drug costs for odevixibat are estimated as weighted average based on the proportions of patients receiving low and high doses. The proportion of patients receiving high dose in the model is estimated as [redacted] and assumed to be constant over the whole model duration. This proportion is estimated in

the model as the complement of (i.e. 1 minus) the ratio of patients who achieved response on the lower dose ([redacted]) and the total proportion of patients achieving response ([redacted]). As outlined in point (8) earlier, these calculations are based on very small numbers and thus, there is substantial uncertainty regarding the proportions of patients likely to be on the higher dose of odevixibat.

Also, the proportion of patients receiving high dose in the model is assumed to be constant over the whole model duration whereas it may be possible that the proportion of patients on higher dose may vary over time. Given the costs of patients receiving high dose is three times that of the patients receiving the low dose, the ERG evaluated the impact of using different values of proportions of patients in high dose of odevixibat in scenario analyses.

5.4 Exploratory analyses undertaken by the ERG

The ERG undertook three broad sets of exploratory analyses. The first set involved fixing errors identified within the ERG's critical appraisal (see Section 5.3.3) and modifying model inputs and assumptions in order to form an ERG-preferred analysis. The second set of analyses involved exploring residual uncertainty using this ERG-preferred model using scenario analyses. The third set of analyses involved a fully incremental comparison of all possible treatment pathways. All exploratory analyses were undertaken including the PAS discount. Methods for applying the ERG's exploratory analyses within the company's model can be found in Appendix 01.

5.4.1 ERG-preferred analyses

The ERG-preferred analysis includes six general amendments to the company's base case model:

(1) Correction of errors/limitations

The model errors/limitations corrected include

- Inclusion of PEBD surgery costs in the first model cycle
- Correcting the error in the estimation of the post PEBD costs for the PEBD non-responders
- Using the half-cycle corrected discount rates for both costs and QALYs
- Using eMIT prices for UDCA and rifampicin (see

- Table 28)

All subsequent exploratory analyses include these error corrections.

(2) Exclusion of productivity costs

In line with the NICE Interim Methods Guide for HSTs[85] and the NICE Methods Guide[83], productivity costs were excluded from the analysis.

(3) Probability of LT in prior PEBD non-responders same as probability of LT in post-PEBD non-responders

The probability of LT without PEBD in the company's model seems to have been estimated for non-PEBD patients regardless of whether they have had a sBA response or not (see section 5.3.4). As such, the ERG believes that this estimate (probability of 6.85% per annum) might be an underestimate for non-responders prior to PEBD. In this analysis, it was assumed that the annual probability of LT for non-responders without prior PEBD was the same as LT probability in PEBD non-responders (probability of 9.90% per annum).

(4) Using ERG meta analyses results for post LT mortality

Using the acute and long-term post-LT mortality risk parameters from the meta-analyses conducted by the ERG (10.92% and 1.42%, respectively).

(5) Inclusion of costs of adverse events

In line with the NICE Methods Guide,[83] costs of adverse events were included.

(6) Amending the utility values

This analysis incorporated:

- Utilities from company's mapping study for odevixibat responders and non-responders (0.858 and 0.697, respectively), estimated assuming a common baseline EQ-5D utility for all patients and applying observed change from baseline for responders and non-responders separately
- Using utilities of 0.715 and 0.581 for PEBD responders and PEBD non-responders, respectively based on a disutility multiplier estimated as average of the multipliers in the two studies identified by the company
- Using a utility of 0.798 for post-LT state, estimated by applying the ratio of utility in post-LT health state and utility in odevixibat response health state in the company's model, to the utility of odevixibat response health state estimated from the mapping study.

(7) ERG-preferred analysis (analyses [1] to [6] combined)

The ERG's preferred analysis involved all changes listed in analyses 1-6. It should be noted that whilst the ERG prefers this analysis to the company's base case, there remains considerable uncertainty surrounding the cost-effectiveness of odevixibat (see Section 5.3.3).

Table 30 presents the results of the ERG's preferred analyses based on the deterministic version of the model. The correction of the remaining model errors increased the ICER from [redacted] to [redacted]; all subsequent ERG exploratory analyses are applied to this corrected model. Excluding the productivity costs increases the ICER to [redacted] and using ERG updated meta-analysis figures for acute and long-term LT mortality increases the ICER to [redacted]. Assuming the probability of liver transplant in prior PEBD non-responders same as post-PEBD non-responders or including the costs of adverse events only had a minor impact on the ICER. Amending the utility values as outlined in section 5.4.1 resulted in an ICER of [redacted] The ERG's preferred analysis (EA7), which combines ERG Exploratory Analysis 1-6, results in an ICER of [redacted]

Table 30: Results of the ERG's preferred analyses, deterministic

Option	LYGs *	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case following clarification response							
Odevixibat	55.67	[redacted]	[redacted]	7.02	[redacted]	[redacted]	[redacted]
Standard of Care	48.65	[redacted]	[redacted]	-	-	-	-
EA1: Company's base case after correction of remaining model errors†							
Odevixibat	55.67	[redacted]	[redacted]	7.02	[redacted]	[redacted]	[redacted]
Standard of Care	48.65	[redacted]	[redacted]	-	-	-	-
EA2: Use of updated meta-analysis figures for acute and long-term LT mortality							
Odevixibat	59.22	[redacted]	[redacted]	5.99	[redacted]	[redacted]	[redacted]
Standard of Care	53.24	[redacted]	[redacted]	-	-	-	-
EA3: Exclusion of productivity costs							
Odevixibat	55.67	[redacted]	[redacted]	7.02	[redacted]	[redacted]	[redacted]
Standard of Care	48.65	[redacted]	[redacted]	-	-	-	-
EA4: Probability of LTx in prior PEBD non-responders same as probability of LTx in post-PEBD non-responders							
Odevixibat	53.57	[redacted]	[redacted]	7.08	[redacted]	[redacted]	[redacted]
Standard of Care	46.49	[redacted]	[redacted]	-	-	-	-
EA5: Inclusion of costs of adverse events							
Odevixibat	55.67	[redacted]	[redacted]	7.02	[redacted]	[redacted]	[redacted]
Standard of Care	48.65	[redacted]	[redacted]	-	-	-	-
EA6: Amending the utility values							
Odevixibat	55.67	[redacted]	[redacted]	7.02	[redacted]	[redacted]	[redacted]
Standard of Care	48.65	[redacted]	[redacted]	-	-	-	-
EA7: ERG preferred analysis (EA1-EA6 combined)							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]	-	-	-	-

EA - exploratory analysis; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
**Undiscounted*
† Analyses EA2-EA7 each include error corrections from EA1

As shown in
Table 30, amending the utility values and excluding the productivity costs to be in line with the NICE Reference Case has the most substantial impact on the ICER for odevixibat versus SoC. Based on the ERG-preferred analysis using the probabilistic version of the model, odevixibat is expected to generate an additional [redacted] QALYs at an additional cost of [redacted]; the corresponding ICER for odevixibat versus SoC is [redacted] per QALY gained. The deterministic version of the model yields a lower ICER of [redacted] per QALY gained. The deterministic ERG-preferred analysis suggests that odevixibat generates 6.06 additional undiscounted LYs and [redacted] additional undiscounted QALYs compared with SoC.

5.4.2 ERG's additional scenario analyses

The ERG undertook further additional analyses using the ERG's preferred version of the model. The ERG scenario analysis includes the following amendments to the ERG preferred model.

(8) Amending the proportions of patients on low doses (33%, 50% and 66%)
Within these analyses, the proportion of patients receiving low dose was amended from the current value used in the model of [redacted] to 33%, 50% and 66%, respectively representing sub-analyses 8a, 8b and 8c.

(9) Mortality of non-responders (to general population mortality)
Within this analysis, the mortality risk for non-responders (both odevixibat non-responders and PEBD non-responders) was set equal to general population mortality according to the patient's age in each model cycle.

(10) Excluding caregiver disutilities
Within this analysis, the caregiver QALYs (which were lost due to disutility of caring for patients with PFIC) were excluded from the analysis.

(11) Amending the starting age of the patients to 3 years
At the start of the model, patients were assigned an age of 3 years within this analysis rather than the starting age of 4.25 years.

(12) Including PEBD in the odevixibat arm
Within this analysis, it was assumed that the annual probability of PEBD in non-responders in odevixibat arm is the same as that for the non-responders in SoC.

(13) Using lower costs for PEBD surgery

Within this analysis, it was assumed that one-off costs associated with PEBD surgery were lower at £15,000 (compared to £22,119 used in the base-case model).

(14) Assuming higher annual loss of response to odevixibat

Within this analysis, the annual loss of response to odevixibat is assumed to be equal to that of PEBD (5%).

Table 31 shows the results of additional scenario analyses applied to the ERG's preferred analysis to explore the impact of alternative parameter values on the model results. As expected, increasing the proportion of patients receiving high-dose treatment increases the ICER. Assuming general population mortality for non-responders increases the ICER slightly. Excluding caregiver disutilities results in an increase in the ICER whilst assuming a lower starting age reduces the ICER (primarily to due to lower drug costs as the dosage is based on the patient weight). The ERG's additional exploratory analyses using the ERG's preferred version of the model produce ICERs which are in the range of [redacted] to [redacted]. These exploratory analyses highlight the significant influence of the assumptions regarding odevixibat dose and inclusion of caregiver disutilities.

Table 31: Results of the ERG's additional scenario analyses

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA7: ERG preferred analysis							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]	-	-	-	-
EA8a: Proportion of patients receiving high dose odevixibat=33%							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
EA8b: Proportion of patients receiving high dose odevixibat=50%							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
EA8c: Proportion of patients receiving high dose odevixibat=66%							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
EA9: General population mortality for non-responders							
Odevixibat	58.36	[redacted]	[redacted]	5.80	[redacted]	[redacted]	[redacted]
Standard of Care	52.55	[redacted]	[redacted]				
EA10: Excluding caregiver disutilities							
Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
EA11: Start age of 3 years							
Odevixibat	57.94	[redacted]	[redacted]	6.15	[redacted]	[redacted]	[redacted]
Standard of Care	51.79	[redacted]	[redacted]				
EA12: Including PEBD in odevixibat arm							
Odevixibat	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
EA13: Assuming lower costs of PEBD							

Odevixibat	57.50	[redacted]	[redacted]	6.06	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				
EA14: Assuming higher annual loss of response to odevixibat							
Odevixibat	55.91	[redacted]	[redacted]	4.47	[redacted]	[redacted]	[redacted]
Standard of Care	51.44	[redacted]	[redacted]				

EA - exploratory analysis; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
**Undiscounted*

5.4.3 ERG's exploratory full incremental analyses

As outlined earlier, company's submitted model assumes that the probability of receiving PEBD in the odevixibat arm is zero resulting in different treatment pathways for the SoC arm and odevixibat arm. Also, there is uncertainty around comparative cost-effectiveness of odevixibat and PEBD, which makes it difficult to determine where in the treatment pathway odevixibat should go, relative to PEBD. Furthermore, the cost-effectiveness results suggests that assuming a lower odevixibat response rate or higher discontinuation rate (i.e. loss of response) results in lower ICER for odevixibat versus SoC. To explore these issues further, and to assess the appropriateness of the proposed positioning of odevixibat in the PFIC treatment pathway, the ERG performed exploratory analyses using fully incremental comparison of possible treatment pathways to provide additional information for the appraisal committee.

These analyses were performed using the ERG preferred model, and two sets of analyses were performed for different population groups (as the treatment pathways in the full incremental analyses were different for these two population groups). The first set of exploratory full incremental analyses were for patients where PEBD may be needed at some point in the future while the second set of exploratory full incremental analyses were for patients within whom PEBD would be instigated now. These second set of exploratory analyses were performed to gauge the impact of withholding odevixibat until patients needed PEBD. The transition probabilities for all these analyses are assumed to be the same as those in the ERG preferred base case analysis.

(a) Full incremental analyses – population 1

These first set of exploratory full incremental analyses were for PFIC patients where PEBD may be needed at some point in the future and the possible treatment pathways are listed below. Death is not mentioned in the treatment pathways below for simplicity but is included in all the analyses (i.e. patients in any health state can die).

(i) SoC (including PEBD)/LT: Starting with off label treatment and then receiving PEBD or LT

(ii) SoC (including PEBD)/Odevixibat/LT: Starting with off label treatment, then receiving PEBD or LT, and then odevixibat for PEBD non-responders (odevixibat non-responders can also receive LT)

(iii) Odevixibat (excluding PEBD)/LT: Starting with odevixibat, and then LT for odevixibat non-responders

(iv) Odevixibat (including PEBD)/LT: Starting with odevixibat, then receiving PEBD or LT for odevixibat non-responders (PEBD non-responders can also receive LT)

(v) SoC (excluding PEBD)/LT: Starting with off label treatment and then receiving LT

All the analyses above except (ii) were possible by amending the drop-down settings or the parameter values in the model whilst analysis (ii) required amending the programming in the model. The details of how these analyses were performed are described in Appendix 1. Table 32 shows the results of the ERG's exploratory fully incremental analysis for PFIC patients for whom PEBD may be needed at some point in the future. The table suggests that "Odevixibat (including PEBD)/LT" pathway dominates the "Odevixibat (excluding PEBD)/LT" pathway, and "SoC (including PEBD)/LT" dominates the "SoC (excluding PEBD)/LT" pathway. The "SoC (including PEBD)/Odevixibat/LT" is extendedly dominated by the "SoC (including PEBD)/LT" pathway and "Odevixibat (including PEBD)/LT" pathway. Thus, only two pathways are left on the efficiency frontier resulting in an ICER of [redacted] for the "Odevixibat (including PEBD)/LT" pathway versus "SoC (including PEBD)/LT" pathway.

Table 32: Results of the ERG's exploratory fully incremental analyses – population 1 (PFIC patients for whom PEBD may be needed at some point in the future)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Odevixibat (including PEBD)/LT**	58.94	[redacted]	[redacted]	7.50	[redacted]	[redacted]	[redacted]
Odevixibat (excluding PEBD)/LT	57.50	[redacted]	[redacted]	--	[redacted]	[redacted]	[redacted]
SoC (including PEBD)/Odevixibat/LT	53.22	[redacted]	[redacted]	--	[redacted]	[redacted]	[redacted]
SoC (including PEBD)/LT**	51.44	[redacted]	[redacted]	--	[redacted]	[redacted]	[redacted]
SoC (excluding PEBD)/LT	49.52	[redacted]	[redacted]	--	[redacted]	[redacted]	[redacted]

EA - exploratory analysis; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
**Undiscounted*
***Strategies on the efficiency frontier*

(b) Full incremental analyses – population 2

These second set of exploratory full incremental analyses were for patients within whom PEBD would be instigated now and the possible treatment pathways are listed below. These second set of exploratory analyses were performed to gauge the impact of withholding odevixibat until patients needed PEBD, which the ERG acknowledges as not likely in clinical practice but these analyses are provided for information of the appraisal committee. As before, death is not mentioned in the treatment pathways below for simplicity but is included in all the analyses (i.e. patients in any health state can die).

(i) PEBD/LT: Starting with PEBD treatment and PEBD non-responders receiving LT
(ii) PEBD/Odevixibat/LT: Starting with PEBD treatment, then receiving odevixibat for PEBD non-responders (odevixibat non-responders can also receive LT)
(iii) Odevixibat (excluding PEBD)/LT: Starting with odevixibat, and then LT for odevixibat non-responders
(iv) Odevixibat (including PEBD)/LT: Starting with odevixibat, then receiving PEBD for odevixibat non-responders (PEBD non-responders can also receive LT)

The first two analyses (i.e. i and ii) required amending the programming in the model whilst the other two analyses (i.e. iii and iv) were possible by amending the drop-down settings in the model. The details of how these analyses were performed are described in Appendix 1.

Table 33 shows the results of the ERG's exploratory fully incremental analysis for PFIC patients for whom PEBD would need to be instigated now. The table suggests that "Odevixibat (including PEBD)/LT" pathway dominates the "Odevixibat (excluding PEBD)/LT" pathway, resulting in three pathways being on the efficiency frontier. The "PEBD/ Odevixibat/LT" pathway has the highest undiscounted LYs accrued of all strategies; this is because patients that do not respond on PEBD or lose response to PEBD are assumed to be put on odevixibat treatment immediately, whereas in the "Odevixibat (including PEBD)/LT" pathway, the patients that do not respond to odevixibat are assumed to receive PEBD surgery according to the transition probabilities (i.e. not immediately). However, due to the lower utility values in the PEBD health states and because the patients start off in PEBD health states, the high LYs in "PEBD/ Odevixibat/LT" pathway only translate to [redacted] QALYs resulting in an ICER of [redacted] versus "PEBD/LT" strategy. The "Odevixibat (including PEBD)/LT" pathway versus ""PEBD/ Odevixibat/LT" pathway has an ICER of [redacted].

Table 33: Results of the ERG's exploratory fully incremental analyses – population 2 (PFIC patients for whom PEBD would need to be instigated now)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER

Odevixibat (including PEBD)/LT**	58.94	[redacted]	[redacted]	-3.67	[redacted]	[redacted]	[redacted]
Odevixibat (excluding PEBD)/LT	57.50	[redacted]	[redacted]	--	[redacted]	[redacted]	[redacted]
PEBD/ Odevixibat/ LT**	62.63	[redacted]	[redacted]	6.44	[redacted]	[redacted]	[redacted]
PEBD/LT**	56.19	[redacted]	[redacted]	--	[redacted]	[redacted]	[redacted]

*EA - exploratory analysis; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year *Undiscounted **Strategies on the efficiency frontier*

5.5 Costs to the NHS and PSS - eligible population and net budget impact

The CS estimates that [redacted] patients will be eligible for treatment with odevixibat in Year 1 based on the following assumptions:

- Based on clinical expert estimate, the company estimates that there are [redacted] patients with PFIC in England
- Of these, [redacted] are excluded due to BSEP mutation based on the NAPPED study, [redacted] have had LT and [redacted] of the remaining patients have had SBD based on clinical expert estimate; resulting in [redacted] patients as the prevalent eligible population
- Based on clinical expert estimate, the company estimates that there are [redacted] newly diagnosed patients each year, and after excluding [redacted] due to BSEP mutation based on the NAPPED study, [redacted] patients are considered as the incident eligible population

This incident eligible population of [redacted] patients is assumed to be same for years 2 to 5. The company estimates the cumulative market share for odevixibat following a positive NICE recommendation as at [redacted] of eligible prevalent patients in year 1, and [redacted] of eligible patients in Years 2, 3, 4 and 5. The company estimated the number of treated patients and the number of patients remaining on treatment in each year (see CS, Table 90), by taking into account patients discontinuing treatment due to a lack of response.

The number of patients remaining on treatment as estimated by the company in years 1 to year 5 are [redacted], [redacted], [redacted], [redacted], and [redacted], respectively. The net budget impact (excluding any cost savings due to reduced resource use) using the PAS price in years 1 to year 5 as estimated by the company are [redacted]; [redacted]; [redacted]; [redacted]; and [redacted], respectively.

Table 34: Net budget impact of odevixibat in England over 5 years (reproduced from CS, Table 90)

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient numbers					
Prevalent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patient group (new patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients (total cumulative)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients remaining on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact - List price					
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact - PAS price					
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG notes the following observations regarding the company's budget impact analyses:

- Patients who have had SBD are excluded from company's budget impact analysis while it is possible that odevixibat would be offered to these patients (note that the PEDFIC1 study included patients who had prior PEBD)
- There seems to be an issue in the transformation of new patients to treated patients. For example, it is not clear how [redacted] new patients in year 1 are translated into [redacted] treated patients. The same issue is also applicable to the patient estimates in years 2 to 5.
- As acknowledged as limitations in section 13.8 of the CS, patients discontinuing due to lack of treatment effect are based on data from the Phase 3 studies and patients may remain on treatment for longer in real clinical practice.

Overall, the ERG believes it is likely that the net budget impact of odevixibat has been underestimated.

5.6 Potential wider costs and benefits not included in the company's economic analysis

The CS (section 13.6) states that odevixibat is anticipated to generate other economic benefits beyond the NHS and PSS sector. These include:

- By delaying progression into the later health states, and increasing the time spent in the earlier health states, the level of care required for patients is lower, and lower productivity losses can be expected as a result.
- Although it has not yet been possible to quantify, it is highly likely that there will be significant long-term savings to patients, since patients may lead normal lives and be less impacted by their symptoms. For example, patients may be able to work more, or obtain further career progression through improved education not inhibited by PFIC.
- In the short term, parents might not have to take time off from work to care for their child suffering with PFIC, or pay for specialised childcare.
- Due to the rarity of the disease, there are limited treatment centres able to initiate the treatment. As a result, there can be substantial journey and transportation costs for the family of the patient.

The ERG considers these expectations are reasonable but as stated in the CS section 13.6, there is no direct evidence currently to support these assertions. The ERG also notes that the extent of patients, caregivers and families' productivity losses and indirect costs will be dependent on the extent of clinical benefits of odevixibat, and the age of patients and caregivers.

5.7 Discussion

The company's systematic literature review did not identify any existing economic analyses of patients with PFIC.

The CS presents the methods and results of a *de novo* health economic model of odevixibat versus standard of care for patients with PFIC, from a societal perspective which includes productivity costs and health effects on caregivers. The model adopts a state transition (semi-Markov) approach and includes the following health states: (i) response, (ii) loss of response, (iii) PEBD response, (iv) PEBD, loss of response, (v) LT, (vi) post-LT and (vii) death. The model uses data from PEDFIC1 to estimate the response rates; other transitions, including those relating to mortality risk, are informed by external data (NAPPED study). The model includes a key assumption that none of the patients in the odevixibat arm receive PEBD. Also, the company's submitted model suggests that lower the response rate of odevixibat, the lower the ICER. Similarly, increased loss of response for odevixibat results in lower ICERs. The ERG considers this reason for this non-intuitive finding is that odevixibat seems to have high cost-benefit ratio and moving the patients off odevixibat to LT, which has a more favourable cost-benefit ratio results in lower ICERs. [redacted]

As part of the company's response to clarification questions from the ERG, the company submitted an updated model which addresses some of the ERG's concerns. The company's updated base case model corrected the errors identified by the ERG and incorporated 3.5% discounting. Additional scenario analyses were presented which address some of the ERG's other concerns regarding the modelled treatment pathway and the cost inputs. The probabilistic version of the company's model (post-clarification) suggests that the ICER for odevixibat versus SoC is [redacted] The deterministic ICER is similar ([redacted]).

The ERG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The ERG's critical appraisal identified several issues relating to the company's original model and the evidence used to inform its parameters. These include: (1) the presence of few minor model errors/limitations, (2) deviation from the NICE reference case by including productivity costs, (3) issues regarding assumptions around PEBD surgery, (4) issues regarding the probability of liver transplant and re-transplant, (5) issues relating to utility values, (6) issues relating to post-LT mortality risk parameters, (7) counterintuitive relationship odevixibat effectiveness and cost-effectiveness, (8) uncertainty around the sBA response, (9) issues relating to treatment discontinuation, and (10) issues relating to drug costs estimation.

The ERG undertook exploratory analyses using the company's updated model. These included: correcting the remaining model errors/limitations; exclusion of productivity costs; assuming that the probability of LT in prior PEBD non-responders was the same as the probability of LT in post-PEBD non-responders; using ERG meta analyses results for post LT mortality; inclusion of costs of adverse events and amending the utility values. The ERG's preferred analysis suggests that the deterministic ICER for odevixibat versus SoC is [redacted] Using the probabilistic version of the model, the ERG's preferred ICER for odevixibat versus SoC is estimated to be [redacted].

Additional exploratory analyses were also undertaken using the ERG's preferred version of the model to explore the impact of alternative values for parameters such as annual loss of response, mortality risks and the impact of altering assumptions regarding drug dosage, inclusion of PEBD surgery for non-responders on odevixibat, and excluding caregiver disutilities. The ERG's additional exploratory analyses using the ERG's preferred version of the model produce ICERs which are in the range of [redacted] to [redacted]. These exploratory analyses highlight the significant influence of the assumptions regarding odevixibat dose and inclusion of caregiver disutilities.

To assess the appropriateness of the proposed positioning of odevixibat in the PFIC treatment pathway, the ERG performed exploratory analyses using fully incremental comparison of possible treatment pathways to provide additional information for the appraisal committee. These analyses suggest that the

"Odevixibat (including PEBD)/LT" treatment pathway, which involves patients starting with odevixibat, then receiving PEBD or LT after odevixibat loss of response, seems to accrue highest QALYs at an ICER of [redacted] versus SoC.

There were a few issues the ERG could not correct due to the limitations with the model structure and lack of availability of data. The company used exponential distributions (i.e. constant probability) for many transitions in the model citing other distributions would necessitate the use of tunnel states and more complex model structure. The ERG was not able to assess whether this choice of exponential models for transitions resulted in systematic bias in the results of the economic model. Also, all analyses were for patients with PFIC (which included mix of patients with PFIC1 and PFIC2) with the transition probabilities were estimated as a weighted average and the response rates were for the combined population (i.e. both patients with PFIC1 and PFIC2). Due to lack of data on response rates of odevixibat separately for patients with PFIC1 and PFIC2, the ERG could not explore the cost-effectiveness in these two groups separately. And, as previously described, the ERG notes that there were negative QALYs in around 5-10% of PSA runs. The ERG was unable to assess the reason(s) for these implausible results due to the constraints in the model programming of the PSA.

6 END OF LIFE

The CS does not make a case that odevixibat meets NICE's End of Life criteria. It should be noted the company's submitted model estimates the mean undiscounted LYs in the SoC arm as 48.65 years (see Table 25).

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness conclusions

The clinical evidence relating to odevixibat for treating PFIC is based on the PEDFIC1 RCT, the PEDFIC2 single-arm study, and the Phase 2 single-arm dose-finding study, with the majority of the evidence coming from the PEDFIC1 and PEDFIC2 studies. The ERG's clinical advisors confirmed that the eligibility criteria for both PEDFIC1 and PEDFIC2 are representative of the PFIC patients typically seen in routine clinical practice in England. In the PEDFIC1 trial, odevixibat demonstrated statistically significantly greater efficacy than placebo in terms of clinically important outcomes. A significantly greater proportion of patients in the odevixibat groups (33%; including [redacted]) experienced at least a 70% reduction in fasting SBA concentration from baseline to the end of treatment or reaching a level ≤70 μmol/L after 24 weeks of treatment, than in the placebo group (0%). A greater proportion of positive pruritus assessments at the patient level over the 24-week treatment period was achieved by patients treated with odevixibat (53.5%) relative to the placebo arm (28.7%).

[redacted] In the PEDFIC2 study, sBA concentrations declined from baseline over the 24-month treatment period in all patients, including those who were previously treated and those who were treatment-naïve, at the time of the data cut-off, with [redacted] No patients were listed for liver transplantation surgery or were added to the list. [redacted] (of [redacted]) patients enrolled in PEDFIC2 had discontinued.

Key uncertainties concerning the clinical effectiveness evidence relating to the use of odevixibat to treat PFIC include: a lack of clarity around the definition of an [redacted] potential inconsistency in dosing between study data and clinical practice; the lack of evidence for the comparative efficacy of odevixibat and PEBD; the effectiveness of odevixibat among patients previously treated with surgical biliary diversion; and the relatively short duration of follow-up in the PEDFIC1 and PEDFIC2 studies, which make it difficult to assess outcomes such as survival and transplant-free survival. In addition, there is little evidence (and no comparative evidence) for the effectiveness of odevixibat among PFIC patients with subtypes other than PFIC1 and PFIC2. The impact of PFIC subtype (1 or 2) on the effectiveness of odevixibat in terms of key outcomes (e.g. SBA response and pruritus response) is also uncertain. Finally, the PEDIFIC2 study, the only study with longer-term follow-up, uses a single-arm, open-label design.

7.2 Cost-effectiveness conclusions

The ERG's preferred assumptions increase the probabilistic ICER for odevixibat versus SoC from [redacted] (the company's base-case) to [redacted], and the deterministic ICER from [redacted] (the company's base-case) to [redacted]. Within the ERG's preferred analysis, the most significant contributor to this higher ICER is the exclusion of productivity costs and use of alternative utility values.

The ERG's additional exploratory analyses using this preferred analysis produce ICERs which are in the range of [redacted] to [redacted]. These exploratory analyses highlight the significant influence of the assumptions regarding drug dose and inclusion of caregiver disutilities.

The ERG's exploratory analyses using fully incremental comparison of possible treatment pathways suggest that the "Odevixibat (including PEBD)/LT" treatment pathway, which involves patients starting with odevixibat, then receiving PEBD or LT after odevixibat loss of response, seems to accrue highest QALYs at an ICER of [redacted] versus SoC.

Overall, the ERG considers the following to represent key areas of uncertainty:

- The level of HRQoL experienced by patients who receive odevixibat or SoC over time, especially HRQoL for patients receiving PEBD
- Disutility of caregivers for patients with PFIC, and the appropriateness of including caregiver disutilities in the analyses

- Dosage of odevixibat that would be realised in clinical practice

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9 APPENDICES

Appendix 1: Technical Appendix

All ERG exploratory analyses were undertaken using the company's updated model following response to clarification questions.

EA1: Fix remaining model errors:

a. Exclusion of PEBD surgery costs in the first model cycle

- In worksheet 'Engine_SoC', set cell AE15 to "=X15+Y15"
- In worksheet 'Engine_Odevixibat, set cell AD15 to "=W15+X15"

b. Incorrect estimation of the post-PEBD costs for the PEBD non-responders.

- In worksheet Engine_SoC', set cell BI15 to "=$BI$7*AE15*(1-pebd_response)+$BI$9*(Y15-(AE15*(1-pebd_response)))"
- Drag formula down to update all following cells
- In worksheet 'Engine_Odevixibat', set cell BI15 to "=$BH$7*AD15*(1-pebd_response)+$BH$9*(X15-(AD15*(1-pebd_response)))"
- Drag formula down to update all following cells

c. Inconsistency in the discount rates between costs and QALYs.

- In worksheet "Engine_SoC", in the formulas in cells BS15:CD15, change BR15 to "AVERAGE($AS14:$AS15)".
- Drag the formulas down to apply to all cells
- In worksheet "Engine_Odevixibat, in the formulas in cells BS15:CD15, change BQ15 to "AVERAGE($AR14:$AR15)"
- Drag the formulas down to apply to all cells

d. eMIT prices for UDCA and rifampicin

- In worksheet "Cost data", set cell H24 to £7.97 and cells H27:28 to £8.68

EA2: Use of updated meta-analysis figures for acute and long-term LT mortality

See section 5.3 for further detail on how figures obtained

In Worksheet 'Clinical data - Efficacy', set cell C104 equal to 10.92%

In Worksheet 'Clinical data - Efficacy', set cell C113 equal to 1.42%

EA3: Exclusion of productivity costs

In worksheet "Key_results", select 'Exclude' from the drop down menu in cell C45

EA4: Probability of LT in prior PEBD non-responders same as probability of LT in post-PEBD non-responders

In worksheet "Clinical data - Efficacy", set cell F70 equal to cell E89

EA5: Inclusion of adverse event costs

In worksheet 'Cost data', select "include" from the drop down menu in cell C130 and select the tick box in cell G130

EA6: Use of alternative utility values

In worksheet 'HRQoL data':

- Set cell E18 to "='QoL mapping'!BR98"
- Set cell E19 to "='QoL mapping'!BR99"
- Set cell E20 to "=H18*AVERAGE(C$36:C$37)"
- Set cell E21 to "=H19*AVERAGE(C$36:C$37)"
- Leave current formula in cell E22
- Set cell E23 to "=0.850*E18/0.914"

EA7: ERG preferred base-case

Implement all analyses above together to obtain the ERG's preferred base-case

Additional sensitivity analyses

The following analyses are all undertaken individually on EA7- ERG preferred base-case

EA8: Alternative proportions of patients receiving high dose odevixibat

- *EA8a: Proportion of patients receiving high dose odevixibat=33%*

  In worksheet 'Cost data', set cell C35 equal to 33%

- *EA8b: Proportion of patients receiving high dose odevixibat=50%*

  In worksheet 'Cost data', set cell C35 equal to 50%

- *EA8c: Proportion of patients receiving high dose odevixibat=66%*

  In worksheet 'Cost data', set cell C35 equal to 66%

EA9: General population mortality for non-responders

In worksheet 'Transitions', set cell S15 equal to D15. Drag formula down all cells in the column

In worksheet 'Transitions', set cell X15 equal to D15. Drag formula down all cells in the column

EA10: Excluding caregiver disutilities

In worksheet 'Key results' select "Exclude" from the dropdown menu in cell C40

EA11: Start age of 3 years

In worksheet 'Key results', set cell C17 to 3

EA12: Including PEBD in odevixibat arm

In worksheet 'Key results', select "Include" from the drop down menu in cell C24

EA13: Assuming lower costs of PEBD

In worksheet 'Cost data', set cell C98 to £15,000

EA14: Assuming higher annual loss of response to odevixibat

In worksheet "Clinical data- Efficacy", set cell D26 equal to cell D58

ERG's exploratory full incremental analyses

These analyses were performed using the EA7- ERG preferred base-case model, and two sets of analyses were performed for different population groups.

(a) Full incremental analyses – population 1

These first set of exploratory full incremental analyses were for PFIC patients where PEBD may be needed at some point in the future and the treatment pathways are listed below.

SoC (including PEBD)/LT:

No changes needed to EA7- ERG preferred base-case model. Use the costs and QALYs of SoC arm

SoC (including PEBD)/Odevixibat/LT:

In worksheet 'Transitions':

- Change the formula in cell I15 to "=G15" and drag the formula down to apply to all cells

In worksheet "Engine_SoC",

- change the formula in cell J15 to "=IF($A$1=1, (L14*Transitions!Q15+M14*Transitions!T15)*'Clinical data - Efficacy'!$D$24+J14*(1-Transitions!I15-Transitions!L15), J14*(1-Transitions!G15-Transitions!L15))" and drag the formula down to apply to all cells
- change the formula in cell L15 to "=IF($A$1=1, K14*(Transitions!J15)+L14*(1-Transitions!O15-Transitions!Q15-Transitions!R15-Transitions!S15), J14*(Transitions!G15)+K14*(Transitions!H15)+L14*(1-Transitions!N15-Transitions!P15-Transitions!R15-Transitions!S15))" and drag the formula down to apply to all cells
- change the formula in cell N15 to "=IF($A$1=1,J14*(Transitions!I15)+(L14*Transitions!Q15+M14*Transitions!T15)*(1-'Clinical data - Efficacy'!$D$24)+N14*(1-Transitions!W15-Transitions!X15), L14*Transitions!P15+M14*Transitions!T15+N14*(1-Transitions!W15-Transitions!X15))" and drag the formula down to apply to all cells

- change the formula in cell BE15 to "=U15*($BF$9+IF(D15<18, $BE$4+($BF$4+$BF$2+$BE$2)*H15, $BF$7+$BE$7+($BE$2+$BF$2)*H15) + IF($A$1=1,VLOOKUP(H15,'General population'!$E$12:$I$34,5,TRUE),0))" and drag the formula down to apply to all cells
- change the formula in cell AB4 to "=SUMU4:AA4"

Use the costs and QALYs of SoC arm

Odevixibat (excluding PEBD)/LT

No changes needed to EA7- ERG preferred base-case model. Use the costs and QALYs of odevixibat arm

Odevixibat (including PEBD)/LT

In worksheet 'Key results', select "Include" from the drop down menu in cell C24. Use the costs and QALYs of odevixibat arm

SoC (excluding PEBD)/LT

In worksheet "Clinical data - Efficacy", set cell F50 equal to zero. Use the costs and QALYs of SoC arm

(a) Full incremental analyses – population 2

These second set of exploratory full incremental analyses were for PFIC patients within whom PEBD would be instigated now and the possible treatment pathways are listed below.

PEBD/LT

In worksheet "Engine_SoC",

- set cell L14 equal to zero
- set cell M14 to "='Clinical data - Efficacy'!D57"
- set cell N14 to "1-M14"

Use the costs and QALYs of SoC arm.

PEBD/Odevixibat/LT

In worksheet 'Transitions':

- Change the formula in cell I15 to "=G15" and drag the formula down to apply to all cells

In worksheet "Engine_SoC",

- set cell L14 equal to zero
- set cell M14 to "='Clinical data - Efficacy'!D57"
- set cell J14 to "=(1-M14)*'Clinical data - Efficacy'!D24"

- set cell N14 to "=(1-M14)*(1-'Clinical data - Efficacy'!D24)"
- change the formula in cell J15 to "=IF($A$1=1,(L14*Transitions!Q15+M14*Transitions!T15)*'Clinical data - Efficacy'!$D$24+J14*(1-Transitions!I15-Transitions!L15), J14*(1-Transitions!G15-Transitions!L15))" and drag the formula down to apply to all cells
- change the formula in cell L15 to "=IF($A$1=1, K14*(Transitions!J15)+L14*(1-Transitions!O15-Transitions!Q15-Transitions!R15-Transitions!S15), J14*(Transitions!G15)+K14*(Transitions!H15)+L14*(1-Transitions!N15-Transitions!P15-Transitions!R15-Transitions!S15))" and drag the formula down to apply to all cells
- change the formula in cell N15 to "=IF($A$1=1, J14*(Transitions!I15)+(L14*Transitions!Q15+M14*Transitions!T15)*(1-'Clinical data - Efficacy'!$D$24)+N14*(1-Transitions!W15-Transitions!X15), L14*Transitions!P15+M14*Transitions!T15+N14*(1-Transitions!W15-Transitions!X15))" and drag the formula down to apply to all cells
- change the formula in BE15 to "=U15*($BF$9+IF(D15<18, $BE$4+($BF$4+$BF$2+$BE$2)*H15, $BF$7+$BE$7+($BE$2+$BF$2)*H15) + IF($A$1=1,VLOOKUP(H15,'General population'!$E$12:$I$34,5,TRUE),0))" and drag the formula down to apply to all cells
- change the formula in cell AB4 to "=SUMU4:AA4"

Use the costs and QALYs of SoC arm

Odevixibat (excluding PEBD)/LT

No changes needed to EA7- ERG preferred base-case model. Use the costs and QALYs of odevixibat arm

Odevixibat (including PEBD)/LT

In worksheet 'Key results', select "Include" from the drop down menu in cell C24. Use the costs and QALYs of odevixibat arm

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **12noon, on Wednesday 21 July 2021** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Priority Issues

Issue 1 HRQoL data reported in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.1, page 10 states "The CS does not report on evidence relating to the outcome health-related quality of life (HRQoL), which is listed in the NICE scope." However, the CS does include HRQoL data from PEDFIC1 (PedsQL).	The sentence should be deleted or further clarified to state that HRQoL data were included in the CS.	The statement is incorrect and may mislead the committee. It should be changed to accurately reflect the CS content.	This sentence has been amended to read: "The outcome health-related quality of life (HRQoL) is listed in the NICE scope; the CS reports on some evidence relating to HRQoL in Appendix 8, however evidence for HRQoL is not presented in Section 9.6 of the CS, along with other clinical effectiveness evidence as this was an exploratory outcome in the studies that provided evidence for the CS (see Section 4.2.1.4)."

Issue 2 Criteria for discontinuation in the SmPC

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 3.2, page 26 states: "The draft SmPC does not stipulate criteria for discontinuing treatment with odevixibat."	The SmPC states that: Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat.	This requires correcting in line with the wording in the SmPC.	The ERG agrees. The text has been amended as suggested by the company.

Issue 3 Costing of odevixibat

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.3.3, page 130 – 132 describes a discrepancy between the weight-based categories used for estimating the daily dose in the model and the dosing guidance. The ERG states that they believe that the dose for patients in the upper section of each weight category should be increased and while 40 µg/kg/day is the target dose, the ERG's statements assume that this is the minimum dose a patient should receive. However, this is incorrect as it is not aligned to the EMA recommendation nor the trials that generated the data. To explain further, the 40 and 120 mcg/kg/day doses are "nominal doses". The doses actually studied in clinical trials (and authorised by the EMA) are dose ranges; 26.7 to 53.3 mcg/kg/day for the nominal 40 mcg/kg/day and 80 to 160 mcg/kg/day for the nominal 120 mcg/kg/day dose.	The company propose that this issue be removed from the ERG report.	The dosing applied in the company's model is aligned with the dosing guidance given in the SmPC, the doses used in the clinical trials of odevixibat and the doses that are expected to be used in clinical practice. Table 30 of the ERG report has been recreated from the PEDFIC1 CSR and these were the thresholds that were used to assign the number and type of capsules used in the study. This table is aligned with the dosing information in Table 2 of the CS (page 24) which has been taken from the draft SmPC. When prescribing odevixibat, clinicians should use this table to decide upon the dose. The ERG's assumptions on dosing are incorrect. By retaining this issue, the ERG report concludes that the costs of odevixibat have been understated and thus the cost-effectiveness overstated and uncertainty in results has been increased, however this is not the case.	It was not clear to the ERG from the CS and company's response to clarification question B28 that the doses used were nominal doses and not minimal. Following this clarification provided by the company in the FAC response, the ERG agrees with the company and this discussion has now been removed from the report. In addition, the following text has been added to section 5.2.4.5 page 108, regarding the description of the cost calculations: "During clarification response the company also provided the mean dosage from the PEDFIC1 trial. The ERG estimated the drug acquisition costs based on the mean dose observed in the trial and compared this to costs estimated by the company using the approach outlined above, and found minimal difference in the drug acquisition costs."

Issue 4 Over-estimation of costs of odevixibat

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG's scenario analyses (Section 5.4.2, page 135 to 137) present a scenario analysis that assumes patients receive the dose associated with the next weight category. This is predicated on the statement that the model has understated the cost of odevixibat.	The company request that this scenario be removed.	As per the response the response to Issue 3, dosing in the model reflects the dosing anticipated in clinical practice.	Based on clarification regarding Issue 3 above, the ERG agrees with the company and has removed this scenario from the ERG report.

Issue 5 Description of non-intuitive results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.3.3 issue 7 (page 128 to 129) discusses non-intuitive findings in the company's cost-effectiveness model, whereby the sooner patients discontinue odevixibat, the more favourable the cost-effectiveness. They go on to state "*The reason for this non-intuitive finding is that odevixibat seems to have a high cost-benefit ratio and moving the patients off odevixibat to LT, which has a more favourable cost-benefit ratio, results in lower ICERs.*" However, this statement is not accurate as it implies that this is the sole reason for these results. The company considers that	The section should be amended to include further discussion of the reasons for these results.	As discontinuation rates increase, the average age of a patients still on treatment is decreased. The cost-effectiveness in younger patients is expected to be higher for two reasons: 1. Younger patients fall into lower weight categories and the cost of treatment is lower. 2. Patient utilities in the model are age adjusted and thus QALY gains are higher for younger patients. Thus, any scenario which involves a higher proportion of the time on treatment being at a younger age is likely to lead to more favourable results.	The ERG agrees and amended the text to read: The reason for this non-intuitive finding is that odevixibat seems to have a high cost-benefit ratio and moving the patients off odevixibat to LT, which has a more favourable cost-benefit ratio, results in lower ICERs. In the FAC response (Issue 5), the company suggested that "*As discontinuation rates increase, the average age of a patients still on treatment is decreased. The cost-effectiveness in younger patients is expected to be higher for two reasons: 1)*

these results are driven by the increasing weight of patients leading to increase in costs as patients get older.			*younger patients fall into lower weight categories and the cost of treatment is lower, and 2) patient utilities in the model are age adjusted and thus QALY gains are higher for younger patients. Thus, any scenario which involves a higher proportion of the time on treatment being at a younger age is likely to lead to more favourable results."* The ERG agrees with these points, however in an exploratory analyses conducted by the ERG which kept the weights and utilities of patients constant over time, the finding that the ICER became more favourable to odevixibat with lower response rate or higher discontinuation rate, was maintained.

Issue 6 Incorrect reporting of patient numbers in PEDFIC1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.1.1, page 38/39 states "Of these 62 patients, 48 patients (77.4%) completed the 24-week placebo-controlled treatment, and of these 48 patients 18 (78.2%) were in the odevixibat 40 µg/kg/day arm, 16 (84.2%) were in the odevixibat	Should read: Of these 62 patients, **49** patients (77.4%) completed the 24-week placebo-controlled treatment, and of these **49** patients 18 (78.2%) were in the odevixibat 40 µg/kg/day arm, 16 (84.2%) were in the odevixibat 120 µg/kg/day arm and 15 (75.0%) were in the placebo arm.	The figure is incorrect and should be corrected (minimal impact).	The ERG agrees. The text has been amended as suggested by the company.

120 µg/kg/day arm and 15 (75.0%) were in the placebo arm." The number of patients completing 24-week treatment is incorrect and should be 49 not 48.			

Issue 7 Error in Figure 9 of the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Figure 9 of the ERG report, the ERG omitted two arrows, representing re-transplant (in both arms of the model) and PEBD loss of response (in the comparator arm).	An additional arrow should be added to the LT health state (in both arms) to reflect the possibility of re-transplant, and an additional arrow should be added to the PEBD loss of response health state (in the comparator arm) to reflect the possibility of remaining in this state rather than progressing to another.	The absence of these arrows misrepresents the treatment pathway used in the economic model.	The ERG agrees and has amended the figure in the ERG report

Issue 8 Errors in reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Certain references, statements and values are either incorrect or missing in the ERG report.	The following amendments are proposed: • On page 84 of the ERG report, the ERG incorrectly reference "Kahn et al." for the quality of life study used in the economic model, which should be changed to Khan et al. • In table 20, the ERG incorrectly reported the annual probability of NAPPED LT in PFIC1 with no prior SBD as 7.52%, which should be changed to 5.07%	The references, statements and values are incorrect or missing.	Please see below • The ERG agrees. The text has been amended as suggested by the company. • The ERG agrees. The text has been amended as suggested by the company.

	• On page 109, the underlined statement in the following sentence "The number of visits to specialist centres per year was informed by a clinical expert" should be replaced with "the PICTURE study."		• Text has been amended to the following: "The number of visits to specialist centres per year in the original model and CS was informed by a clinical expert (2 visits per year). Following final results of the PICTURE study, made available to the ERG during clarification (Addendum B), this was changed to [redacted] per year based on the average of [redacted] carers responses."

Additional issues

Issue 9 Comment on non-randomised trial data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.1.3, page 44 states "European Medical Agency guidance on performing clinical trials in medicines recommends that trials aiming to demonstrate/confirm efficacy are controlled, with randomised allocation to arms.[20]" This statement is misleading given that this study is an extension to the randomised study PEDFIC1. As is often the case with extension studies in	We would suggest deleting this and replacing with something like "The open label, uncontrolled study design of PEDFIC2 should be taken into consideration during review of data from that study."	The statement is misleading given the nature of the disease area and the approval by the EMA.	The ERG agrees that further nuance is needed for factual accuracy. The text has been amended to more accurately capture the context of the study design of PEDFIC2: "European Medical Agency guidance on performing clinical trials in medicines recommends that trials aiming to demonstrate/confirm efficacy are controlled, with randomised allocation to arms.[20] The PEDFIC2 study, however, is a long-term

areas of high unmet need, the extension study was uncontrolled and in approving odevixibat the EMA has accepted this data.			extension of the PEDFIC1 RCT, and therefore its design does not contradict these recommendations. It should be borne in mind, however, that additional patients (including patients with additional PFIC subtypes) were recruited directly into the PEDFIC2 study, and therefore the open label, uncontrolled study design of PEDFIC2 should be taken into consideration during review of data from that study (particularly of the Cohort 2 data)."

Issue 10 Interpretation of subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.4.1, page 63 states "However, the company's clarification response[2] (question B10) provides data that indicates [redacted]	This interpretation of the data is incorrect and should be removed. Although there is variation in the response rates, this is likely to be due to the small numbers included in the subgroup analysis and some other confounding baseline variables – there is no evidence for a potential [redacted].	The interpretation is incorrect and may mislead the committee.	The ERG agrees. This passage has been deleted and the paragraph after it has been rephrased to emphasise a lack of statistical significance between treatment arms.

[redacted]."			

Issue 11 Lack of reporting of clinical opinion received

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report omits the expert clinical opinion that was received by Albireo throughout the development of the CS in a number of sections.	The following amendments are proposed: • On page 83 of the ERG report, to add: "The model structure and treatment pathway were validated by a clinical expert." • In table 19 of the ERG report, to add "Validated by a clinical expert" for the Source of the annual loss of response to odevixibat (TP1) • In table 19 of the ERG report, to add "Validated by a clinical expert" for the Source of the annual loss of response to PEBD (TP4) • On page 104, to replace "It was unclear to the ERG how the company decided the most appropriate source to use" with the following text: "At clarification stage (Question B37), the company confirmed that the multiplier was selected by a clinical	The absence of expert clinical opinion in the ERG report understates the face validity of these parameters.	• The text has been amended to "The company stated that the model structure and treatment pathway were validated by a clinical expert" • Following text has been added "validated by the company's clinical advisor" • Following text has been added "validated by the company's clinical advisor" • Text amended in the ERG report to state "At clarification stage (Question B37), the

	expert, but was considered conservative, with the true value likely to be smaller."		company confirmed that the multiplier was selected by a clinical expert, but was considered conservative as the value was likely to decrease as patients get older and become more aware of the stoma bag"

Issue 12 Lack of clarity in the inclusion of AE costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 85, the ERG report that "No treatment-related AE costs or disutilities are applied in the model", without specifying that AE costs are explored in scenario analysis of the CS.	The text is proposed to be changed to "No treatment related disutilities are applied in the model. AE costs are explored in a scenario analysis but were not applied in the base case."	The current statement is incomplete in the description of the model methods and scenarios explored.	The ERG agrees. The text has been amended as suggested by the company.

Issue 13 Lack of accuracy in the reporting of sources collected from an SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report did not state that the sources used to model LT mortality (acute and long-term) were identified as part of an SLR, as described in the CS.	The following amendments are proposed: • In table 19, to add the underlined text in the following statement: "Meta-analysis conducted by the company, <u>with sources identified in an SLR</u>." • In table 19, to add the underlined text in the following statement: "Pooled data analysis of digitised Kaplan Meier curves […], <u>with sources identified in an SLR.</u>"	The CS Appendix 17.9 reported that "The studies identified to inform mortality from LTx […] were identified as part of a systematic literature review", which the ERG report did not fully characterise.	The ERG agrees. The text has been amended as suggested by the company.

	• On page 97, to remove the underlined text in the ERG's following statement: "Relevant data to inform these probabilities were sought from the published literature, although it was not clear how these were identified."		

Issue 14 Lack of clarity in the justification for assumptions made in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Certain assumptions made in the CS are not described in the ERG report alongside their justification or the additional data provided at clarification stage by Albireo.	• On page 88, the ERG report states that "The company's model assumes that if patients have an sBA response they will also have a pruritus response" without specifying that this assumption is based on data provided by Albireo at the clarification stage (Question B7). It is proposed that the underlined statement is added to the ERG's sentence: ", which is based on a data review performed by Albireo, […]". • On page 106, the ERG states that "No wastage costs were included in the model for odevixibat and 100% treatment adherence is assumed" without including Albireo's justification at clarification stage (question B30). It is proposed that the following statement is added to the ERG's sentence: "[…] as demonstrated by the 99% compliance in PEDFIC1." • On page 107, the ERG states that it is "unsure why NHS reference costs were not used to estimate LT costs". It is proposed that the following statement is added: "In response to a clarification question, the company stated that a micro-costing approach using NHS reference costs would	The current statements fail to acknowledge that these assumptions are supported by patient data.	The proposed changed are not factual inaccuracies. However, the ERG has amended the following text in response to each bullet point to add further clarity: • Following text added: "In response to clarification question B7, regarding justification for this assumption, the company stated that this is based on a data review performed by the company, showing that all patients with an sBA response also had a pruritus response." • Following text added: "In response to clarification question B30, the company state that they do not anticipate capsule splitting and therefore no wastage costs are included. In addition,

	underestimate all the resources needed in the year of LT, as documented by Singh et al., 2017(Singh and Longworth 2017) in the UK.		100% treatment adherence is expected based on the 99% median overall compliance in the PEDFIC1 trial and 97% in the PEDFIC2 trial, calculated from the case report forms. These numbers were slightly lower when calculated from the eDiary (93% in PEDFIC1, 96% in PEDFIC2)." • Following text added: "In response to clarification question B33, the company stated that NHS costs were not used as it was not clear how accurately a micro-costing approach would capture all resources needed and the cost from TA443 had been used in previous appraisals."

Marking of confidential data

Issue 15 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 10 the following is marked AIC: [redacted]	This is no longer AIC and can be unmarked.	Correction of confidential marking.	The ERG agrees. The marking has been amended as suggested by the company.

Issue 16 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 10 and 12 the following is marked AIC: The planned [redacted]	This can be remarked as follows: The planned Odevixibat vs External Control [redacted] comparison [redacted] with external controls [redacted]	Correction of confidential marking.	The ERG agrees. The marking has been amended as suggested by the company.

Issue 17 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 32/33 the text relating to numbers of patients enrolled at UK trials centres in PEDFIC1, PEDFIC2 and the phase 2 study is not marked AIC: In addition, PEDFIC1 should read PEDFIC2 in the following sentence: "The Clinical Study Report (CSR)[13] states that patients were enrolled into the PEDFIC1 trial at 33 investigational sites across 14 countries in Europe (18 sites across Belgium, France, Germany, Italy, Netherlands, Poland, Spain, and the UK), the US (6 sites) and rest of world (RoW) (9 sites across Australia, Canada, Israel, and Turkey)."	The text should be marked as follows: The Clinical Study Report (CSR)[12] states that patients were enrolled into the PEDFIC1 trial at 33 investigational sites across 14 countries: France (4 sites), Germany (4 sites), the UK (3 sites), Italy (2 sites), the Netherlands (2 sites), Belgium (1 site), Poland (1 site), Sweden (1 site), the US (8 sites), Turkey (4 sites), Australia (1 site), Canada (1 site), Israel (1 site) and Saudi Arabia (1 site). [redacted] patients were enrolled at sites in the UK.[12] The Clinical Study Report (CSR)[13] states that patients were enrolled into the PEDFIC2 trial at 33 investigational sites across 14 countries in Europe (18 sites across Belgium, France, Germany, Italy, Netherlands, Poland, Spain, and the UK), the US (6 sites) and rest of world (RoW) (9 sites across Australia, Canada, Israel, and Turkey). [redacted] patients were enrolled at sites in the UK.[13] The Phase 2 study (A4250-003) was an exploratory Phase 2 single and multiple dosing open-label dose-escalating study. The CSR[14] reports that the study was conducted across seven sites in Sweden, Denmark, France, Germany and the UK,	Correction of confidential marking.	The ERG agrees. The marking has been amended as suggested by the company.

	however the EU Clinical Trials Register entry for this study (2015-001157-32)[19] states that patients were recruited from sites in Sweden, Denmark, France and Germany, [redacted] enrolled in the UK.		

Issue 18 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 43 and 59 the protocol deviations in PEDFIC2 are not marked AIC.	On page 43 the text should be marked as follows: [redacted] in the PEDFIC2 study had a protocol deviation considered to [redacted]" (CSR, page 97). On page 59 the text should be marked as follows: In the PEDFIC2 study, an important protocol deviation was reported for [redacted] of the 69 patients dosed, as of the cut-off date (CSR,[13] page 97). [redacted].	Correction of confidential marking	The ERG agrees. The marking has been amended as suggested by the company.

Issue 19 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63: part B of figure 5 is not marked confidential	Part B of figure 5 should be marked AIC.	Correction of confidential marking.	The ERG agrees. The marking has been amended as suggested by the company.

Issue 20 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 64: Figure 6, part A is marked confidential.	Figure 6, **part A** does not need to be marked (part B should remain AIC).	Correction of confidential marking.	The ERG agrees. The marking has been amended as suggested by the company.

Issue 21 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 73, Table 16: PEDFIC2 data is marked AIC.	PEDFIC2 data in table 16 does not need to be marked.	Correction of confidential marking.	The ERG agrees. The marking has been amended as suggested by the company.

Additional issue noted by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 110, Table 23. Costs incorrectly reported for post PEBD and post LT health states	Post PEBD health state costs changed from £1,564 to £1,814	During the FAC the ERG noted an error in their report in which the costs for post PEBD and post-LT	This has been amended in the ERG report

	Post-LT health state cost changed from £1,814 to £1,564	in Table 23 had been reported the wrong way round	
Section 4.6.3, page 79. The potential inconsistency between odevixibat dosage used in PEDFIC2 and clinical practice was not included in the key uncertainties relating to the clinical effectiveness.	The following text has been added: "A second key uncertainty relates to an inconsistency between the dose administered in the PEDFIC2 study and the recommended dose detailed in the SmPC. Patients were started on the higher dose to begin with (although some patients received the 40 µg/kg/day dose for 3 or 6 months in PEDFIC1), and therefore it is possible that some patients will have received a higher dose than the recommended starting dose for at least three months. Additionally, patients from PEDFIC2 who achieved an adequate clinical response on the 40 µg/kg/day dose in PEDFIC1 would have received a higher dose in PEDFIC2 than they would have in clinical practice, according to the SmPC dosing instructions. The company clarified that this was to maintain blinding in PEDFIC1 (see Section 4.2.1.2). Nevertheless, the ERG believes that the trial data may not accurately reflect clinical practice and may potentially have led to the efficacy of odevixibat being potentially overestimated in a number of cases in the findings of the PEDFIC2 study."	This issue was omitted and NICE flagged this as a potentially important issue.	This has been amended in the ERG report (and also in the executive summary (Section 1.3) and overall conclusions (Section 7.1)).

References

Singh, Jeshika, and Louise Longworth. 2017. 'COMPARISON OF METHODS FOR ESTIMATING CONTEMPORARY COSTS: AN APPLICATION TO LIVER TRANSPLANTATION IN THE UNITED KINGDOM', *International Journal of Technology Assessment in Health Care*, 33: 620-28.