Medicinrådet

Bilag til Medicinrådets anbefaling vedr. odevixibat til behandling af progressiv familiær intrahepatisk kolestase

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. odevixibat
2. Ansøgers endelige ansøgning vedr. odevixibat

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22. november 2022
MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	14.12.2022
Leverandør	Albireo AB
Lægemiddel	Bylvay (odevixibat)
Ansøgt indikation	Behandling af patienter med progressiv familiær intrahepatisk kolestase (PFIC)

Forhandlingsresultat

Amgros har opnået følgende priser på Bylvay (odevixibat):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Bylvay (odevixibat)	200 µg	30 stk. hårde kapsler	29.312	[redacted]	[redacted]
Bylvay (odevixibat)	400 µg	30 stk. hårde kapsler	58.624	[redacted]	[redacted]
Bylvay (odevixibat)	600 µg	30 stk. hårde kapsler	87.936	[redacted]	[redacted]
Bylvay (odevixibat)	1200 µg	30 stk. hårde kapsler	175.872	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på området, men følgende tabel viser de årlige lægemiddelomkostninger for en patient på 4 år, 10 år og 16 år, der får hhv. 40 og 80 µg/kg dagligt.

Tabel 2: De årlige lægemiddelomkostninger for Bylvay (odevixibat)

Lægemiddel	Dosering	Alder på patient	Gennemsnits-vægt	Årlige lægemiddelomkostninger SAIP pr. år
Bylvay (odevixibat)	40 µg/kg	4 år	[redacted]	[redacted]
Bylvay (odevixibat)	40 µg/kg	10 år	[redacted]	[redacted]
Bylvay (odevixibat)	40 µg/kg	16 år	[redacted]	[redacted]
Bylvay (odevixibat)	80 µg/kg	4 år	[redacted]	[redacted]
Bylvay (odevixibat)	80 µg/kg	10 år	[redacted]	[redacted]
Bylvay (odevixibat)	80 µg/kg	16 år	[redacted]	[redacted]

** Der er taget højde for antagelser om spild og dosering jfr. Medicinrådets vurderingsrapport.*

Status fra andre lande

Norge: Under vurdering[1].
Sverige: Vurderes regionalt[2].
England: Anbefalet i februar 2022[3].

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/odevixibat-bylvay
[2] https://janusinfo.se/download/18.13de125317a50669b3ad105/1624878378867/Odevixibat-vid-PFIC-tidig-bedomningsrapport-210615.pdf
[3] https://www.nice.org.uk/guidance/hst17/chapter/1-Recommendations

Medicinrådet

Application to the DMC for the assessment of odevixibat (Bylvay®) for Progressive Familial Intrahepatic Cholestasis (PFIC)

DMC Version 5.0

Information highlighted in YELLOW in this dossier is considered confidential information

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1. Basic information

Contact information	
Name	Maria Hall
Title **Phone number** **E-mail**	Senior VP Global Market Access, Albireo Pharma +44 7802 625767 maria.hall@albireopharma.com

Overview of the pharmaceutical	
Proprietary name	Bylvay®
Generic name	odevixibat
Marketing authorization holder in Denmark	Albireo AB Arvid Wallgrens Backe 20 413 46 Göteborg Sweden e-mail: medinfo@albireopharma.com
ATC code	A05AX05
Pharmacotherapeutic group	Alimentary tract and metabolism (ATC Level 1: A)
Active substance(s)	odevixibat
Pharmaceutical form(s)	Oral (hard capsules)
Mechanism of action	Odevixibat is a reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT). By blocking the actions of IBAT, odevixibat reduces the amount of bile acid that is transported from the intestines into the liver. This will prevent the build-up of bile acids and damage to the liver tissue.
Dosage regimen	The recommended dose of odevixibat is 40 mcg/kg administered orally once daily in the morning. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 mcg/kg/day.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months and up.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Oral capsules: 200mcg/400mcg/600mcg/1200mcg 30 capsules per package
Orphan drug designation	Yes

2. Abbreviations

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
CEAC	cost-effectiveness acceptability curve
CEP	cost-effectiveness plane
CIC	chronic intrahepatic cholestasis
Cmax	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
DKK	Danish krone
DMC	Danish Medicines Council (Medicinrådet)
DSMB	Data and Safety Monitoring Board
EASL	European Association for the Study of the Liver
EC	European Commission
ECG	electrocardiogram
ED50	dose required to produce 50% of the response
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimension quality of life measure
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19
FIC-(1)	familial intrahepatic cholestasis-(1)
GBP	British pound
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 new-born
HR	hazard ratio
HRQoL	Health-related quality of life
HST	highly specialised technology
IBAT	ileal bile acid transporter
ICER	Incremental cost-effectiveness ratio
IE	ileal exclusion
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INN	International Non-proprietary Name
LTx	liver transplantation
MAA	marketing authorisation application

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MDR3	multidrug resistant 3 protein
MOA	mechanism of action
n	number of subjects with an observation
NAPPED	Natural course and Prognosis of PFIC and Effect of biliary Diversion
NDA	new drug application
NLS	native liver survival
ObsRO	observer reported outcome
ODD	orphan drug designation
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
PSSRU	Personal Social Services Research Unit
QALY	quality adjusted life year
QoL	quality of life
RoW	Rest of World
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
SE	Standard error
SEK	Swedish krone
SF-6D	Short Form 6-Dimension
SoC	standard of care
TEAE(s)	treatment-emergent adverse event(s)
TLV	Tandvårds-och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency)
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

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3. Tables and figures

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4. Summary

4.1 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 surgical 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 [1].

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. Pruritus severity is the leading factor in the decision to seek a liver transplant.

4.2 Current treatment options

There is no pharmaceutical treatment with EMA approval for use in PFIC except for odevixibat. The initial treatment option for PFIC is nutritional management and off-label oral therapies. Off-label treatments include ursodeoxycholic acid (UDCA) and rifampicin to reduce pruritus [3]. A minority of patients respond to these medications, and do so only transiently [4].

Once pharmaceutical options have been exhausted due to escalating symptoms of intractable pruritus, growth failure and nutritional deficiencies, surgical biliary diversion (SBD) (e.g., partial external biliary diversion, PEBD), is an option. PEBD aims to decrease the size of the bile acid pool by interrupting the enterohepatic circulation [5] and involves use of a 10–15 cm jejunal conduit between the fundus of the gallbladder and abdominal skin where a permanent stoma is created, requiring use of a stoma bag [1]. Diversion of bile interrupts the enterohepatic circulation of bile salts, diminishes subsequent reuptake and decreases the pool of bile salts. 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 [55].

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 [56]. 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 [57].

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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 [6] [7].

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.

4.3 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 and is considered a medicinal alternative to surgical biliary diversion. European marketing approval for odevixibat was granted on July 16, 2021 for the treatment of PFIC in patients aged 6 months and older (https://www.ema.europa.eu/en/medicines/human/EPAR/bylvay) [8].

Odevixibat is an oral therapy administered once daily in the morning [8]. 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 [8]. 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 [8].

The expected benefit of treatment with odevixibat in Denmark is that patients with PFIC treated with odevixibat will be able to avoid surgical biliary diversion (e.g., PEBD) and the associated difficulties with having a stoma bad, and may be able to avoid the need for liver transplantation entirely. For PFIC patients who do eventually require liver transplantation, the need for liver transplantation would be delayed and patients would be better off in the period prior to when liver transplantation becomes necessary and possible in Denmark.

4.4 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 [9] [10]. 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 [11] [12]. 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.

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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) [10]. 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 for more than 72 weeks and reductions in sBA have been maintained. In the PEDFIC1 trial 43.5% of patients treated at 40 µg/kg/day met response criteria for lowering sBA (at least a 70% reduction from baseline or reaching a level ≤70 µmol/L) [9], and 25.0% of non-responders at 40 µg/kg/day did respond following increase of the dose to 120 µg/kg/day [13]. This results in an overall estimated response rate of 57.63%.

Pruritus response to treatment with odevixibat reported in the PEDFIC1 study is even stronger than the reduction in sBA. Taking the % of patients reporting a positive pruritus response at least 50% of the time as response criteria, 73.9% of patients treated at 40 µg/kg/day met response criteria [9], and 37.5% of non-responders at 40 responders at 40 µg/kg/day did respond following increase of the dose to 120 µg/kg/day [13]. This results in an overall estimated response rate of 83.7%.

The clinical relevance of this decrease in sBA 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 [5] [14].

Odevixibat directly addresses the elevated sBA 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.

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.

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

4.5 Economic 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 (base on off-label medication and PEBD surgery). A life-time horizon (maximum age 100) 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.

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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.

In the base case, PFIC patients accrued an additional [redacted]) vs. patients treated with Standard of Care at an additional cost of [redacted] (applying discount rates of 3.5%, 2.5, and 1.5%, for years < 35, 36-70, 71+ respectively). This results in a base case ICER of DKK [redacted] / QALY. 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.

While the prevalence of PFIC in Denmark is subject to uncertainty, the total current population of PFIC patients has been estimated at around 10 and it has been estimated that around half of the population might be eligible for treatment with odevixibat. The estimated budget impact in year 1 was [redacted] patients in Denmark were treated with odevixibat, growing to [redacted] PFIC patients were expected to be treated with odevixibat.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 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 [2].

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 [15]. 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 (via the Ileal Bile Acid Transporter (IBAT)) back into the bloodstream so they can return to the liver to be reused.

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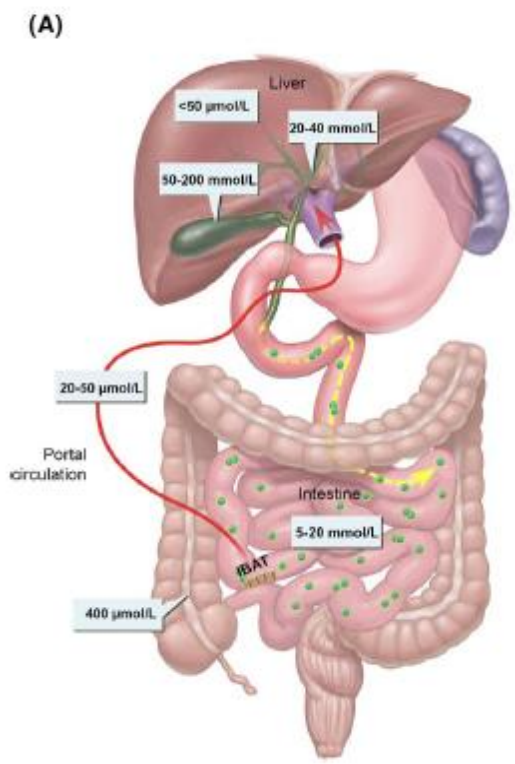
Figure 1. Bile acid cycle



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, Chen Z, Romero R, et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. The Journal of Pediatrics. 2015;167(2):390-396.e393. [16]

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 [15].

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 [1]. 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 [1].

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 [15]. It is considered to be induced by the stimulation of nonmyelinated subepidermal free nerve ends due to increased serum bile acids (sBA) [17].

5.1.2 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 1), although at least three other subtypes have been described in the literature [1] [18] [7] [19]. PFIC1 and PFIC2 together represent approximately two-thirds of cases of PFIC, and PFIC3 approximately one-third [20]. 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.

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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.

PFIC1 is due to mutations in the ATP8B1 gene, resulting in a deficiency of the FIC1 protein. The FIC1 protein is located on the canalicular membrane of hepatocytes and facilitates the movement of phospholipids from the outer to the inner leaflet of the plasma membrane.

PFIC2, also referred to as bile salt export pump (BSEP) deficiency, is due to mutations in the ABCB11 gene, resulting in a deficiency of the BSEP. BSEP is a transporter protein expressed at the canalicular membrane of hepatocytes and is the primary exporter of bile acids. PFIC2 can be further subdivided based on the BSEP genetic variant. Three BSEP variants are reported (BSEP1, BSEP2, and BSEP3).

The BSEP3 (or "truncated BSEP") variant refers to mutations that are predicted to have a non-functional protein and have the most severe disease form of PFIC2 (e.g. lowest native liver survival, hepatocellular carcinoma) [5].

PFIC3 is caused by mutations in the ABCB4 gene resulting in a deficiency of the multidrug resistance protein 3 (MDR3). MDR3 is a phospholipid translocase involved in phospholipid secretion.

PFIC types 1 and 2 have an episodic form, referred to as benign recurrent intrahepatic cholestasis types 1 and 2. It is now generally recognized that, within each subtype, PFIC and the episodic forms represent two extremes of a continuous spectrum of phenotypes of the one disease [21].

5.1.3 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 PFIC2 but the severity of the condition differs between individuals.

As shown in Table 1, 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 [18].

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Table 1. 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 (*ATP8B1*)	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.
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 [18] 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), loss of sleep, irritability, poor attention, and impaired school performance [19].

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Pruritus is one of the two indications for liver transplantation in children with PFIC. [redacted] [22].

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 [4].

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) [23]. Portal hypertension and decompensation may be evident in the first year of life in PFIC2 and in early childhood in PFIC1 [18] [20].

PFIC results in progressive liver disease, usually progressing to cirrhosis within the first decade of life, that typically leads to liver failure [19]. 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 [24]. Those with an *ABCB4* mutation (PFIC3) have a more heterogeneous presentation and may be diagnosed later in childhood [18]. Progression to cirrhosis is typically slower in patients with PFIC3, and is usually first identified in late childhood and young adulthood [1] [24].

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 new born (HDN); late HDN (seen in infants aged 1 week to 6 months) may be associated with serious and life threatening intracranial haemorrhage [25].

Individuals with PFIC may also display signs of rickets and osteopenia and have an increased risk of fractures associated with vitamin D deficiency [26] [27].

Benign recurrent intrahepatic cholestasis is a type of PFIC characterised by episodes of cholestasis lasting from weeks to months, with irresistible pruritus. In a proportion of those with benign recurrent intrahepatic cholestasis, 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 benign recurrent intrahepatic cholestasis phenotype later evolved into a severe PFIC1 phenotype [14]. Similarly, 11 patients who previously presented with a benign recurrent intrahepatic cholestasis type 2 phenotype later presented with severe BSEP

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deficiency (PFIC2) phenotypes (i.e. continuous cholestasis and/or pruritus and continuous hepatocellular damage) and had pathological mutations [5].

5.1.4 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 [5] [14]. PFIC1 and PFIC2 patients underwent SBD at a median age of 5.9 years and 2.3 years, respectively [5] [14].

Only 44% of PFIC1 patients and 32% of PFIC2 patients were alive with their native liver at 18 years of age [5] [14]. 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 ($p<0.001$) [5].

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 [28].

5.1.5 Mortality

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) [23]. Therefore, without LTx, PFIC may lead to fatal liver conditions, including end-stage liver disease and liver cancer, as early as in childhood (Table 1). 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 reports pre-transplant mortality to be 9% for PFIC1 and 5% for PFIC2 [5] [29] [30].

Mortality is generally reported in studies following LTx (Table 2). Varamparampil et al. 2019 observed increased mortality in PFIC1 following LTx compared to PFIC2/3/4 (27% compared to 15%) [31]. Ruth et al. 2018 noted earlier presentation of disease was found to be significantly associated with mortality ($p< 0.01$) for PFIC1 [28]. In contrast, one study observed that for PFIC3, living-donor LTx for PFIC3 has favourable outcome with 0% mortality at 3 years follow-up [32].

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) [33].

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Table 2. Mortality rates in European and global studies

Study	Country	Methods	Population	Age at transplant	Mortality
Acar (2019) [32]	Turkey	Retrospective data analysis	22 patients with PFIC3	Median 2.4 years (n=13)	PFIC3: 0% (3 years post-LTx)
Davit-Spraul (2010) [33]	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) [28]	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) [34]	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) [35]	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) [5]	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) [14]	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) [36]	Germany	Retrospective chart review: 15-year follow-up	49 children with PFIC	38/49 (76%) underwent LT. PFIC1 and PFIC2 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

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cholestasis of pregnancy; LPAC, low phospholipid-associated cholestasis; LTx, liver transplant; NR, not reported; PFIC, progressive intrahepatic cholestasis

5.1.6 Impact of symptoms on patients with PFIC

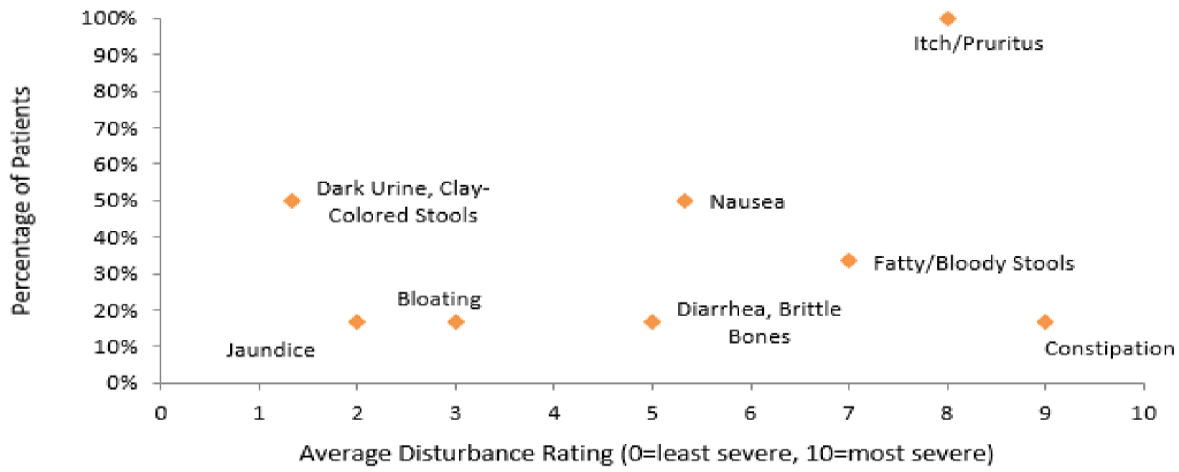
PFIC may manifest with many symptoms, and there are several aspects of the condition that have a negative impact on health-related quality of life (HRQoL).

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.

As shown in Figure 2, pruritus is the most common and debilitating symptom, with pruritus-related sleep disturbance reported by 67% of PFIC patients [37]. 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) [37].

Again, highlighting the gravity of this symptom, [redacted] [22].

Figure 2. Disturbance rating for PFIC symptoms



Source: Adapted from Torfgard et al. 2018 [37]

Growth retardation and failure to thrive is another worrying symptom for carers and clinicians, particularly affecting PFIC1 patients (Table 3).

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Table 3. 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 HRQoL compared to healthy children [16]. PedsQL and Patient Satisfaction Questionnaire (PSQ) have been used most frequently to measure HRQoL in PFIC; however these instruments may not adequately assess the specific symptoms of PFIC [23].

Three studies have reported HRQoL outcomes in patients with PFIC after LTx and partial external biliary diversion (PEBD) surgery [38] [39].

In one study (Yee, 2018) patients who underwent SBD all experienced improvements in HRQoL, mainly due to improved sleep (73.4%), improved mood (67.4%) and less itching (63.3%) [39]. Wassman et al. (2018) reported that post-PEBD HRQoL is similar to healthy children. However, 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 [38].

Overall HRQoL before and after PEBD surgery was reported in only one study of 7 PFIC patients age 10-19 years [40]. 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 HRQoL. Among younger patients (age 10-11), HRQoL improved following PEBD surgery. Alternatively, worsening HRQoL or no change in HRQoL was noted in older patients (age 12-19, see Figure 3) [40].

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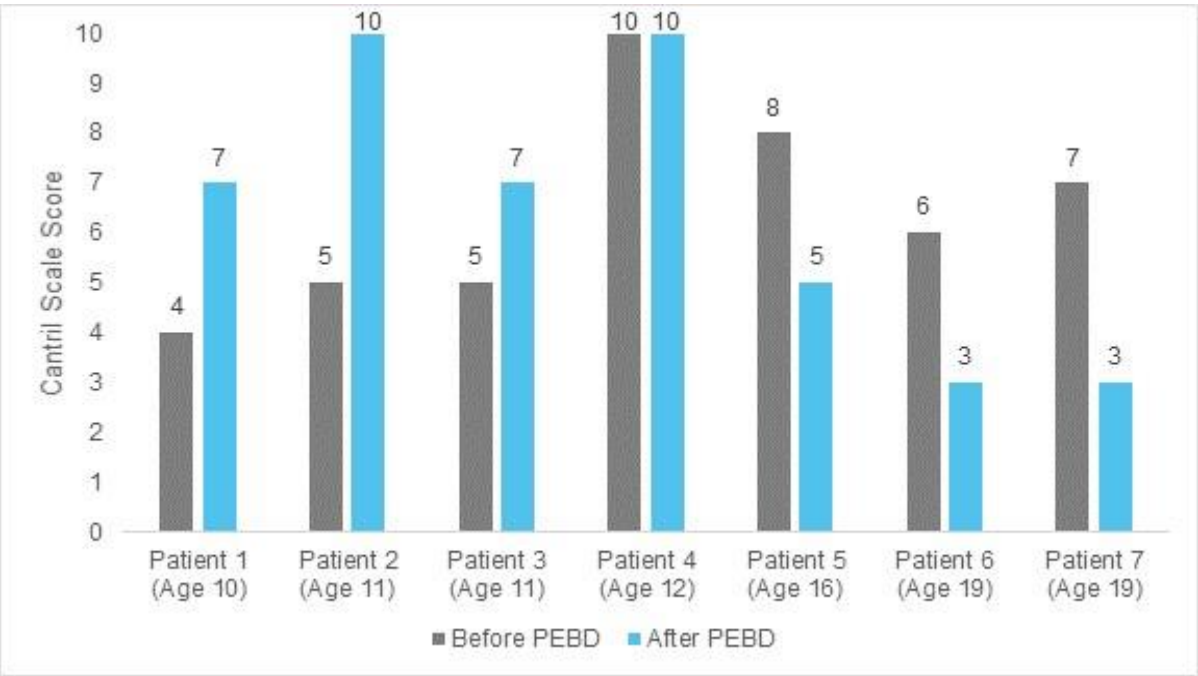
Figure 3. Health-related quality of life before and after PEBD surgery



Source: Kwak et al, 2005 [40]

Wassman et al. (2018) also reported HRQoL 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 [38]. 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 HRQoL scores than the healthy controls. The study by Yee et al (2018) observed that LTx was associated with more frequent post-surgery complications than biliary diversion [39]. 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 [41].

Many individuals with PFIC and their caregivers tend to be anxious about LTx because of the extreme nature of the procedure and associated risks.

The further complications and impact of LTx on patients and caregivers is discussed in section 5.2.1.4

5.1.7 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

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itching every few hours, such as applying lotion, showering, foot soaks and distraction techniques such as tickling [42].

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 [26].

5.1.8 Impact of odevixibat

Current off-label pharmacological treatment is ineffective, leading to the need for surgical procedures (e.g. 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.

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

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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 analogue of partial external biliary diversion (PEBD) surgery, which avoids the highly invasive procedure and follow-up care involving a stoma bag.

By improving symptoms such as pruritus, sleep and growth (height and weight z-scores), delaying disease progression and potentially avoiding entirely the need for 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.

5.1.9 Subgroups with different efficacy

The mechanism of action of odevixibat requires that the enterohepatic circulation of bile acids and bile salt transport into biliary canaliculi is preserved. Conditions, medications or surgical procedures that impair either gastrointestinal motility, or enterohepatic circulation of bile acids, including bile salt transport to biliary canaliculi have the potential to reduce the efficacy of odevixibat. For this reason, patients with PFIC2 who have a complete absence or lack of function of Bile Salt Export Pump (BSEP) protein (i.e. patients with BSEP3 subtype of PFIC2) will not respond to odevixibat.

There are limited or no clinical data with odevixibat in PFIC subtypes other than 1 and 2. In the clinical studies, only 5 patients with PFIC3 and 1 patient with MyoB5 mutation (i.e. PFIC6) were included (see section 7.1.2.2: long term follow-up study cohort 2). Albeit the very limited data available for these patients in cohort 2, Albireo has extensively and satisfactorily substantiated to the EMA that extrapolation to a broad PFIC population is justified [43]. Although it has to be acknowledged that the pathomechanisms of various subtypes of PFIC differ considerably, extrapolation is based on: 1) the fact that odevixibat inhibits the IBAT receptor which is universally shared in all PFIC patients, 2) discussion on potential limitations for extrapolation as mentioned in the Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018) and 3)

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the observed clinical relevant reductions in pruritus in all studied PFIC types, provided some residual function of the various transporters in the hepatocyte exists. Therefore, a general indication in PFIC can be supported [43].

Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Periodic liver function tests should be considered for patients with severe hepatic impairment.

5.1.10 Patient populations relevant for this application

PFIC is a rare disease estimated to affect between one in every 50,000 to 100,000 children born worldwide [20]. 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 [20].

KOLs have been unable to provide precise numbers for the prevalence and incidence of PFIC patients in Denmark. A hepatologist from Aarhus University Hospital advised that there are approximately 10 PFIC patients in total across Denmark, and about half of these would be eligible for treatment with odevixibat (e.g. due to absence of liver transplantation). Estimated incidence, prevalence (Table 4) and estimated number of eligible patients to be treated with odevixibat (Table 5) in Denmark are based on extrapolation of the available KOL feedback under the assumption that there would be a new PFIC case every 2 years in Denmark.

In terms of gender, recent reviews suggest PFIC affects males and females equally [18].

Table 4. Incidence and prevalence in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	0	1	0	1	0
Prevalence in Denmark	8	9	9	10	10
Global prevalence *	1:50,000-1:100,000 births	1:50,000-1:100,000 births	1:50,000-1:100,000 births	1:50,000-1:100,000 births	1:50,000-1:10,0000 births

*[20]

Table 5. Estimated number of patients eligible for treatment with odevixibat

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to be eligible to use the pharmaceutical in the coming years	6	6	7	7	8

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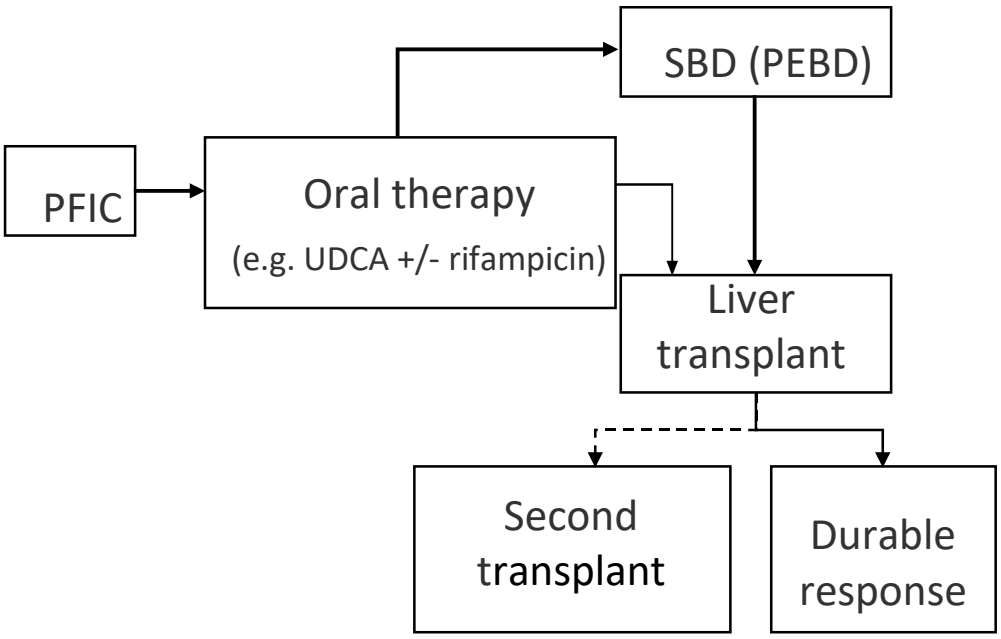
5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

There are currently no treatment guidelines in Denmark for the treatment of patients with PFIC. KOL feedback indicates that treatment with off-label medications for pruritus is offered, and further feedback informs that is surgical biliary diversion (i.e., PEBD surgery) is also offered, as in other countries. Liver transplantation surgery is considered where patients experience liver failure, cirrhosis, hepatocellular carcinoma, and persistent pruritus.

The treatment pathway for PFIC in Denmark is shown in Figure 4.

Figure 4. Current treatment pathway for PFIC



Notes: PEBD, partial external biliary diversion, SBD, surgical bile diversion; UDCA, ursodeoxycholic acid; SBD is most commonly PEBD

5.2.1.1 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 [44]. Calcium intake and adequate exposure to sunlight are also essential.

Deoxycholic acid may also be included to assist in fat absorption.

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5.2.1.2 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 other than the recently approved odevixibat.

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 [4].

UDCA is commonly prescribed because of its ability to promote bile flow which can subsequently assist with pruritus; however not all patients respond [1] [4]. 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 [23] [45] [33]. 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 [33].

In the literature review carried out for this assessment, 20 studies were identified that investigated UDCA for treatment of PFIC (Appendix A – Literature search for efficacy and safety of intervention and comparator(s)). 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 [45]. 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 [46]. 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 [47].

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.

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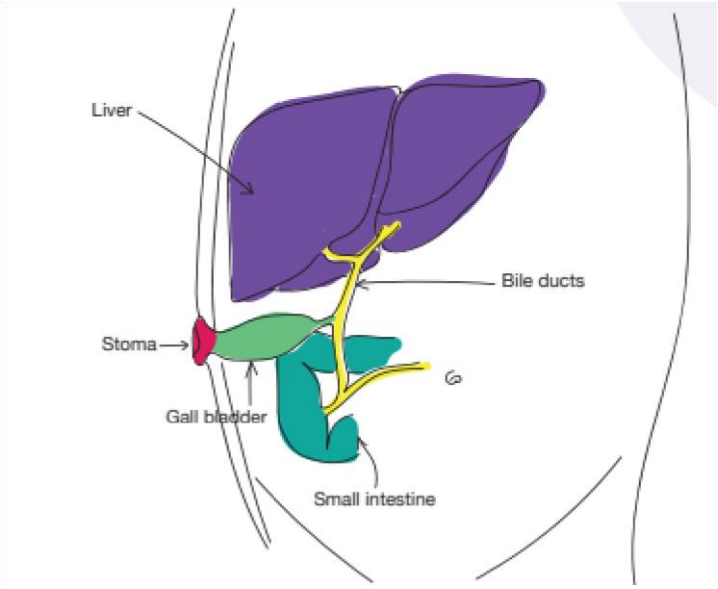
Other off-label therapies that are used less frequently than UDCA and rifampicin include antihistamines such as chlorpheniramine to alleviate pruritus. Although antihistamines do not affect serum bile acids, they may reduce the sensation of pruritus [48]. Cholestyramine is an oral bile acid binding resin. It forms nonabsorbable micelles with the bile acids in the intestines and prevents bile acids from entering the enterohepatic cycle [1].

5.2.1.3 Surgical biliary diversion (e.g., PEBD)

Pruritus that is intractable despite medical treatment, elevated sBA, growth failure and nutritional deficiencies necessitate 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 reduce sBA, 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 PFIC2 [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 5) [1]. Diversion of bile interrupts the enterohepatic circulation of bile salts, diminishes subsequent reuptake and decreases the pool of bile salts.

Figure 5. Partial external biliary diversion



Source: Children's Liver Disease Foundation, (2019) [44]

PEBD is often used as the first line surgery in PFIC1 and PFIC2 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 [49] [50] [51].

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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	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 [52]

Results from the NAPPED study show that SBD is associated with a significant decrease in the levels of sBAs in PFIC1 and PFIC2 patients [5] [14]. 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 [5] [14]. Patients with PFIC2 have significantly higher native liver survival after biliary diversion surgery (Figure 24). Similarly, in PFIC1 SBD tended to be associated with NLS (Figure 26).

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 [5] [14] [30]. 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 25) [5]. 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 27) [14].

For further results from the NAPPED study see section 7.2.

A systematic literature review and meta-analysis by Verkade et al (2020) [53] 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 [52]. In this analysis, in ten studies that evaluated pruritus improvement post-PEBD, [redacted]

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[redacted]

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	49	35	35
Post PEBD level	0.98, <0.0001	0.86, <0.0001	0.72, 0.04
Absolute reduction*	0.77, <0.0001	0.78, 0.003	0.57, 0.32
Percent reduction*	0.94, <0.0001	0.83, <0.0001	0.40, 0.167
Long-term response (decreased need for liver transplantation)			
Patients, n	32	18	18
Post PEBD level	0.95, <0.0001	0.90, <0.0001	0.61, 0.23
Absolute reduction*	0.79, <0.0001	0.88, <0.0001	0.51, 0.46
Percent reduction*	0.92, <0.0001	0.90, <0.0001	0.50, 0.40

* 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 [52]

However, for many patients, biliary diversion is not a permanent solution because of refractory pruritus or end-stage liver disease [23] [54]. While successful surgery is associated with reduction in SBA, improved pruritus, better sleep and improved liver function, pruritus may return after a few years [49]. 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 [49].

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 [19].

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 [55].

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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 [56]. 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 [57].

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 [19]. As with any surgery there is a risk of complications with PIBD.

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 [5] [14]). 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.

5.2.1.4 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 [6] [7]. 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] [18]. 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 [34].

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% [58]. 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

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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 [59].

The need for suitable organ donors also needs to be considered.

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 [60] (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 single centre in the US. Median follow-up was 12 years. Leading indications for liver transplantation were cholestatic liver disease (40%), re-transplantation (21%), and fulminant hepatic failure (14%). Source: Venick et al, 2018 [60]

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.

5.2.2 Choice of comparator

There are no EMA approved pharmaceutical therapies for treatment of PFIC other than odevixibat. Odevixibat is considered as the medicinal analogue of partial external biliary diversion (PEBD) surgery (i.e. surgical biliary diversion, SBD) and therefore standard of care including PEBD may be considered as the relevant comparator.

Off-label oral drug treatments, such as ursodeoxycholic acid (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. However, off-label medications to treat PFIC does not represent a direct comparator.

5.2.3 Description of the comparator

There are no pharmaceutical comparators to odevixibat for treatment of PFIC. Standard care in Denmark may include off-label UDCA, rifampicin, cholestyramine and/or naltrexone to treat symptoms, and PEBD surgery (described above in section 5.2.1.3) prior to liver transplantation.

5.3 The intervention

Odevixibat (Brand name: Bylvay®) 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

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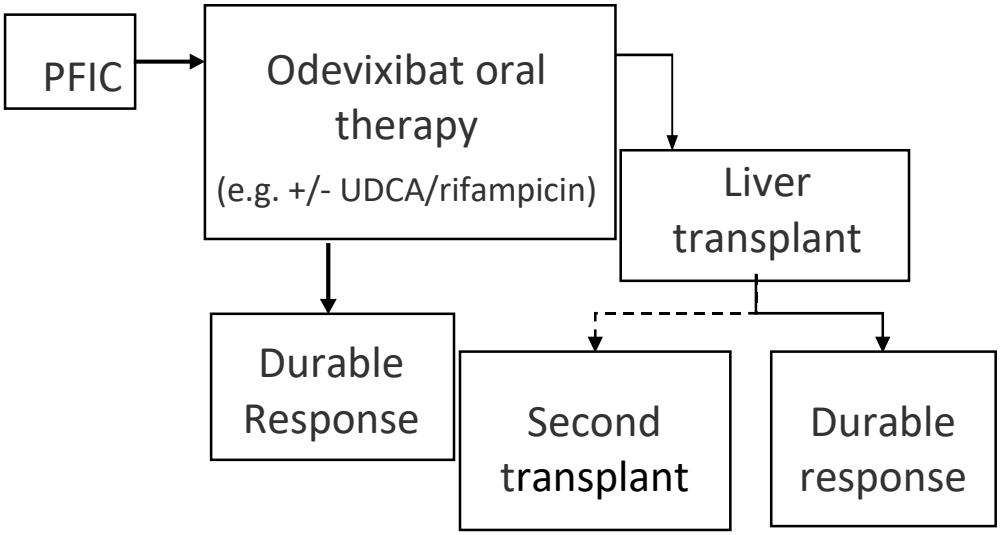
bile acids through the colon and lowering hepatic bile acid load and serum bile acids (EMA, 2021). By inhibiting the IBAT with high selectivity and potency, odevixibat has the potential to reduce the systemic accumulation of bile acids that result from cholestasis, relieve pruritus, improve liver function, and modify the progression of liver damage in patients with PFIC without surgical intervention.

Odevixibat is a once-a-day orally administered medication approved for the treatment of PFIC in children 6 months and older [8]. 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 represented in Figure 6 These off-label medications may include UDCA, rifampicin, cholestyramine and/or naltrexone to treat symptoms. Dosing information for odevixibat is presented in Table 9.

Figure 6. Anticipated treatment pathway for PFIC using odevixibat



Note: UDCA, ursodeoxycholic acid

Table 9. Odevixibat treatment and dosing

Subject	Description
Pharmaceutical formulation	Hard capsules produced in 4 strengths: 200 µg, 400 µg, 600 µg, and 1200 µg.
Method of administration	Odevixibat (Bylvay®) is for oral use. To be taken with or without food in the administration morning [8]. 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.
Doses	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 [8] Number of Bylvay® capsules needed to achieve the nominal dose of 40 µg/kg/day

Body weight (kg)	Number of 200 µg capsules		Number of 400 µg capsules

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<table>
<tr><th>Subject</th><th>Description</th></tr>
<tr><td></td><td>
<table>
<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>
<tr><td>45.5 to < 55.5</td><td>10</td><td>or</td><td>5</td></tr>
<tr><td>≥ 55.5</td><td>12</td><td>or</td><td>6</td></tr>
</table>
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 mcg/kg/day dose, with a maximum daily dose of 7200 µg per day.

Number of Bylvay® capsules needed to achieve the nominal dose of 120 µg/kg/day
<table>
<tr><td>Body weight (kg)</td><td>Number of 600 µg capsules</td><td></td><td>Number of 1 200 µg capsules</td></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>
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<tr><td>≥ 55.5</td><td>12</td><td>or</td><td>6</td></tr>
</table>
Capsule strength/number in bold is recommended based on predicted ease of administration.
</td></tr>
<tr><td>Dosing frequency</td><td>Administered orally once daily in the morning. Odevixibat can be taken with or without food [8].</td></tr>
<tr><td>Average length of a course of treatment</td><td>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.</td></tr>
<tr><td>Anticipated average Interval between courses of treatments</td><td>Not applicable</td></tr>
<tr><td>Anticipated number of repeat courses of treatments</td><td>Not applicable</td></tr>
<tr><td>Dose adjustments</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. 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 [8].</td></tr>
</table>

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Subject	Description
Diagnostic Testing and Monitoring	Assessment of liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and total bilirubin) is recommended for all patients prior to initiating Bylvay®, with monitoring per standard clinical practice. For patients with liver function test elevations, more frequent monitoring should be considered. Assessment of fat-soluble vitamin levels (Vitamins A, D, E) and international normalised ratio (INR) are recommended for all patients prior to initiating Bylvay®, with monitoring per standard clinical practice.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A detailed description of the literature search (conducted March 25, 2021) is provided in Appendix A – Literature search for efficacy and safety of intervention and comparator(s). In summary, Albireo Pharma has used a global systemic literature review (SLR) as the evidence base for this submission.

A full PRISMA diagram outlining the selection process in the global SLR is given in the Appendix A – Literature search for efficacy and safety of intervention and comparator(s) with a full list of exclusions on a full-text level.

6.2 List of relevant studies

Odevixibat has been approved by both the EMA and FDA, based on the results of the Phase 3 PEDFIC1 trial.

Table 10. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Manuscript accepted, expected publication Q2 2022 NICE Highly Specialised Technology Evaluation Odevixibat for progressive familial intrahepatic cholestasis [ID1570] Committee Papers [61] Bylvay - European Public Assessment Report [43]	A4250-005: A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC1)	NCT03566238	May 16, 2018 - July 28, 2020
	A4250-008: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With Progressive Familial	NCT03659916	September 28, 2018 – Likely 2023

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
	Intrahepatic Cholestasis Types 1 and 2 (PEDFIC2)		

For detailed information about included studies, refer to Appendix B – Main characteristics of included studies.

An exploratory single-arm open-label Phase 2 study to demonstrate the safety and efficacy of odevixibat (A4250) in children with cholestatic pruritus (Study A4250-003, NCT02630875) was conducted between August 25, 2015 – March 17, 2017. Additionally, an ongoing Compassionate Use / Expanded Access Program exists for patients to access odevixibat (NCT04483531), but this is not included in this assessment.

Furthermore, [redacted]

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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.

- 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 [14]

PFIC2: van Wessel et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. Journal of Hepatology 2020 [5]

7. Efficacy and safety

PFIC is an orphan disease, with odevixibat being the first medicine authorized by the EMA/FDA for treatment. Consequently, there is one phase 3 randomised controlled study comparing odevixibat to placebo directly (PEDFIC1), as well as an ongoing open-label extension study (PEDFIC2).

7.1 Efficacy and safety of odevixibat compared to placebo for patients with PFIC

7.1.1 Relevant studies

7.1.1.1 PEDFIC1

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 [9] [10]. Patients who completed the PEDFIC1 treatment period could continue into an optional 72-week open-label extension study (PEDFIC2; 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 7). The study was conducted at sites in the US, Canada, the EU, the Middle East, and Australia.

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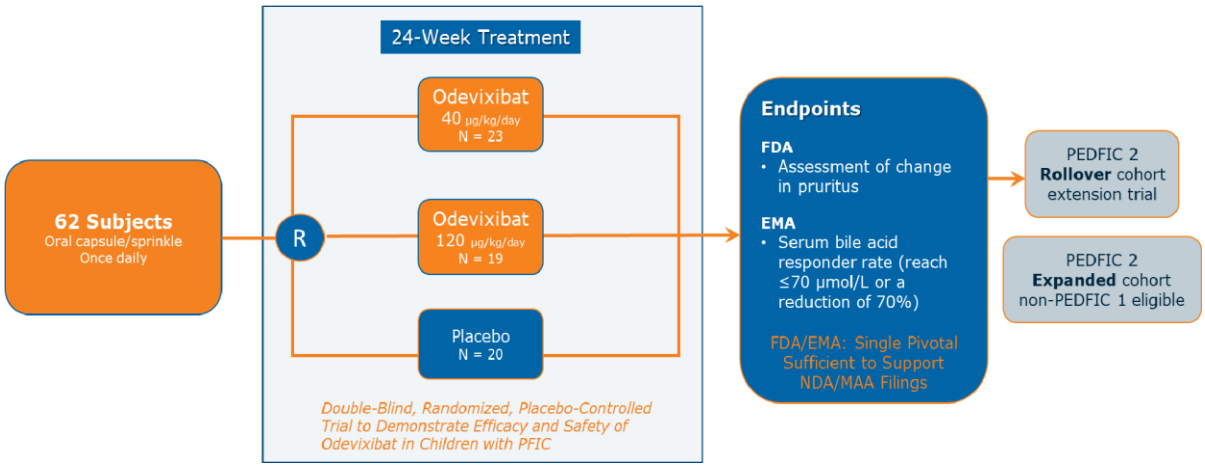
Figure 7. PEDFIC1 phase 3 study design



Source: PEDFIC1 CSR [9]; Thompson et al, 2020 [10]

Baseline demographics and characteristics are described in Table 11. 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 11. 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: PEDFIC1 CSR [9]; Thompson 2020 [10]

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.

7.1.1.2 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 8) [11] [12]. 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.

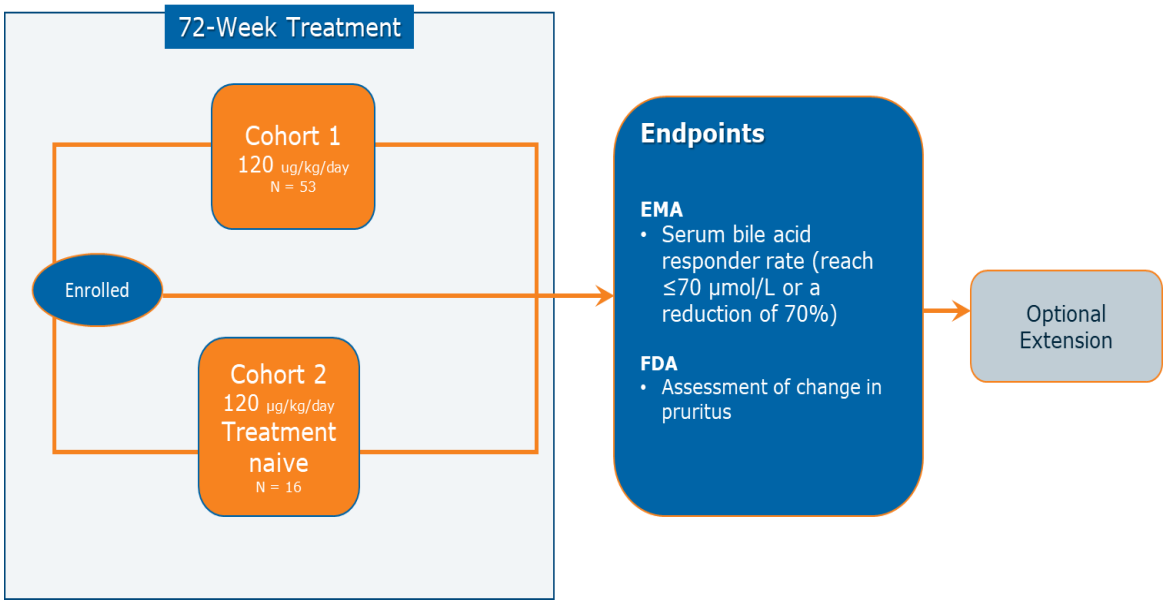
Eligible patients were enrolled into this open-label extension study and treated with a daily dose of 120 µg/kg/day of odevixibat for 72 weeks.

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.

[redacted]

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 8. PEDFIC2 open-label extension study



Note: patient numbers are as per the data cut-off of 15 July 2020
Source: PEDFIC2 CSR [11]; Thompson et al, 2020 [12]

Patient characteristics for PEDFIC2 are displayed in Table 12. 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%). [redacted]

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.

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Table 12. Summary of patient characteristics for PEDFIC2

	Cohort 1 PEDFIC1			Cohort 2 Treatment naïve
	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 – 12.6)	37.35 (2.2 – 10.4)	41.48 (11.2 – 19.2)

Source: PEDFIC2 CSR [11]; Thompson et al, 2020 [12]

For further details of study characteristics refer to Appendix B – Main characteristics of included studies. For further details of baseline characteristics of patients included in each study refer to Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.1.2 Efficacy and safety – results per study

7.1.2.1 PEDFIC1 results

7.1.2.1.1 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), summarized in Table 13. 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.

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Table 13. 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)	(23.19, 65.51)	(6.05, 45.57)	(19.57, 49.55)
Proportion difference without adjusting for stratification factors (odevixibat — placebo)		0.435	0.211	0.333
95% CI[a]		(0.2195, 0.6551)	(0.0210, 0.4557)	(0.0861, 0.4955)
Proportion difference adjusting for stratification factors (odevixibat — placebo)		0.441	0.216	0.307
95% CI[b]		(0.2361, 0.6464)	(-0.0050, 0.4380)	(0.1260, 0.4879)
Odds Ratio (odevixibat / Placebo)		NC	NC	NC
95% CI[c]		(4.228, -)	(1.002, -)	(2.767, -)
1-sided p-value[d]		0.0003	0.0174	0.0015
1-sided "adjusted" p-value[e]		0.0015	0.0174	-
Proportion of positive pruritus assessments				
mean (SE)	28.74 (5.209)	58.31 (6.205)	47.69 (8.110)	53.51 (5.006)
Median	23.35	60.12	45.51	58.04
min, max	0.9, 79.2	1.8, 97	0, 91.3	0, 97
LS mean (SE)[f]	30.10 (9.119)	58.34 (8.580)	51.81 (9.459)	55.08 (7.639)
LS mean difference (SE) (odevixibat — placebo)[f]		28.23 (9.182)	21.71 (9.892)	24.97 (8.240)
95% CI[f]		(9.83, 46.64)	(1.87, 41.54)	(8.45, 41.49)
1-sided p-value[f]		0.0016	0.0163	0.0019
1-sided "adjusted" p-value[e]		0.0019	0.0163	-

Notes: NC = not calculable

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 (1991) adjusting for stratification factors.

d. Based on the Cochran-Mantel-Haenszel test adjusting for stratification factor (PFIC type).

e. For an individual dose (40 µg/kg/day / 120 µg/kg/day), 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. based on ANCOVA model with rounded AM and PM baseline scores as covariates, and treatment group and stratification factors (PFIC type and age category) as fixed effects

Source: PEDFIC1 CSR [9]

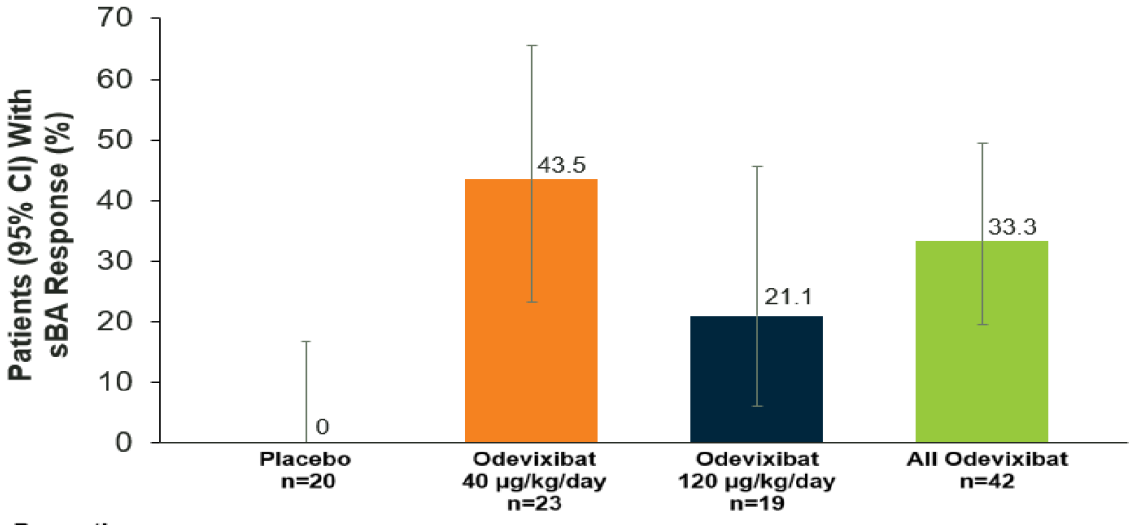
7.1.2.1.1.1 Serum bile acids

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 13; Figure 9) [10]. 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 10). Further analysis found 25.0% of non-responders at 40 µg/kg/day did respond at 120 µg/kg/day [13].

Patients with both PFIC types responded to odevixibat and sBA concentration was reduced to a similar level in both PFIC1 and PFIC2 patients (Figure 11). 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), and odevixibat 120 µg/kg/day (adjusted p = 0.0174). In addition, a post hoc analysis comparing the results for the 40 and 120 µg/kg/day groups showed no statistically significant difference in the proportion of sBA responders between the two odevixibat dose groups (CMH stratified by PFIC type, 2-sided, p = 0.1083) [9].

Figure 9. Serum bile acid response at week 24



Abbreviations: CI, confidence interval; SBA, serum bile acid
Notes: An sBA response was defined as ≤70µmol/L at week 24 or a reduction from baseline to week 24 of ≥70%.
Source: Thompson et al, 2020 [10]

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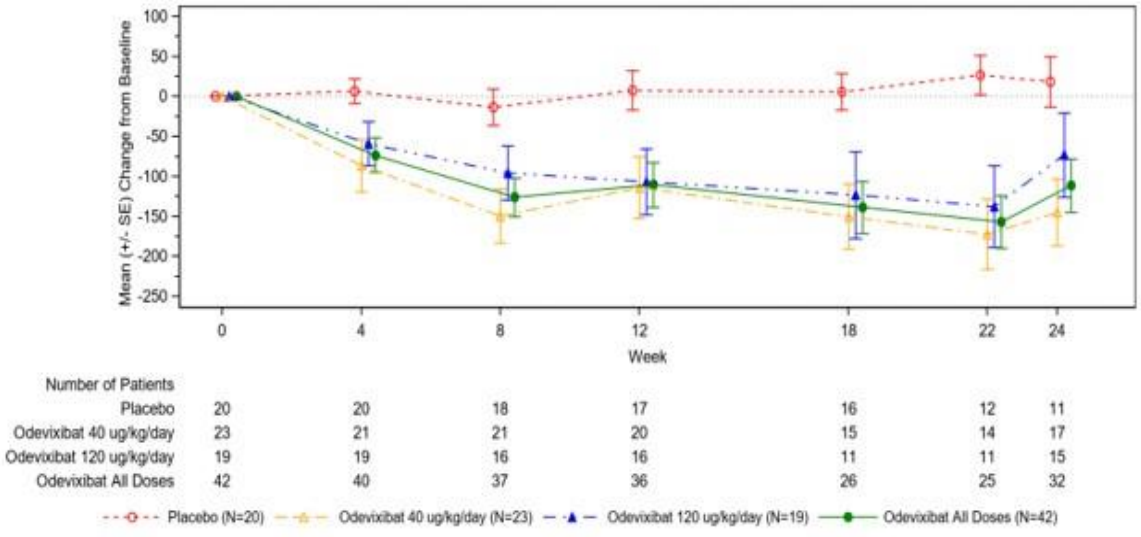
Figure 10. Mean (±SE) change from baseline in sBA concentration (µmol/L) by visit (Full analysis set)



Notes: Raw means; sBA, serum bile acid
Source: PEDFIC2 CSR [9]

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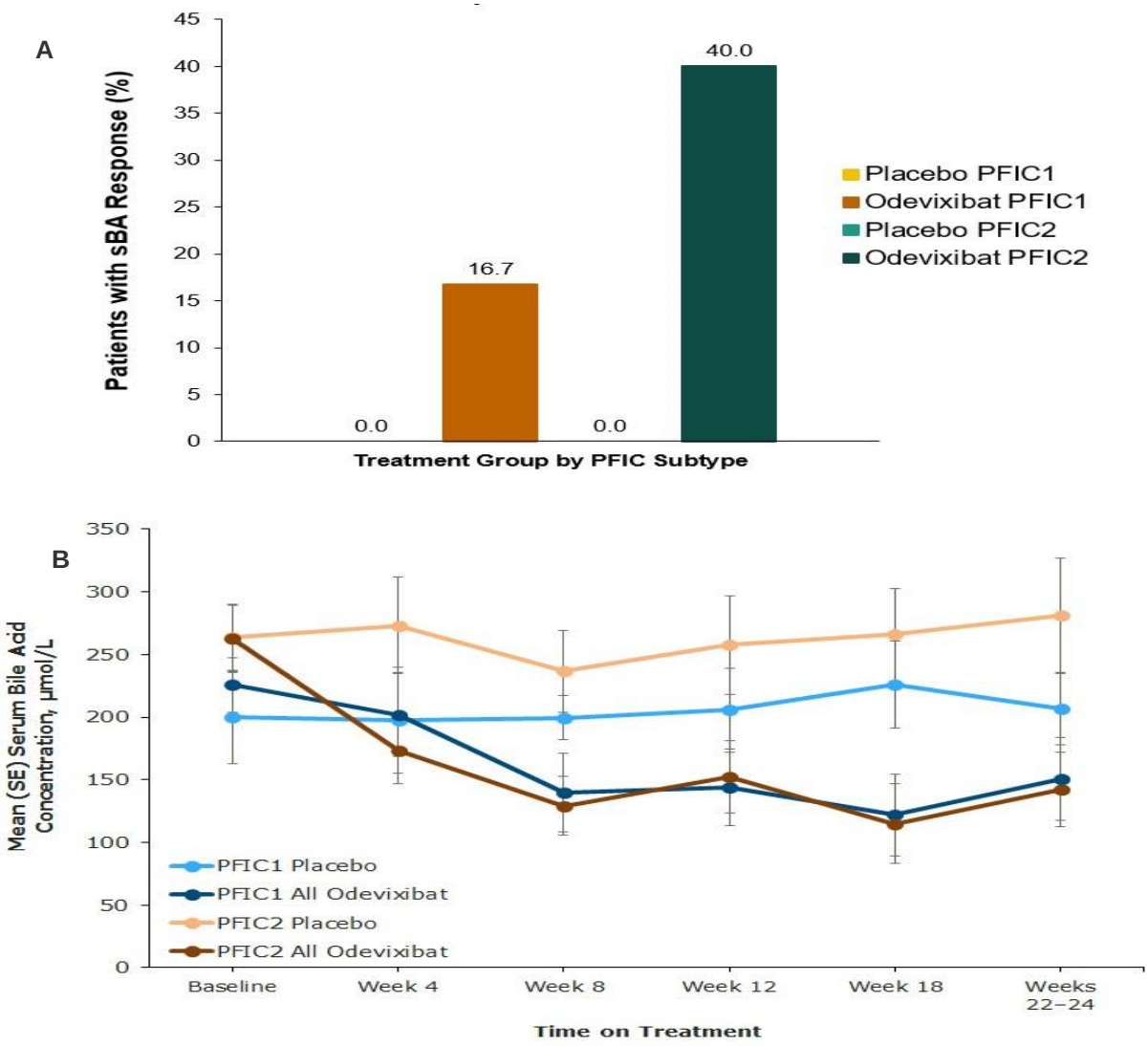
Figure 11. sBA response at week 24 (A) and sBA over time (B) in patients according to PFIC type



Abbreviations: PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid
Source: Thompson et al, 2020 [10]

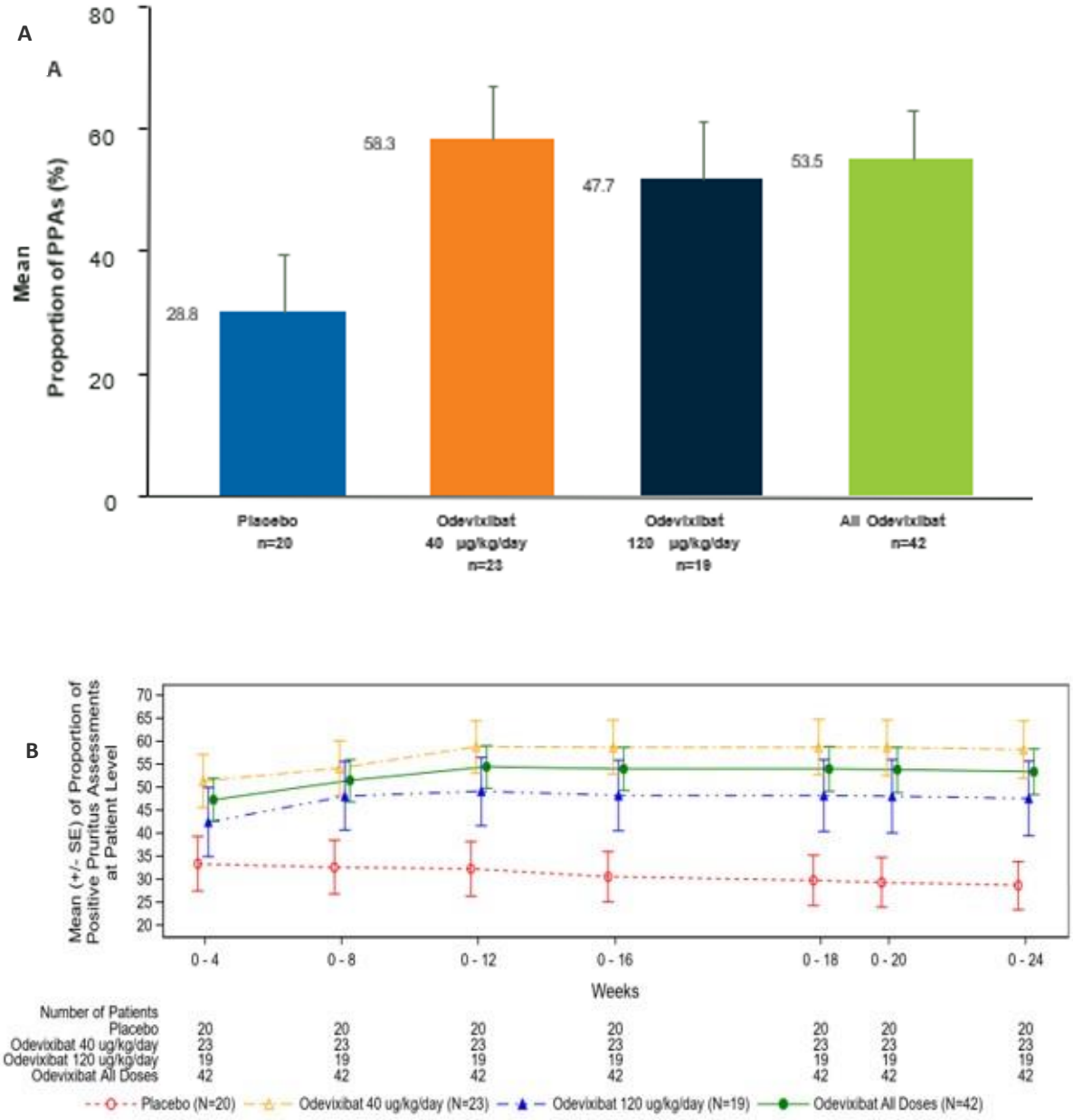
7.1.2.1.1.2 Pruritus

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 13; Figure 12). 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, and 58.3% and 47.7% in the odevixibat 40 µg/kg/day and 120 µg/kg/day dose groups, respectively, compared with 28.7% in the placebo group [9]. Greater than a fall of one point in the mean score is considered clinically meaningful.

The magnitude of the treatment effect was similar in patients with PFIC1 and PFIC2 and was persistent over time (Figure 13).

A *post hoc* analysis comparing the results for the 40 and 120 µg/kg/day groups showed no statistically significant difference 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 = 0.5008).

Figure 12. Proportion of positive pruritus assessments at the patient level over 24 weeks (A) and by timepoint (B)



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 [9]; Thompson et al, 2020 [10]

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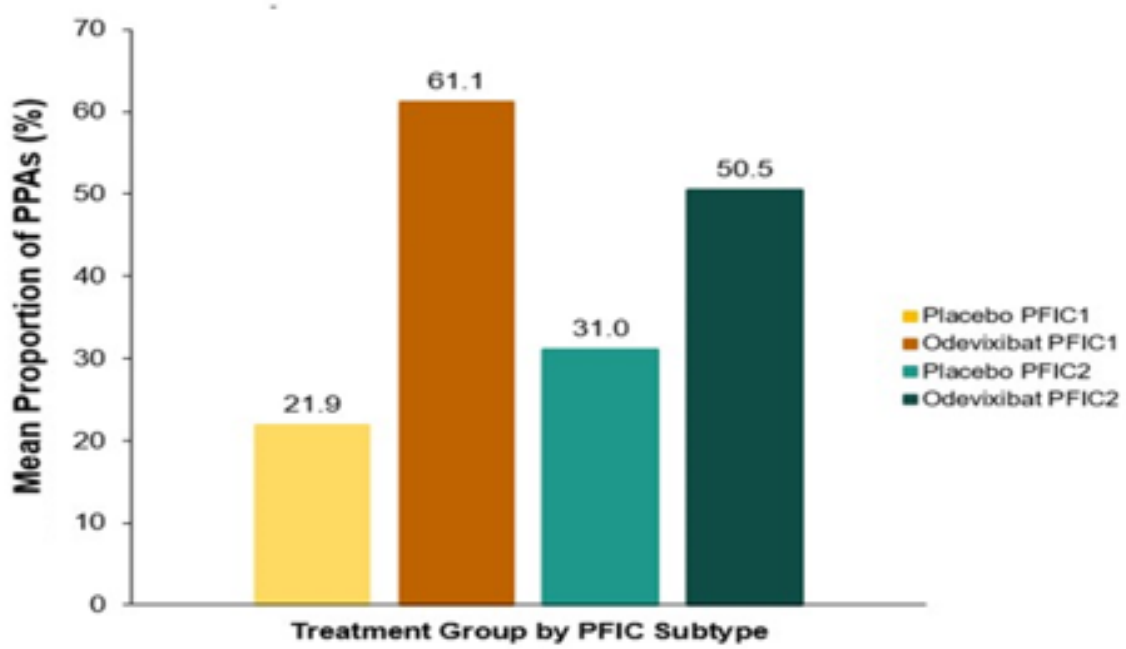
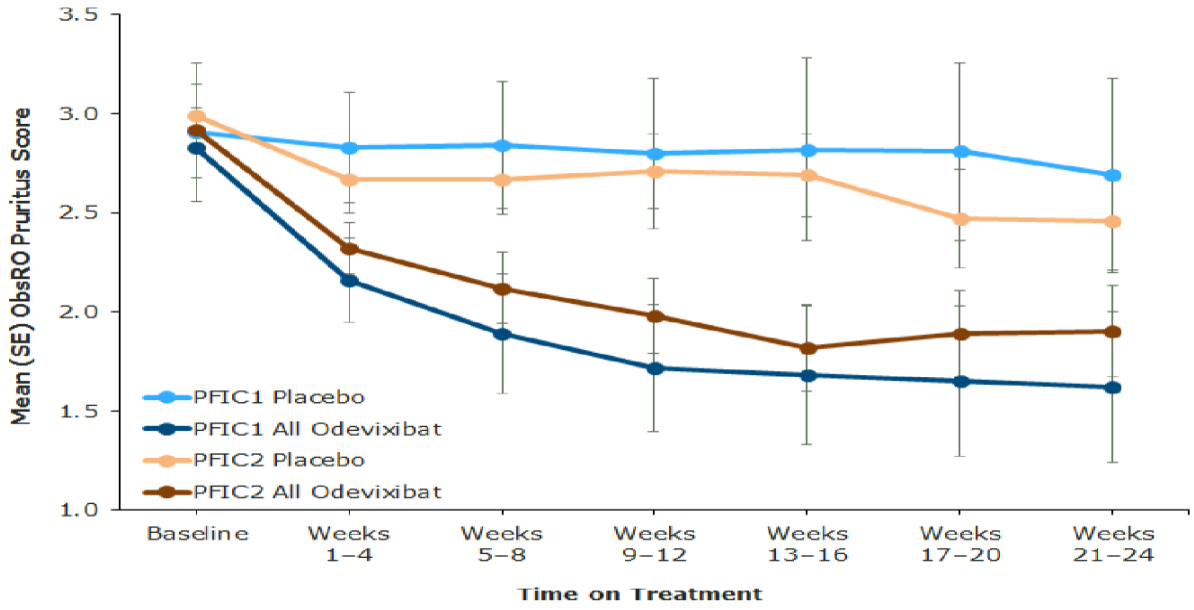
Figure 13. Proportion of positive pruritus assessments over 24 weeks (A) and ObsRO Pruritus Score by timepoint (B) according to PFIC type

A



B



Abbreviations: PFIC, progressive familial intrahepatic cholestasis; PPAs, positive pruritus assessments
Notes: Raw means; PPAs defined as a scratching score of ≤1 or a ≥1-point drop from baseline on an observer-reported instrument.
Source: PEDFIC1 CSR [9]; Thompson et al, 2020 [10]

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7.1.2.1.1.3 Proportion of patients achieving a positive pruritus assessment for >50% of the time during the 24-week treatment period (secondary endpoint)

[redacted]

Table 14. Analysis of the number (%) of patients achieving a positive pruritus assessment for more than 50% of the time (ObsRO instrument, full analysis set)

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

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 [9]

7.1.2.1.2 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.

7.1.2.1.2.1 Sleep analysis

Treatment with odevixibat led to improved sleep for patients, as determined based on caregiver responses using the Albireo ObsRO instrument (Figure 14).

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, minimal changes from baseline were observed for these sleep parameters. Additionally, a greater improvement from baseline 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 was wide variability in the data at both baseline and weeks 21–24 (ranging from approximately 0 to 100) indicating that a small number of patients with high values likely skewed these results.

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, also showed improvements for odevixibat-treated patients compared with those who received placebo.

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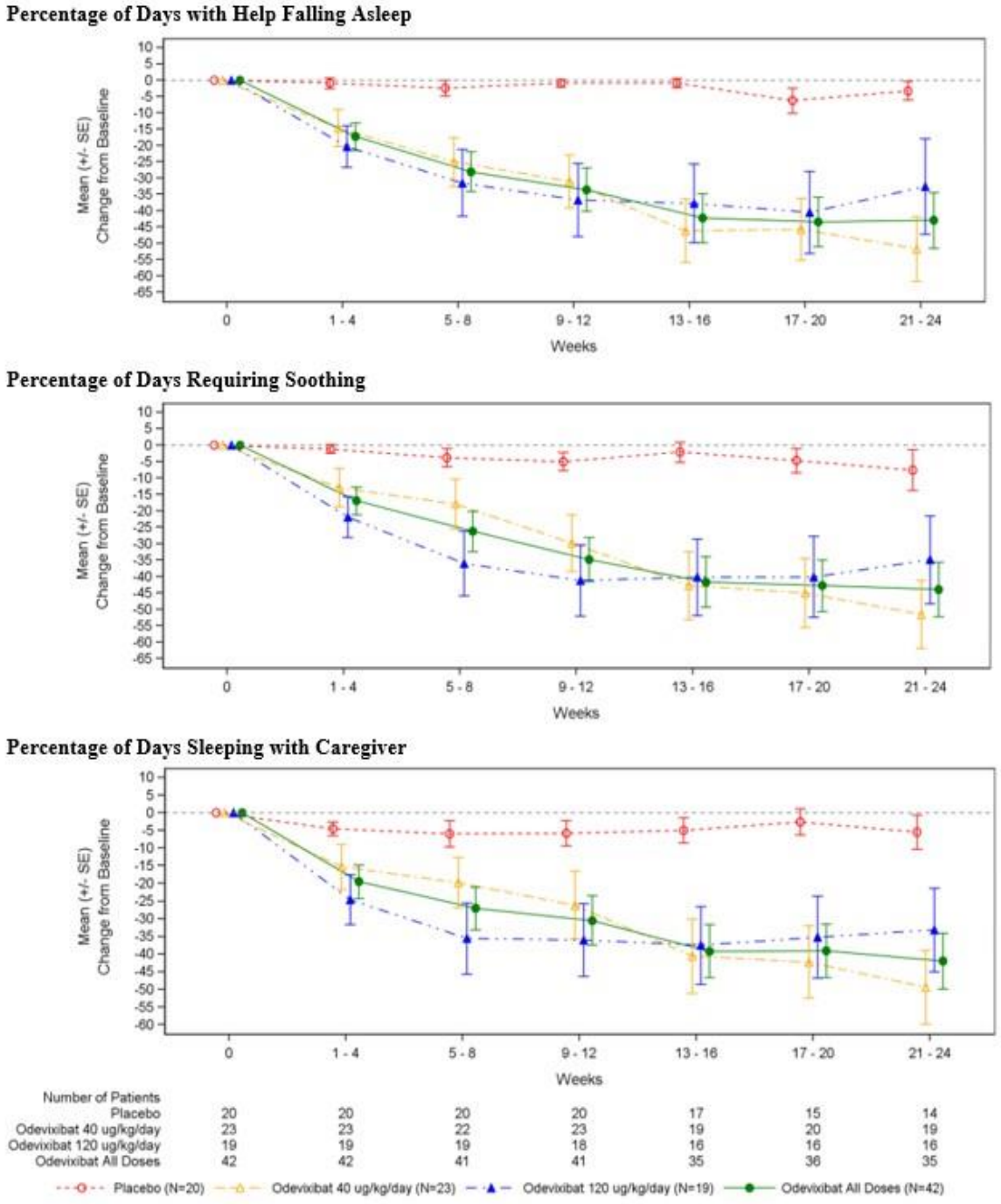
Figure 14. Mean (±SE) change in sleep parameters from baseline over time – Albireo ObsRO Instrument (full analysis set)



Note. Sleep parameters reported by caregivers on the Albireo ObsRO Instrument assessing baseline and outcomes over 4 week intervals.
Source: PEDFIC1 CSR [9]

7.1.2.1.2.2 Growth analysis

Patients in the placebo and 120 µg/kg/day groups had more impaired growth, 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 40 µg/kg/day group with a larger improvement in mean height z-score (0.01 and 0.05 at Weeks 12 and 24, respectively) and weight z-score (0.20 and 0.29, respectively) relative to the placebo group which showed declines in height z-score at both time points (0.03 and 0.16, respectively) with some improvement in weight z-scores (0.13 and 0.10, respectively).

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

7.1.2.1.2.3 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 25.9 and 13.8 U/L in the 40 and 120 µg/kg/day dose groups, respectively, compared with a small mean increase of 1.7 U/L in the placebo group. Further decreases in ALT were observed to week 24 with mean changes from baseline of 27.9, and 25.3 U/L in the 40 and 120 µg/kg/day dose groups, respectively, compared with a mean increase of 3.7 U/L in the placebo group.

For total bilirubin, mean changes from baseline to Week 24 were -1.4 and -1.1 mg/dL, for the 40 µg/kg/day and 120 µg/kg/day groups, respectively, and -0.6 mg/dL for placebo. Small mean reductions in GGT were also observed at week 24 in patients on odevixibat, compared with a mean increase in the placebo group.

7.1.2.1.2.4 PedsQL (exploratory endpoint)

Caregiver-reported total scores on the PedsQL increased from baseline to Week 24 for patients treated with odevixibat indicating improvement in QoL with mean increases from baseline of 7.76 for odevixibat overall and 5.51 and 11.00 for the 40 and 120 µg/kg/day groups, respectively; minimal change from baseline was observed for the placebo group (0.48).

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 15) [9].

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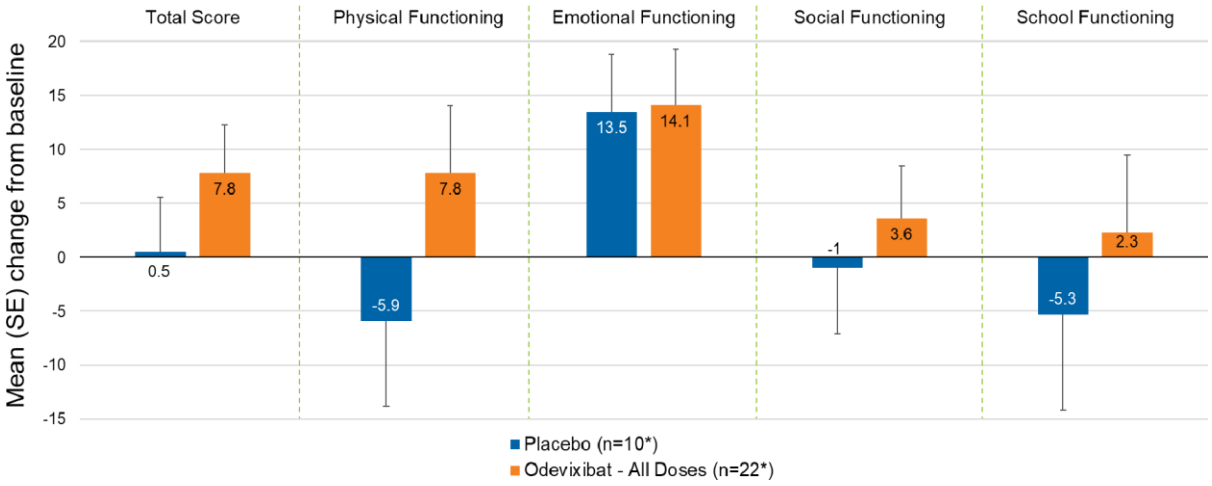
Figure 15. Caregiver-reported change from baseline to week 24 in PedsQL Total and Domain Scores

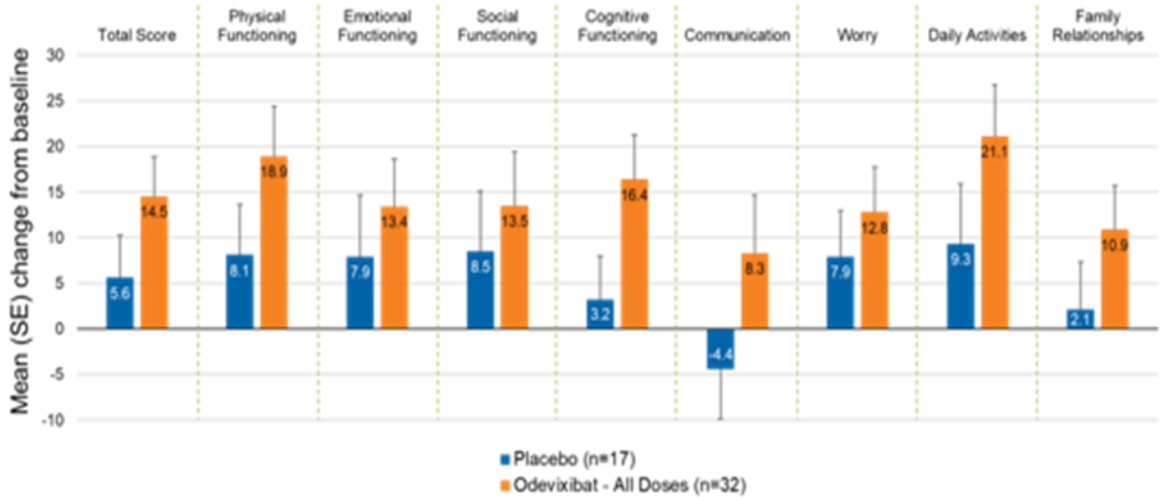


*For School Functioning, n=6 for placebo and n=15 for odevixibat – all doses.
N, number of patients with available assessments; PedsQL, Pediatric QoL Inventory; SE, standard error.
Source: PEDFIC1 CSR [9]

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. 10.8, and 20.0 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 16).

Figure 16. Change from baseline to week 24 in PedsQL Family Impact Module Total and Domain scores



Notes: n, number of patients with available assessments; PedsQL, Pediatric Quality of Life Inventory; SE, standard error.
Source: PEDFIC1 CScccccc

7.1.2.1.2.5 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] 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 [9].

7.1.2.1.3 PEDFIC1 safety

Patients on treatment or placebo experienced similar rates of having at least one TEAE (Table 15). 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 15. Summary of treatment-emergent adverse events (PEDFIC1)

	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 [9]; Thompson et al, 2020 [10]

TEAEs were reported in ≥5% of patients who received odevixibat vs placebo: diarrhoea (31% vs 5%), pyrexia (29% vs 25%), upper respiratory tract infection (19% vs 15%), vomiting (17% vs 0%), ALT increased (14% vs 5%), and blood bilirubin increased (12% vs 10%) (Table 16).

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

Table 16. Common treatment-emergent adverse events (PEDFIC1)

MedDRA SOC preferred term	Placebo N=20	Odevixibat 40 µg/kg N=23 n (%)	Odevixibat 120 µg/kg N=19 n (%)
Gastrointestinal disorders	6 (30.0)	14 (60.9)	8 (42.1)
Diarrhoea	1 (5.0)	9 (39.1)	4 (21.1)
Vomiting	0	4 (17.4)	3 (15.8)
Abdominal pain	0	2 (8.7)	1 (5.3)
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	1 (5.0)	1 (4.3)	2 (10.5)
Investigations	4 (20.0)	7 (30.4)	8 (42.1)
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	1 (5.0)	2 (8.7)	1 (5.3)
Blood alkaline phosphatase increased	1 (5.0)	1 (4.3)	2 (10.5)
General disorders and administration site conditions	5 (25.0)	9 (39.1)	5 (26.3)
Pyrexia	5 (25.0)	7 (30.4)	5 (26.3)
Skin and subcutaneous tissue disorders	6 (30.0)	3 (13.0)	2 (10.5)
Pruritus	1 (5.0)	2 (8.7)	1 (5.3)

Abbreviations: MedDRA, Medical Dictionary for regulation Authorities; SOC, system organ class
Source: PEDFIC1 CSR [9]

Among patients who received odevixibat, the most commonly reported drug-related TEAEs were AST/ALT/bilirubin increases, and diarrhoea. All other drug-related TEAEs were reported in only one patient who received odevixibat (Table 17).

In the placebo group, drug-related TEAEs included one report each (5%) of ALT increased, AST increased, blood bilirubin increased, constipation and frequent bowel movements.

Table 17. Drug-related treatment-emergent adverse events (PEDFIC1)

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	1 (5.0)	3 (13.0)	4 (21.1)	7 (16.7)
Alanine aminotransferase increased	1 (5.0)	2 (8.7)	2 (10.5)	4 (9.5)
Blood bilirubin increased	1 (5.0)	2 (8.7)	2 (10.5)	4 (9.5)
Aspartate aminotransferase increased	1 (5.0)	2 (8.7)	1 (5.3)	3 (7.1)
Gastrointestinal disorders	2 (10.0)	2 (8.7)	3 (15.8)	5 (11.9)
Diarrhoea	0	2 (8.7)	2 (10.5)	4 (9.5)

Abbreviations: MedDRA, Medical Dictionary for regulation Authorities; SOC, system organ class
Source: PEDFIC1 CSR [9]

The majority of adverse events were mild to moderate in severity. Eight patients experienced SAEs over the course of the 24-week treatment period, including three patients on odevixibat 120 µg/kg/day and five patients on placebo. No treatment-emergent SAEs were reported in the 40 µg/kg/day treatment group. All SAEs were assessed as unrelated to study treatment.

For further details of efficacy and safety results, refer to Appendix D – Efficacy and safety results per study and Appendix E – Safety data for intervention and comparator(s).

7.1.2.2 PEDFIC2 results

7.1.2.2.1 Primary endpoint results

7.1.2.2.1.1 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 13.25 µmol/L (-5.41 µg/mL), a decrease of 5.8%, in patients who had received 40 µg/kg/day in PEDFIC1, and 24.39 µmol/L (-9.96 µg/mL), a decrease of 14.9%, in patients who had received 120 µg/kg/day.

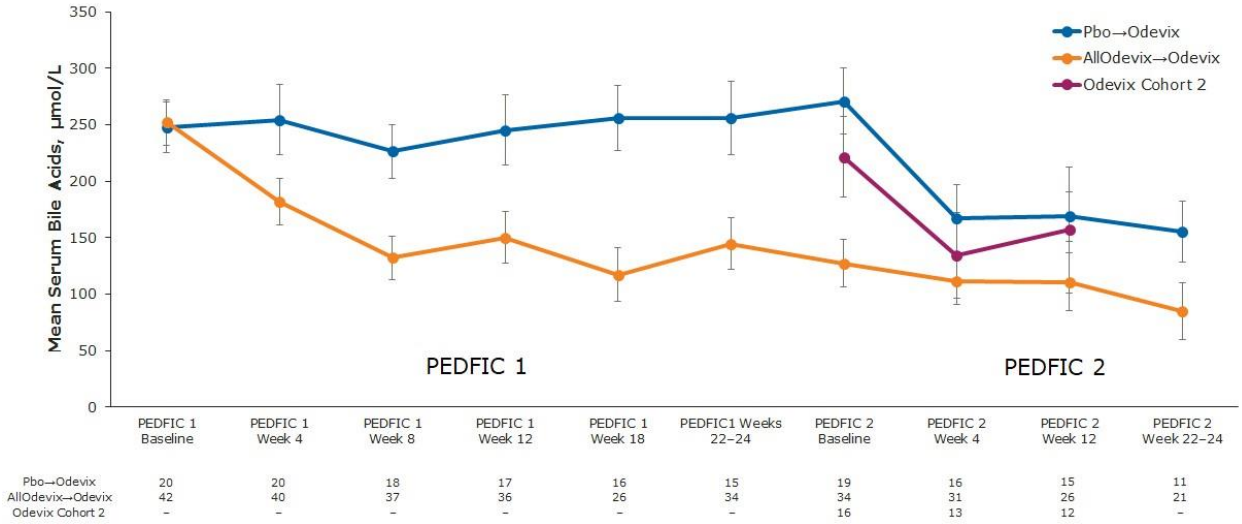
For patients who had received placebo in PEDFIC1, mean change to week 24 following the start of treatment with odevixibat 120 µg/kg/day was 143.73 µmol/L (-58.71 µg/mL), a decrease of 36.8%, and for patients in Cohort 2 was 104.10 µmol/L (-42.52 µg/mL), a decrease of 48.2%. Note that only five patients in Cohort 2 had data available at Week 22/24 at the time of the data cut-off.

Table 18. Summary of change in serum bile acids (µmol/L) after 24 weeks of treatment

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		
Baseline[c], n	19	15	34	19	16	35
Mean (SE)	104.89 (26.217)	155.87 (34.430)	127.38 (21.232)	270.79 (29.034)	221.53 (35.274)	248.27 (22.604)
Median	28.00	134.00	102.00	264.00	168.25	245.50
Min, max	1, 327	2.5, 439	1, 439	11, 528	10.5, 465	10.5, 528
Week 22/24, n	12	9	21	11	5	16
Mean (SE)	79.08 (30.569)	93.11 (44.211)	85.10 (25.123)	155.59 (26.810)	213.20 (85.683)	173.59 (31.445)
Median	11.75	15.00	12.50	181.50	230.00	186.75
Min, max	1.5, 254.5	3, 313.5	1.5, 313.5	3, 266	4, 409	3, 409
Change from baseline, n	12	9	21	11	5	16
Mean (SE)	-13.25 (17.614)	-24.39 (15.726)	-18.02 (11.892)	-143.73 (48.601)	-104.10 (38.770)	-131.34 (35.076)
Median	-5.75	-13.00	-6.00	-97.00	-89.50	-93.25
Min, max	-151.5, 125	-96.5, 55	-151.5, 125	-441, 71.5	-235, -10	-441, 71.5
% change from baseline, n	12	9	21	11	5	16
Mean (SE)	-5.76 (28.628)	-14.77 (21.745)	-9.62 (18.429)	-36.78 (13.966)	-48.20 (18.416)	-40.35 (10.933)
Median	-27.28	-19.41	-19.41	-29.29	-50.54	-34.90
Min, max	-92.9, 277.8	-96, 100	-96, 277.8	-98.7, 65	-95.7, -2.4	-98.7, 65

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 [11]

Figure 17. Mean (±SE) change in serum bile acid concentration (µmol/L) during PEDFIC1 and PEDFIC2 (week 24)



Source: Thompson et al, 2020 [12]

7.1.2.2.1.2 Pruritus

Interim results displayed in Figure 18 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 32.6% after 24 weeks of treatment at 120 µg/kg/day in PEDFIC2. The proportion of positive pruritus assessments was higher for patients who had received 40 µg/kg/day in PEDFIC1 and transitioned to 120 µg/kg/day in Study PEDFIC2 (37.0%) 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 was higher than that observed for patients previously treated with odevixibat.

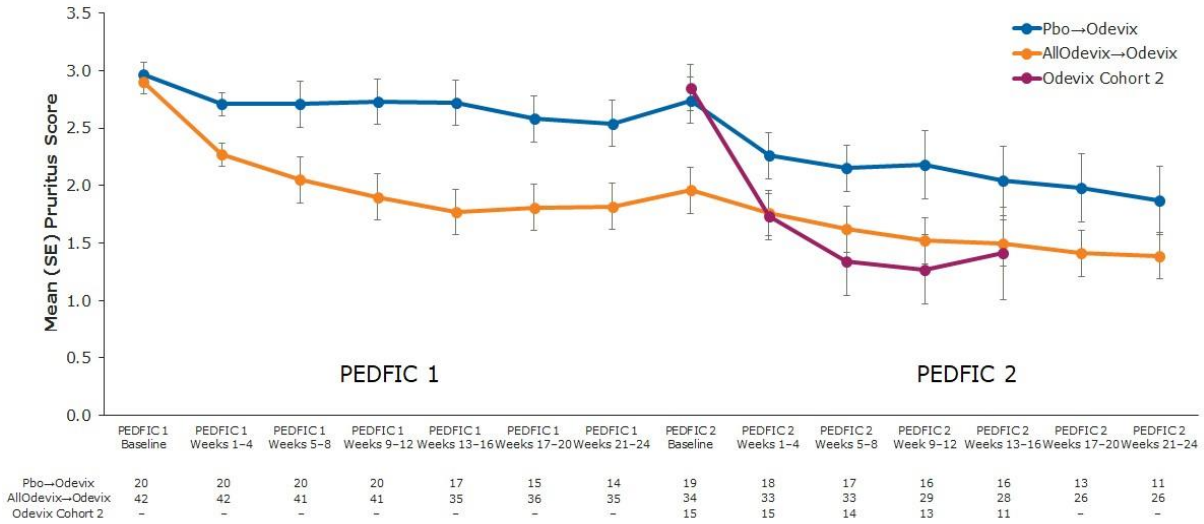
- Following transition from placebo in PEDFIC1 to 120 µg/kg/day in PEDFIC2, the proportion of positive pruritus assessments at the patient level was 56.3% over the 24-week treatment period.
- Similarly, in Cohort 2, the proportion of positive pruritus assessments at the patient level was 61.6% over the 24-week treatment period, although limited data were available for this cohort at that time.

Table 19. Summary of 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	15	11	26	11	5	16
Mean (SE)	37.03 (9.384)	26.60 (8.721)	32.62 (6.510)	56.26 (10.869)	61.63 (19.866)	57.94 (9.352)
Median	25.53	20.97	23.25	71.25	90.63	74.77
Min, max	0, 92.1	0, 85.6	0, 92.1	5.1, 98.8	10.1, 97.3	5.1, 98.8

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 [11]

Figure 18. Mean (±SE) of the proportion of positive pruritus assessments by grouped weeks



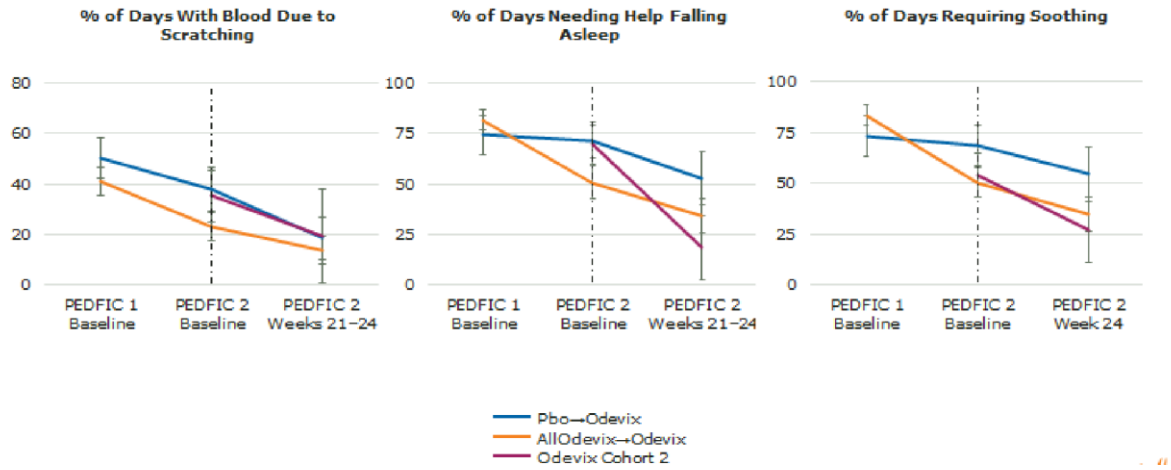
Note: Raw mean scores.
Source: Thompson et al, 2020 [12]

Consistent with the improvements observed in the proportion of positive pruritus assessments over time at the patient level, improvement 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 19). Mean changes from PEDFIC2 baseline to week 24 for this group of patients was 0.52 overall and was 0.60 for the 40 to 120 µg/kg/day group and 0.44 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, statistically significant changes from PEDFIC1 baseline in scratching scores were

observed in odevixibat-treated groups in Cohort 1, including odevixibat overall (1.55; 2-sided p < 0.0001), 40 to 120 µg/kg/day group (1.44; 2-sided p = 0.0005), and 120 to 120 µg/kg/day group (1.70; 2-sided p = 0.0011) [11]. Other sleep parameters also continued to improve during PEDFIC2 (Figure 19).

Figure 19. Mean change in observer-reported sleep parameters during PEDFIC1 and PEDFIC2



Note: Raw mean scores.
Source: : PEDFIC1 CSR [9]; PEDFIC2 CSR [11]

7.1.2.2.2 Secondary endpoints

7.1.2.2.2.1 Biliary diversion surgery or liver transplantation

Data on file [62]

[redacted]

7.1.2.2.2.2 Growth analysis

Improvement in height and weight scores was noted during treatment with odevixibat 120 µg/kg/day (Figure 20 and Figure 21).

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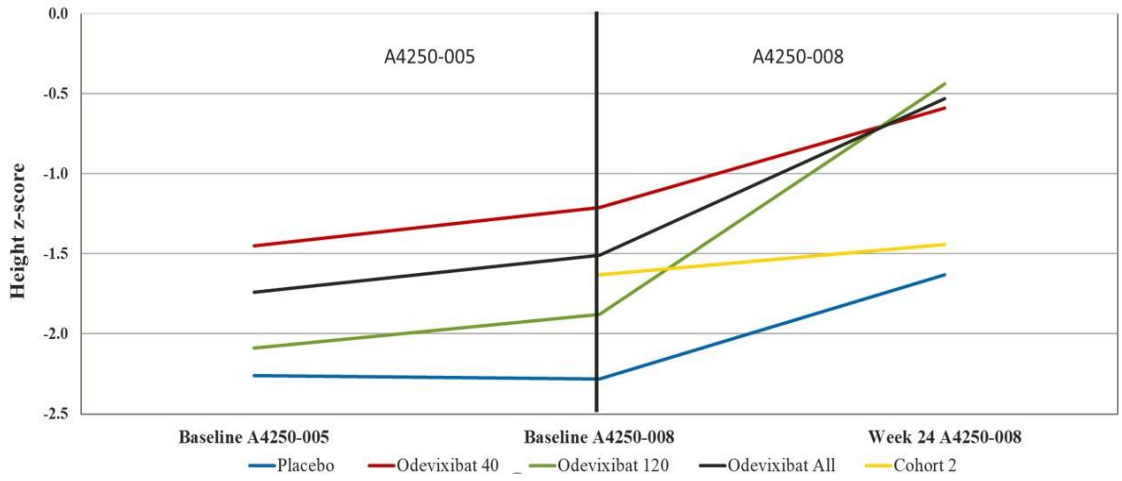
For patients in Cohort 1 who had previously received odevixibat in PEDFIC1, mean (SE) change from baseline to week 24 in height z-score was 0.34 (0.111), with greater improvement noted for those who had received 120 µg/kg/day (0.56 [0.204]) than those who had received 40 µg/kg/day (0.19 [0.115]). Mean (SE) changes from baseline to week 24 in weight z-scores were 0.31 (0.127) and 0.08 (0.184) for patients who had received odevixibat 40 µg/kg/day and 120 µg/kg/day, respectively [11].

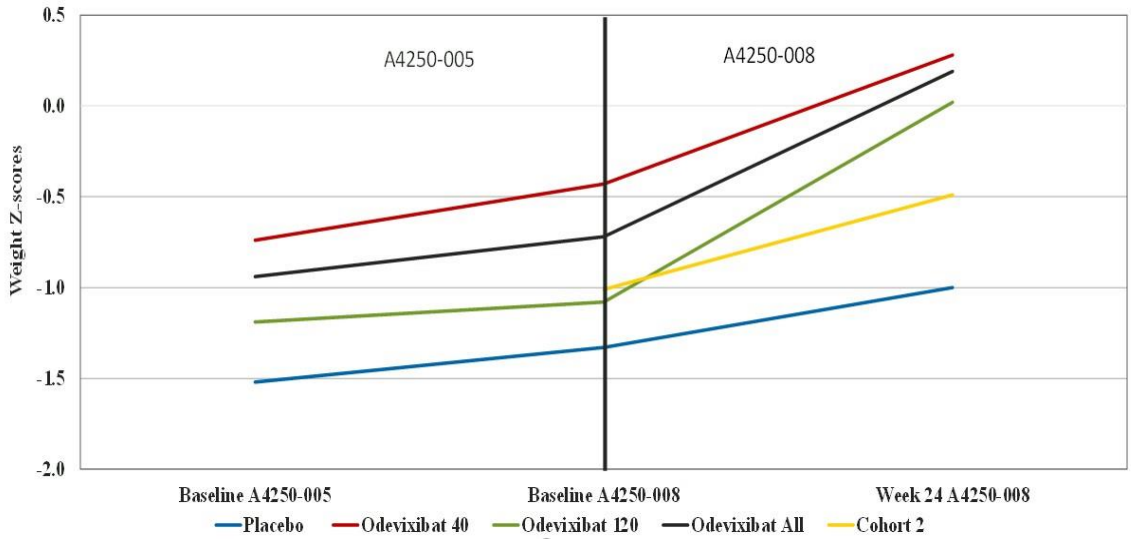
For patients in Cohort 1 who had received placebo in PEDFIC1, mean (SE) changes in height and weight z-scores were 0.40 (0.178) and 0.47 (0.193). Only one patient in Cohort 2 had growth data available at week 24 [11].

Figure 20. Mean height z-scores over time on treatment for PEDFIC1 and PEDFIC2



Note: Raw mean scores.
Source: PEDFIC2 CSR [11]

Figure 21. Mean weight z-scores over time on treatment for PEDFIC1 and PEDFIC2



Note: Raw mean scores.
Source: PEDFIC2 CSR [11]

7.1.2.2.3 Subgroup analysis

[redacted]

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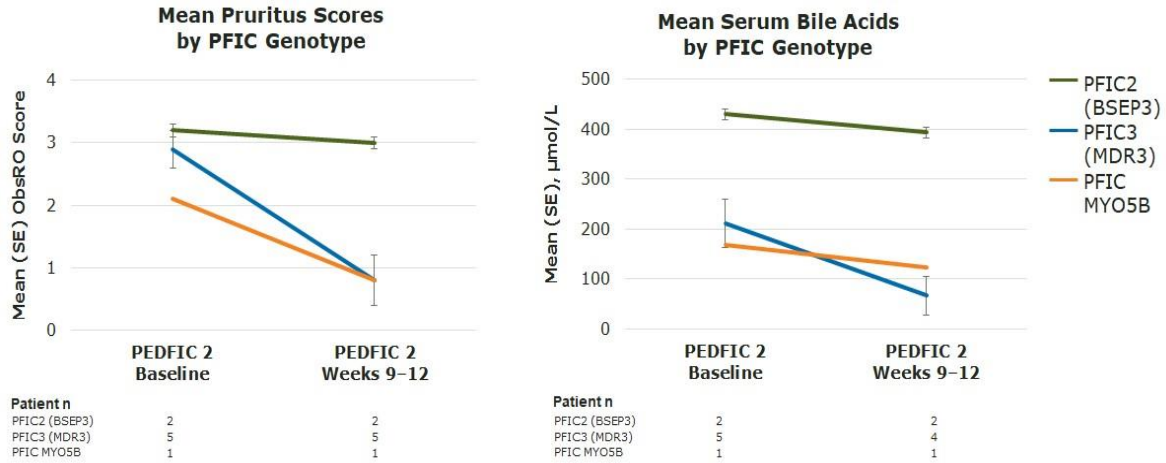
One patient with PFIC6 (Myo5B deficiency) was enrolled in PEDFIC2 Cohort 2. The patient had improvement in both pruritus scores and sBA reduction at weeks 9-12 [11]. Two patients with BSEP 3 mutation (complete protein truncation leading to non-functional protein) were included in Cohort 2 of PEDFIC2 – these patients had no improvement in pruritus or sBA at week 9-12.

Figure 22. Post-hoc analysis: Mean change in pruritus scores and serum bile acids by PFIC genotype subtype to PEDFIC2 week 12 – Cohort 2



Note: Raw mean scores.
Source: PEDFIC2 CSR [11]

7.1.2.2.4 PEDFIC2 safety

Of the 69 patients who received odevixibat, 50 (73%) experienced at least one TEAE (Table 20). 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 20. Summary of treatment-emergent adverse events (PEDFIC2)

	Odevixibat 120 µg/kg			
	Cohort 1			Cohort 2 N=16 n (%)
	40 µg/kg N=19 n (%)	120 µg/kg N=15 n (%)	Placebo N=19 n (%)	
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 [11]

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 (Table 21Table 93). In general, the incidence of these commonly reported events was similar across the treatment groups in Cohort 1.

Table 21. Common treatment-emergent adverse events (PEDFIC2)

System organ class preferred term	Odevixibat 120 µg/kg			
	Cohort 1			Cohort 2 N=16 n (%)
	Placebo N=19 n (%)	40 µg/kg N=19 n (%)	120 µg/kg N=15 n (%)	
Infections and infestations	8 (42.1)	10 (52.6)	8 (53.3)	1 (6.3)
Upper respiratory tract infection	5 (26.3)	5 (26.3)	4 (26.7)	0
Otitis media	1 (5.3)	1 (5.3)	2 (13.3)	0
Investigations	5 (26.3)	7 (36.8)	4 (26.7)	5 (31.3)
Blood bilirubin increased	2 (10.5)	3 (15.8)	1 (6.7)	3 (18.8)
Alanine aminotransferase increased	1 (5.3)	1 (5.3)	0	2 (12.5)
Gastrointestinal disorders	7 (36.8)	6 (31.6)	5 (33.3)	2 (12.5)
Diarrhoea	0	4 (21.1)	2 (13.3)	0
Constipation	2 (10.5)	1 (5.3)	2 (13.3)	0
Vomiting	1 (5.3)	0	2 (13.3)	2 (12.5)
Respiratory, thoracic and mediastinal disorders	3 (15.8)	4 (21.1)	6 (40.0)	2 (12.5)
Cough	2 (10.5)	3 (15.8)	5 (33.3)	0
General disorders and administration site conditions	4 (21.1)	4 (21.1)	4 (26.7)	2 (12.5)
Pyrexia	4 (21.1)	3 (15.8)	4 (26.7)	2 (12.5)
Skin and subcutaneous tissue disorders	2 (10.5)	2 (10.5)	6 (40.0)	1 (6.3)
Pruritus	2 (10.5)	2 (10.5)	2 (13.3)	0
Blood and lymphatic system disorders	2 (10.5)	3 (15.8)	2 (13.3)	1 (6.3)
Splenomegaly	2 (10.5)	1 (5.3)	1 (6.7)	1 (6.3)

Source: PEDFIC2 CSR [11]

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 22). All other drug-related TEAEs were reported in only one patient.

Table 22. Drug-related treatment-emergent adverse events (PEDFIC2)

	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 n (%)**	**Cohort 1 (placebo) N=19 n (%)**	**Cohort 2 N=16 n (%)**
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 [11] [12]

For further details of efficacy and safety results, refer to Appendix D – Efficacy and safety results per study, and Appendix E – Safety data for intervention and comparator(s).

7.1.3 Comparative analyses of efficacy and safety

Based on the data available for off-label oral therapies and biliary diversion surgery, that included only uncontrolled, mainly retrospective studies (see Appendix A – Literature search for efficacy and safety of intervention and comparator(s)) for the studies identified in the systematic literature review), it was not possible to carry out any indirect comparison.

As described in section 5.2, other than odevixibat, 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 clinical SLR identified 21 studies that reported on the use of UDCA or rifampicin in patients with PFIC. These are listed in Appendix A – Literature search for efficacy and safety of intervention and comparator(s) and described in section 5.2.1.2.

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.

As described in section 7.2, 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 [5] [14]. The NAPPED study compares outcomes in PFIC1 and PFIC2 with or without biliary diversion surgery.

The NAPPED studies are described in detail in section 7.2. A complete list of citations for NAPPED analyses and a critical appraisal is shown in Appendix A – Literature search for efficacy and safety of intervention and comparator(s).

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.

Method of synthesis

N/A. There are no studies to compare PEDFIC estimates of the efficacy of odevixibat vs. placebo for treatment of PFIC with.

Results from the comparative analysis

N/A. There are no studies to compare PEDFIC estimates of the efficacy of odevixibat vs. placebo for treatment of PFIC with.

7.2 Natural course and Prognosis of PFIC and Effect of biliary Diversion (NAPPED)

As described in section 6.2, 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

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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 [14].

NAPPED currently comprises 68 referral centres from Europe, North America, South America, Africa, Asia, and Australia [14].

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 23. 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 [14]. Most recent published analysis of the PFIC2 population has a data cut-off in March 2019 [5]
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 [14]); PFIC2 N=264 (van Wessel, 2020 [5])
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

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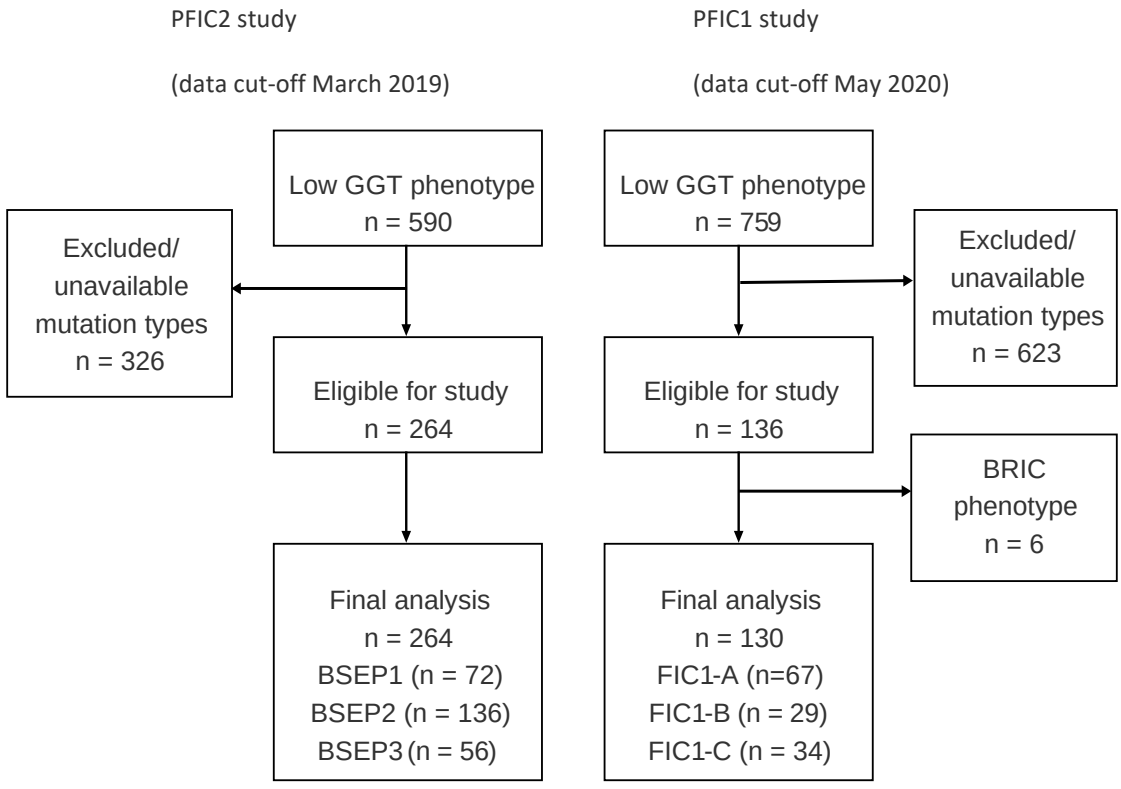
Study name	NAPPED (Natural course and Prognosis of PFIC and Effect of biliary Diversion)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow-up ended at last visit, liver transplantation or death.
Outcomes (including scoring methods and 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, LTx, or death. PFIC2 (van Wessel, 2020 [5]): 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 LTx, death, or last visit, whichever occurred first)

7.2.1 NAPPED patient disposition

The number of patients included in each part of the study are shown in Figure 23. Of note, The PFIC2 NAPPED study included patients of the BSEP3 subtype (with mutations leading to non-functional protein).

Figure 23. Patient disposition in NAPPED – PFIC1 and PFIC2 studies



Source: van Wessel 2020 [5]; van Wessel 2021 [14]

7.2.2 NAPPED baseline characteristics

Baseline characteristics of the two studies are shown in Table 24.

Table 24. 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 (%)** **Rifampicin, n (%)** **Phenobarbital, n (%)** **Cholestyramine, n (%)** **Antihistamines, n (%)**	 41/103 (40) 16/103 (16) 10/103 (10) 12/103 (12) 9/103 (9)	 122/264 (46) 52/264 (20) 16/264 (6) 40/264 (15) 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 [5]; van Wessel 2021 [14]

In patients with PFIC1 [14], 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 [5].

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7.2.3 NAPPED key results

7.2.3.1 NAPPED PFIC2

The following results are reported in van Wessel et al (2020) [5].

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 sBA (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 24) in BSEP1 and BSEP2. Note that this evidence not implemented in the economic model.

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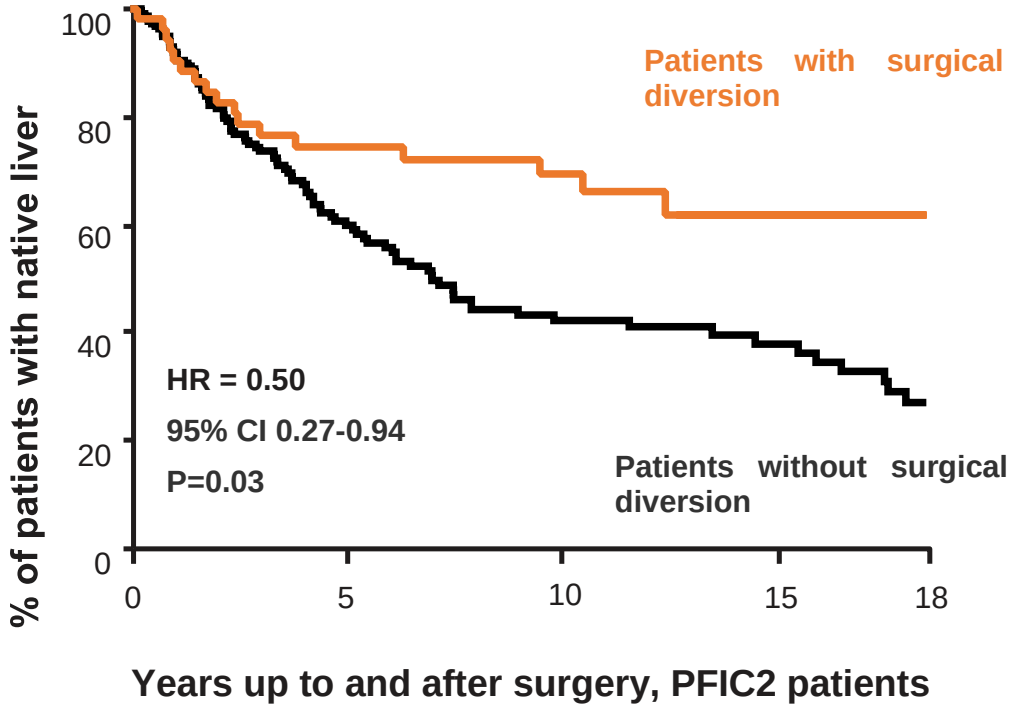
Figure 24. Observed native liver survival in PFIC2 (BSEP1 and BSEP2) patients undergoing SBD or not



Note: The clock-reset approach allows visualization of native liver survival up to SBD (black, all patients) and after SBD (orange, 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. Patients in analysis: n = 173. Number at risk over time not provided in source. This evidence not implemented in the economic model.
Source: Adapted from Van Wessel et al. 2020 [5]

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 25; 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%). Note that this evidence not implemented in the economic model.

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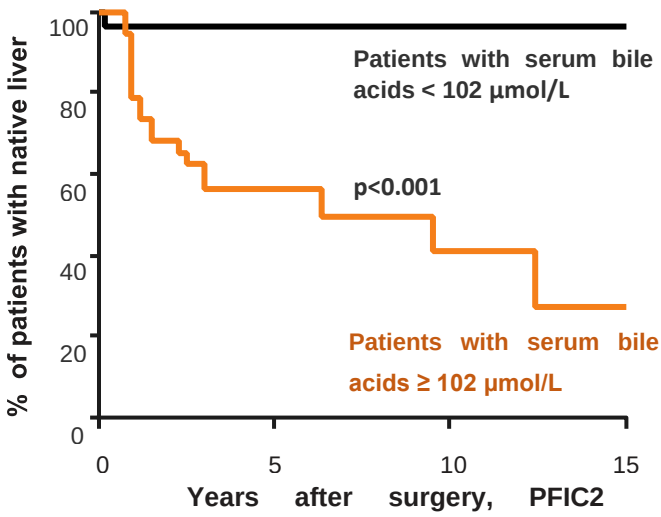
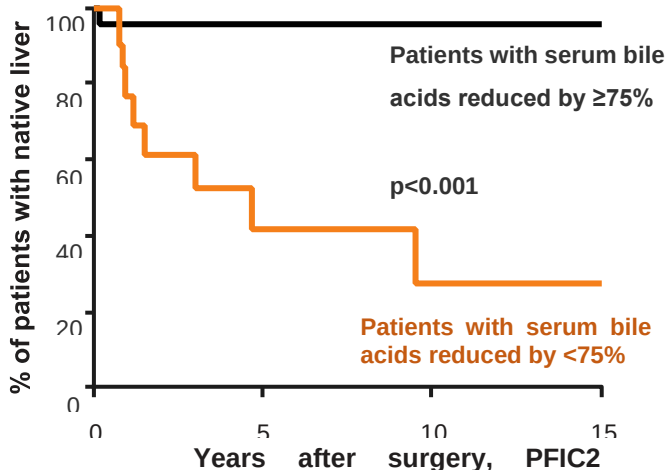
Figure 25. Observed native liver survival after surgical biliary diversion, stratified for postsurgical SBA cut-offs (PFIC2 patients)

A



N° at risk				
<102 µmol/L	27	23	16	9
≥102 µmol/L	20	8	5	1

B



N° at risk				
<75% decrease SBA	14	4	2	1
≥75% decrease SBA	24	21	14	8

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. This evidence not implemented in the economic model.
Source: Adapted from Van Wessel et al. 2020 [5]

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7.2.3.2 NAPPED PFIC1

The following results are reported in van Wessel et al (2021) [14].

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 LTx.

A total of 8 patients (6%) died prior to LTx, 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 26). 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). Note that this evidence not implemented in the economic model.

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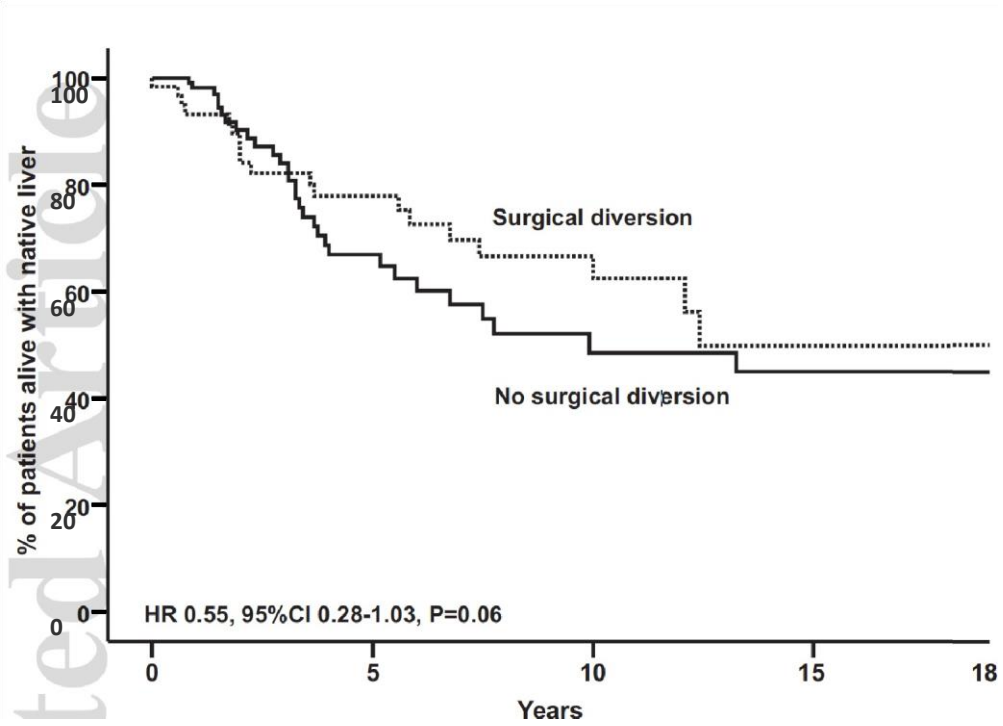
Figure 26. Observed native liver survival in PFIC1 patients undergoing SBD or not



Note: Number at risk not presented in source. This evidence not implemented in the economic model.
Source: Van Wessel et al. 2021 [14]

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 27). 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%).

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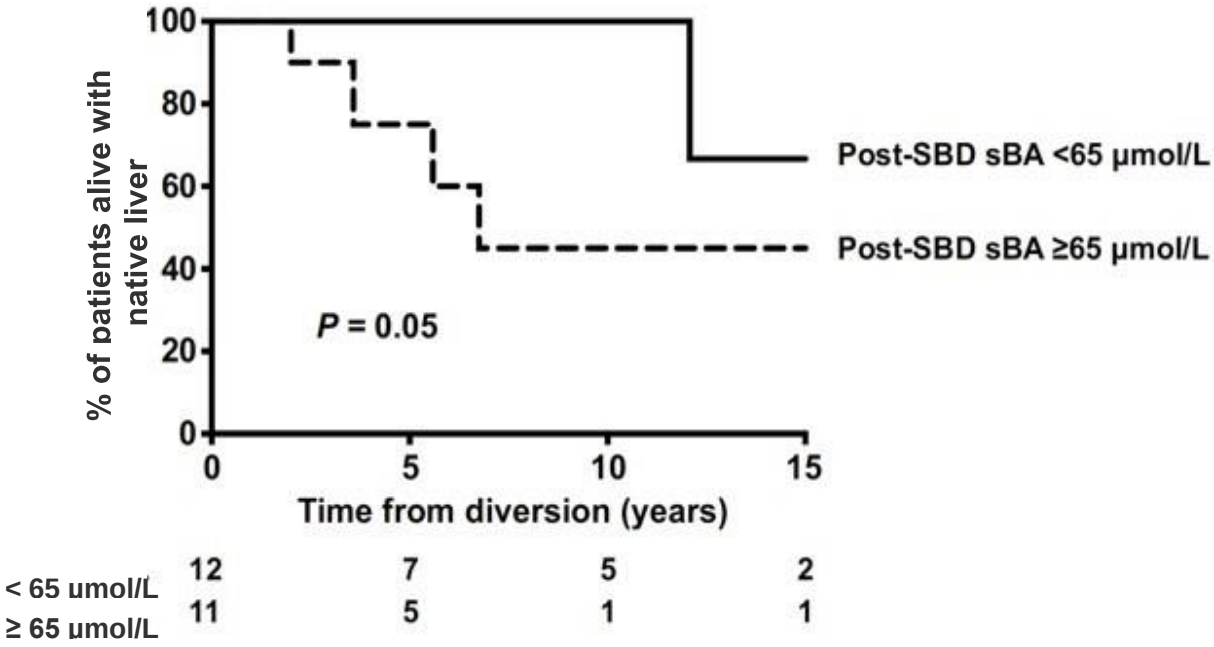
Figure 27. Observed native liver survival after surgical biliary diversion, stratified for postsurgical sBA cut-offs (PFIC1 patients)



Note: This evidence not implemented in the economic model.
Source: Adapted from Van Wessel et al. 2021 [14]

8. Health economic analysis

A cost-utility analysis was conducted based on a Danish adaptation of an Excel-based cost-effectiveness model originally developed for NICE in the UK. As treatment with odevixibat is a medically analogous to PEBD surgery, standard of care consisting of off-label medications and partial external biliary diversion (PEBD) surgery is considered the basic comparator to odevixibat for treatment of patients with PFIC.

8.1 Model

8.1.1 Danish model structure

The clinical pathway depicted in Figure 6, has been translated into an eight state Markov model, as depicted in Figure 28.

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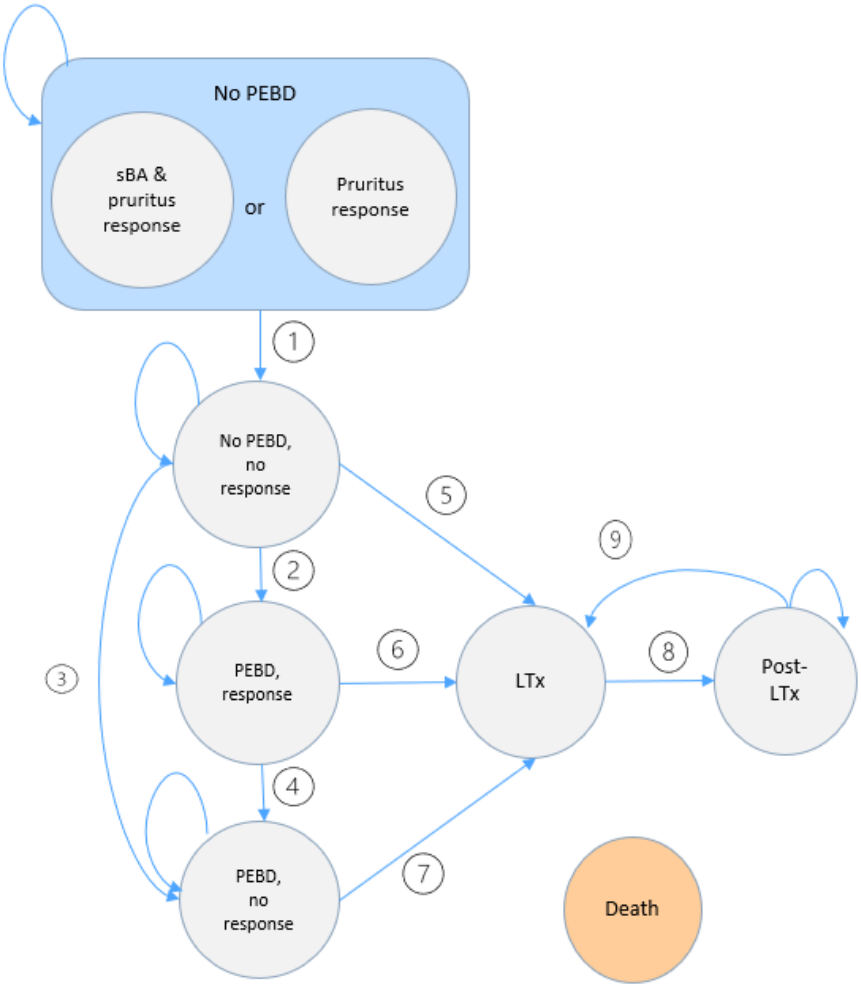
Figure 28. Model schematic



Abbreviations: LTx, 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 LTx is driven by the exacerbation of pruritus resulting from elevated bile acids. A proportion of patients require a secondary LTx, which occurs in the same year as the first LTx, as described in the literature [54]. The primary benefit of odevixibat is captured in the delayed time to LTx. 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.

Differences between PFIC1 and PFIC2 are captured in the progression to LTx and outcomes post-LTx (including re-transplant), given the differences in clinical management and outcomes across these populations.

The model structure has been developed around Markov models with similar health-states submitted to HTA bodies in related conditions; obeticholic acid for treating primary biliary cholangitis (NICE TA443 [63]) and inotersen for treating hereditary transthyretin amyloidosis (NICE HST9 [64], DMC [65]).

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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 LTx, and long-term improvements in quality of life by reducing or eliminating pruritus.

8.1.2 Key assumptions

Key assumptions informing the model structure are presented in Table 25.

Table 25. 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 beyond study data. 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 OvEC 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 analogous, 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 [3].
Patients with a pruritus response have the QoL of a healthy child reported in Kamath et al. [16]	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. [16]	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.

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The modelled health states are intended to 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 [63] and HST9 [64]). 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 NAPPED study show that pruritus is the leading reason for liver transplantation in PFIC patients (s) [22]. LTx (and PEBD in other countries) 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 (see below, Table 27), these patients are assumed to have a pruritus response following their sBA response.

8.1.3 Additional key features

Table 26. 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 DMC guidance, which states the time horizon should be long enough to reflect all important differences in costs or outcomes between technologies being compared	DMC methods guide [66]
Discount for costs and health outcomes	3.5%, 2.5%, 1.5% corresponding to model years 1-35, 36-70, 71+	In line with DMC methods guide and Danish Finance Ministry guidance.	DMC methods guide [66] and Danish Finance Ministry [67]
Perspective	Restricted Societal	The perspective of costs is that of the Danish healthcare system, in addition costs to patients traveling and participating in their healthcare, in line with DMC guidance. The perspective for health effects is restricted to patients.	DMC methods guide [66]
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 CSR [9]

Note: [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

No cost-effectiveness studies for PFIC have been identified and consequently, none were used to inform the development of this model.

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8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

The direct clinical evidence for efficacy of odevixibat is limited to patients with PFIC1 and PFIC2 from one Phase 3 trial (PEDFIC1) [9]. There are no specific reasons to expect differences between Danish PFIC patients' responses to treatment with odevixibat vs. non-Danish PFIC patients.

8.2.1 Presentation of input data used in the model and how they were obtained

8.2.1.1 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 27). 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 [13].

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 [redacted], with a mean exposure time of [redacted] giving a discontinuation rate [redacted] per patient year, which results in an annual probability of discontinuing odevixibat of [redacted]

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Table 27. 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†	[redacted]			
Pruitius response at least 50% of the time¥				
Pruritus response‡				

Notes: †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; ‡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.

8.2.1.2 Response to standard of care

Response to off-label medications included within 'standard of care' (excluding surgical interventions) is assumed to be 0%. This was confirmed by clinicians and the literature on management of PFIC [20], as currently used symptomatic oral therapy is not considered sufficient to control patients' pruritus or the progression of liver disease.

Response to PEBD surgery is informed by NAPPED, where 24 out of 38 patients had an sBA response in PFIC2 (63%) [5] and 12 out 23 had an sBA response in PFIC1 (52%) [14]. 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. These NAPPED estimates are therefore used in the base case.

8.2.1.3 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. A summary of the transition probabilities corresponding to transitions illustrated in Figure 28 is presented in Table 28. Transitions relating into PEBD health states are set to zero in the base case model. However, the functionality to consider PEBD surgery remains programmed in the model in order to allow DMC reviewers the flexibility of understanding how PEBD surgery could affect the care pathway.

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Table 28. 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] [14]
3	PEBD, no response	NAPPED study [5] [14]
4	Loss of response to PEBD	Assumption
5	LTx without PEBD	NAPPED study [5] [14]
6	LTx after PEBD response	Assumed 0%
7	LTx after PEBD nonresponse	NAPPED study [5] [14]
8	LTx to post-LTx	General population
9	Re-transplant	Meta-analysed/pooled LY mortality sourced, [31] [36] [41]
-	Mortality	Bull et al [54]

Notes: Abbreviations: LTx, 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.

8.2.1.3.1 Probability of LTx

The annual probability of LTx (without prior PEBD) is derived from NAPPED. Estimates are modelled for PFIC1 and PFIC2 separately where possible, given the differences in clinical presentation and outcomes following LTx. See section 5.2.1.4.

8.2.1.3.1.1 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 29.

Table 29. Probability of LTx without prior PEBD

PFIC1	PFIC2	Joint*
5.07%	7.52%	6.85%

Notes: *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.

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The probability of LTx without PEBD in PFIC2 patients is derived from the 'no surgical biliary diversion' curve in Figure 24. An annual probability of 7.52% was obtained by digitising the 'no surgical biliary diversion' curve and assuming an exponential distribution (see Table 30) [29].

Table 30. Exponential model results for LTx without PEBD in PFIC2

	Constant term	Standard error	95% CI
Coefficient	0.0782	0.0069	0.0657 - 0.0931

Abbreviations: CI, confidence interval; LTx, 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 26 [14]. An annual probability of 5.07% was obtained by digitising the "no surgical biliary diversion" curve and assuming an exponential distribution (Table 31).

Table 31. Exponential model results for LTx without PEBD in PFIC1

Age, years	Constant term	Standard error	95% CI
Coefficient	0.0520	0.0104	0.0351 - 0.0769

Abbreviations: CI, confidence interval; LTx, liver transplant; PEBD, partial external biliary diversion.

A rate ratio (Table 32) is applied to patients with a pruritus response only (no sBA response) and is calculated based on the proportion of PFIC1 and PFIC2 patients receiving LTx due to intractable pruritus in the NAPPED study [22]. 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, and results in the possibility that patients with only a Pruritus response may have a liver transplant in the subsequent model cycle.

Table 32. 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

Notes: *Joint rate ratio is calculated as a weighted average using the proportion of PFIC 1 and 2 in the PEDFIC1 trial. Abbreviations: LTx, liver transplant.

8.2.1.3.1.2 Probability of LTx with prior 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 33.

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Table 33. 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 [5]. The relevant NAPPED curves used to obtain the transition probabilities to LTx in PEBD non-responders are reproduced in Figure 26 and Figure 27.

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 34 and Table 35.

Table 34. 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 35. 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

Abbreviations: CI, confidence interval

8.2.1.3.2 Mortality

Background mortality is modelled using general population life tables for Denmark [68] 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 [29] [30]. 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, then the model was calibrated using the 'Goal Seek' function in Excel to find the annual probability of death that gave the appropriate pretransplant mortality for PFIC1 and PFIC2 respectively. Table 36 summarises the mortality rates for these states.

Table 36. Annual probability of death prior to surgery

Event	PFIC1	PFIC2	Joint*
Mortality	0.35%	0.24%	0.27%

Notes: *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.

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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 [69]. A summary of the data used is presented in Table 37 and Table 38. Additional detail on each of these data sources is provided in Appendix G – Extrapolation.

Acute mortality rates from the literature varied (between 0% and 37%). Given these variations, a meta-analysis (see Appendix G – Extrapolation) 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 [41]
- Outcomes of LTx for paediatric recipients with progressive familial intrahepatic cholestasis (abstract), Valamparampil et al., 2019 [31]
- Fifteen years single centre experience in the management of progressive familial intrahepatic cholestasis of infancy, Wanty et al., 2004 [36]

No specific suitable Danish data was available, and so an alternative estimate of acute post-LTx mortality from NHS transplant data [69] was included for scenario analysis, which reflects year-one mortality in children with LTx for any indication in the UK.

Table 37. Summary of data used for LTx mortality (acute – in year of LTx)

Annual probability			Reference
PFIC1	**PFIC2**	**Joint***	
1.02%	1.02%	1.02%	Wanty et al., 2004 [36]
37%	15.4%	21.32%	Valamparampi et al., 2019 [31]
25%	25%	25%	Ayodgdu et al., 2007 [41]
11.31%	11.31%	11.31%	Meta-analysed rate (annual)
2.7%	2.7%	2.7%	NHS transplant report, 2020 [69]

Notes: *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. A pooled estimate was used instead using the following two sources:

- Fifteen years single centre experience in the management of progressive familial intrahepatic cholestasis of infancy, Wanty et al., 2004 [36]
- Progressive familial intrahepatic cholestasis: a single-centre experience of living LTx during two decades in Japan, Hori et al., 2011 [70]

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 [69].

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Table 38. 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 [36]
3.57%	3.57%	3.57%	Hori et al., 2011 [70]
1.91%	1.91%	1.91%	Pooled analysis of Hori and Wanty survival curves
0.70%	0.70%	0.70%	NHS transplant report, 2020 [69]

Notes: *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.

8.2.1.3.3 Re-transplantation

Secondary LTx occurs in a significant proportion of children with PFIC, according to clinicians. Estimates from Bull et al., 2018, are used in the model base case. [54] Retransplant is assumed to occur in the same year as the first transplant (Table 39).

Table 39. Rate of re-transplantation in PFIC1 and PFIC2

Population	Re-transplant rate
PFIC1	4%
PFIC2	12%
Joint*	9.81%

Notes: *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 [54]

8.2.1.3.4 Time to event data – summarized:

In the model, changes in sBA were used to predict long-term outcomes in PFIC1 and PFIC2 patients. As described in section 5.2.1.3, 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 25) [5]. 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 27) [14].

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 7.2.3.

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8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

PFIC is an orphan disease which is known to be treated in two specialist hospital settings in Denmark: Rigshospitalet in Copenhagen, and Aarhus University Hospital, in Aarhus. No known data exists which would give reason to distinguish between expected efficacy of odevixibat amongst newly diagnosed PFIC patients in Denmark vs. the available clinical efficacy data from the PEDFIC1 trial. Danish KOL input has indicated that the average age of treatment initiation is 3-5 years, and that there is a 50/50% gender ratio.

Table 40. Patient population

Patient population Important baseline characteristics	**Clinical documentation / indirect comparison etc. (including source)**	**Used in the model (number/value including source)**	**Danish clinical practice (including source)**
Age	4.25 [9]	4.25	KOL expected to be similar
% Female	50 [9]	50	KOL expected to be similar

8.2.2.2 Intervention

The expected use of odevixibat in Danish clinical practice is as licensed by the EMA [8]. Please consult Table 9 in section 5.3 for full details of administration, dosing, discontinuation. Non-responders to treatment at 40 µg/kg will be up-dosed to 120 µg/kg, and treatment will continue until lack of response is confirmed, or to the point where responders no longer respond. It is expected that treatment with odevixibat will be concomitant with off-label symptomatic medications such as UDCA, Cholestyramine, Rifampicin, and Naltrexone. Dosing of medications in the model is based on Danish age-weight norms (Table 50) [71] .

Table 41. Intervention

Intervention	**Clinical documentation (including source)**	**Used in the model (number/value including source)**	**Expected Danish clinical practice (including source if known)**
Posology	Dosing is initiated at 40 µg/kg/day. 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 [8].	Distribution of responders at 40 µg/kg/day and at 120 µg/kg/day as observed in the PEDFIC1 trial [9].	Distribution of responders in Denmark at 40 µg/kg/day and at 120 µg/kg/day is expected as observed in the PEDFIC1 trial.

8.2.2.3 Comparators

Standard of care includes off-label oral drug treatments, such as UDCA and rifampicin, and PEBD surgery. Off-label medications have very limited symptomatic efficacy and do not alter the underlying disease or change the

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course of disease are assumed to have no treatment effect. PEBD surgery results in treatment response for most patients [5], [14], but no known data exists which would give reason to distinguish between expected efficacy of PEBD surgery amongst PFIC patients in Denmark vs. the available clinical efficacy data for PEBD response from the NAPPED trial.

8.2.2.4 Relative efficacy outcomes

There is no reason to expect different response rates relative to 'standard of care' including off-label medications and/or PEBD surgery in Denmark relative to any other country (section 8.2.1.2).

8.2.2.5 Adverse reaction outcomes

Common treatment-emergent adverse events occurring in > 5% patients in the PEDFIC1 trial [9] were included in the model as presented in Table 42. Annual probabilities are converted from the 24 week incidence according to the formula: 1-EXP(-observed incidence in 24 weeks*(52.5 weeks per year/24 weeks). There is no reason to expect different patterns of adverse reactions in Denmark. Associated costs are presented in Table 56.

Table 42. Adverse reaction outcomes

Event	Incidence in PEDFIC 1 (24 weeks)		Annual probability of event per cycle	
	SoC	Odevixibat	SoC	Odevixibat
Diarrhoea	5%	31.0%	10.36%	49.24%
Vomiting	0%	16.7%	0.00%	30.60%
Abdominal pain	0%	7.1%	0.00%	14.39%
Upper respiratory infection	15%	19.0%	27.97%	34.01%
Nasopharyngitis	5%	7.1%	10.36%	14.39%
Alanine aminotransferase ↑	5%	14.3%	10.36%	26.86%
Blood bilirubin ↑	10%	11.9%	19.65%	22.92%
Aspartate aminotransferase ↑	5%	7.1%	10.36%	14.39%
Blood alkaline phosphatase ↑	5%	7.1%	10.36%	14.39%
Pyrexia	25%	28.5%	42.12%	46.39%
Pruritus	5%	7.1%	10.36%	14.39%

Given the clinical consensus on the presence of extrahepatic complications following LTx in PFIC1 and PFIC2, 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 43 were identified in a systematic literature review [72]. Associated costs are presented in Table 57.

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Table 43. Post liver transplant complications

Event	Population		
	PFIC 1	PFIC2 (BSEP deficiency)	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%

Notes: *Joint population estimates were calculated as a weighted average of PFIC 1 and 2 in PEDFIC 1. Abbreviations: LTx, liver transplant; PFIC, progressive familial intrahepatic cholestasis.

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

In the model, changes in sBA were used to predict long-term outcomes in PFIC1 and PFIC2 patients. As described in section 5.2.1.3, 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 25) [5]. 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 27) [14].

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 LTx, by PFIC subtype where possible, as described in section 8.2.1.3.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

As described in section 8.1.1, the cost-effectiveness model includes eight health states encompassing the most significant events in PFIC. Health state utility values used in the model base case were based on literature identified in a systematic literature review, including the impact on utility associated with short stature. The SLR included searches of Medline and Embase databases (via Ovid), Cochrane Library databases (via Wiley online), the Centre for Reviews and Dissemination database (via york.ac.uk/crd), as well as the EconLIT and ScHARRHUD databases. Due to the rarity of PFIC and lack of HRQoL data in PFIC that could be used in the cost-effectiveness analysis, HRQoL data identified from children with related conditions have been used. For example, paediatric patients suffering chronic intrahepatic cholestasis (including patients with PFIC) [16], patients suffering pruritus

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[73] , and paediatric patients who had received liver-transplants. The identified utilities were based on mapping generic paediatric Quality of Life inventory values to UK EQ-5D-3L values using a published and validated algorithm [74]. In the absence of reliable estimates derived specifically form a population of patients with PFIC, this approach has been accepted by the National Institute for Health and Care Excellence in the UK [61]. As there is no algorithm for mapping the generic paediatric quality of life scale to the EQ-5D-5L, there was no potential to apply Danish EQ-5D-5L weights to adjust the obtained utilities for the associated health states. It is uncertain what difference on estimated health state utilities could be expected from health state utilities based on the EQ-5D-5L.

While non-Danish data has been used to inform health state-utilities in the economic model, given the rarity of PFIC, it is believed that the utility data used in the economic model is the most appropriate that is available, and there is no specific reason to expect that the quality of life data that is available is inappropriate to use in the Danish context for patients with this severe disease.

Further details of the literature search for HRQoL data are presented in Appendix H – Literature search for HRQoL data, and details of the utility mapping are presented in Appendix I – Mapping of HRQoL data.

Utility values used in the model are reported in below in Table 44. Age-based utility multipliers based on the Danish Medicines Council Methods Guidelines “Appendiks: Aldersjustering for sundhedsrelateret livskvalitet” have been applied in order to age-adjust utilities in the model [75].

8.4.1.1 Without PEBD

A study by Kamath et al [16] reported HRQoL 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 [74].

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 HRQoL in patients with no response to treatment.

The PedsQL scores were mapped to the EQ-5D using the algorithm by Khan et al [74] [76] (see Appendix I – Mapping of HRQoL data). Patient-reported scores are used in the base case.

A disutility associated with short stature is applied to 'loss of response' states from an HRQoL study in children with chronic kidney disease [73]. A multiplier of 0.977 was obtained for quality of life in patients with short stature versus those with normal growth [73].

8.4.1.2 With PEBD

A disutility of stoma bag is applied to the 'After PEBD' scores to obtain utilities in post-PEBD states [77]. 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) [77].

8.4.1.3 With LTx

LTx and post-LTx utilities were also informed by the literature [38]. 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) [78].

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 [74] [76] (see Appendix I – Mapping of HRQoL data) [79]. An option for applying a NICE Evidence Review Group-preferred utility for post liver transplant utility has been added, but is not applied in the base case.

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

8.4.1.4 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 [73], and mapped to the EQ-5D as described in the section 8.4.1.5. 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 [20]. 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. [74]. This is equivalent to a multiplier of 0.977.

8.4.1.5 Mapping algorithm – PedsQL to EQ-5D

The mapping algorithm used to obtain UK EQ-5D utilities form the PedsQL scores is from Khan et al [74]. The summary of coefficients and resulting scores from regression used can be found in Appendix I – Mapping of HRQoL data.

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8.4.2 Health state utility values used in the health economic model

Table 44. 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 [16]	Utility in "Healthy" children (section 8.4.1.1)
Loss of response	0.830	Al-Uzri et al., 2013 [73] Kamath et al., 2015 [16]	Utility in children with chronic intrahepatic cholestasis and short stature multiplier (section 8.4.1.1)
After PEBD			
sBA & pruritus response	0.659	Hornbrook et al., 2011 [80], Kamath et al., 2015 [16]	Utility in "healthy" children and stoma bag utility (See section 8.4.1.1 and 8.4.1.2)
Loss of response	0.599	Kamath et al., 2015 [16], Hornbrook et al., 2011 [80] and Al Uzri et al., 2013 [73]	Utility in "healthy" children and stoma bag utility (See section 8.4.1.1 and 8.4.1.2)
LTx	0.710	Kini et al., 2011 [78]	See section 8.4.1.3
Post-LTx	0.850	Parmar et al., 2017 [79]	See section 8.4.1.3

Note: Utility sources identified in systematic literature review.

Mapping of the PedsQL in PEDFIC1 was carried out but was not used in the base case analysis (see Appendix I – Mapping of HRQoL data).

8.5 Resource use and costs

All costs were valued in 2021 Danish Kroner (DKK). Where necessary, costs were converted to DKK using purchasing power parity exchange rates from the OECD [81] prior to inflation adjustment.

The resource use in the model was informed by the burden of illness (PICTURE) study [82] which evaluated resource use frequencies and caregiver burden of PFIC ([redacted]). Clinician consultation visits (average number of visits and proportion of patients) are reported in Table 45. 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 47 and was applied to all pre-LTx states.

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Table 45. PICTURE study resource use in PFIC, clinical consultations in the last 12 months

	% patients			Mean number of visits (annual)		
	No surgery (n=63)	Post-PEBD (n=4)	Post-LTx (n=4)	No surgery (n=63)	Post-PEBD (n=4)	Post-LTx (n=4)
Paediatrician	[redacted]					
Hepatologist						
Gastroenterologist						
Dietitian						
Emergency Medicine						
Orthopaedist						
Physiotherapist						
Psychologist						
Speech and language therapist						
Endocrinologist						
GP visit						
Nurse visit						
Stoma care						

Abbreviations: GP, general practitioner; LTx, liver transplant; PEBD, partial external biliary diversion.

Costs for clinical consultation considered in the model are presented in Table 46.

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Table 46. Healthcare resource use categories

Type of consultation	Unit cost (DKK)	Source of cost
Paediatrician	730	www.laeger.dk/sites/default/files/paediatri_takstkort_pr_040121_0.pdf: consultation - 0120
Hepatologist	662	www.laeger.dk/sites/default/files/internmedicin_takstkort_pr_040121.pdf: consultation - 0110 internal Medicin taskort
Gastroenterologist	662	www.laeger.dk/sites/default/files/internmedicin_takstkort_pr_040121.pdf: consultation - 0110 internal Medicin taskort
Dietitian	534	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Kliniske diætister average total pay 2020 (samlet løn) 454624.289500363 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Emergency medicine	1718	Converted from UK 2020 NICE PSSRU estimate £181 using OECD 2020 PPP exchange rate 6.597435 DKK/0.699569 GBP, inflated to 2021 based on 2020 inflation rate 1.007
Orthopaedist	667.59	www.laeger.dk/sites/default/files/ortopaediskkirurgi_takstkort_pr_040121_1.pdf: consultation 0110 ortopaediskkiurgi taskort
Physiotherapist	532	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Fysioterapeuter average total pay 2020 (samlet løn) 453236.549179268 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Psychologist	1548	www.laeger.dk/sites/default/files/boernepsykatri_takstkort_pr_040121.pdf: 0150 Behandlingsforløb med primært psykoterapeutisk behandlingssigte
Speech and language therapist	532	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Fysioterapeuter average total pay 2020 (samlet løn) 453236.549179268 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Endocrinologist	662	www.laeger.dk/sites/default/files/internmedicin_takstkort_pr_040121.pdf: consultation 0110 internal Medicin taskort
GP visit	146	https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf
Nurse visit	591	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Nurse average total pay 2020 (samlet løn) 503018.52641154 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Stoma care	14738	Reference: Buchanan et al. Managing the long term care of inflammatory bowel disease patients: The cost to European health care providers. Average of the cost of stoma care for ulcerative colitis and Crohn's disease, converted by PPP and inflated to 2021 DKK. (1002+1555 euros)/2 (2008 prices) converted by PPP to 2008 DKK (x7.944128 / 0.806152) and then inflated to 2021 DKK (x105.4 / 90.1)

Abbreviations: GP, general practitioner

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Table 47. Proportion of PFIC patients administered tests in the last 12 month and unit costs of test

	% patients	Unit cost (DKK)	Source of cost
Serum bilirubin cv	[redacted]	24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2294
Serum bile acid		24	assume as equal to glucose: No unit cost provided https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3682
Complete blood count		61	assume as (B-Haemoglobin https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2403, B - THROM; https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5438)
Alanine aminotransferase (ALT)		24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3982
Alpha fetoprotein (AFP)		79	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5195
Gamma glutamyl transpeptidase (GGT)		24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3939
Aspartate aminotransferase (AST)		24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3994
Prothrombin (PT)		919	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5618
Glucose		24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2380
Albumin		24	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3886
Vitamin A, E, D, K status		596	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2944
TSH		79	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=6769
Ultrasound (abdominal)		860	internmedicin_takstkort_pr_040121 specialist service 2309 (gastroenterology)

8.5.1 Intervention costs

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.

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 48 summarises the cost per pack of odevixibat and Table 49 summarises the daily and annual cost for each weight band. Table 50 summarises the mean weight by age group in the model based on Danish age-weight norms [71].

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Table 48. Cost per pack of odevixibat

Odevixibat dose	Capsule	Capsule strength (mcg)	Cost per pack (DKK)	Tablets per pack	Cost per tablet (DKK)
Low dose (40 mcg/kg)	Sprinkle	200	[redacted]	30	[redacted]
	Swallow	400		30	
High dose (120 mcg/kg)	Sprinkle	600		30	
	Swallow	1200		30	

Table 49. Daily and annual cost by weight band

Weight	Daily dose		Capsules/day		Daily cost (DKK)		Annual cost (DKK)	
	Low dose	High dose	Sprinkle	Swallow	Low dose	High	Low dose	High dose
4	200	600	1		[redacted]			
7.5	400	1200	2					
12.5	600	1800	3					
17.5	800	2400	4					
19.5	800	2400		2				
25.5	1200	3600		3				
35.5	1600	4800		4				
45.5	2000	6000		5				
55.5	2400	7200		6				

Notes: 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.

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Table 50. 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	12.86	12.23	13.78	13.12	12.55	13.45
5	14.82	14.46	15.88	15.53	14.64	15.71
6	16.81	16.59	18.06	17.91	16.70	17.99
7	18.98	18.68	20.47	20.28	18.83	20.38
8	21.15	20.70	22.95	22.63	20.93	22.79
9	23.93	23.01	26.12	25.30	23.47	25.71
10	26.82	25.74	29.39	28.46	26.28	28.93
11	29.75	28.75	32.74	31.92	29.25	32.33
12	32.93	31.98	36.42	35.62	32.46	36.02
13	36.36	35.44	40.37	39.45	35.90	39.91
14	40.64	39.11	45.15	43.39	39.88	44.27
15	45.69	42.84	50.63	47.28	44.26	48.96
16	50.96	46.44	56.25	50.97	48.70	53.61
17	56.00	49.79	61.53	54.38	52.89	57.96
18	60.42	52.89	66.14	57.54	56.65	61.84
25	63.96	55.77	69.87	60.49	59.87	65.18
35	66.33	58.49	72.43	63.28	62.41	67.86
45	83.98	69.49	83.98	69.49	76.74	76.74
55	87.26	72.38	87.26	72.38	79.82	79.82
65	88.67	75.25	88.67	75.25	81.96	81.96
75	88.01	73.94	88.01	73.94	80.98	80.98

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.

8.5.2 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 51 [83]. 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 [63] and the burden of illness study (cholestyramine) [82].

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Table 51. Acquisition costs, standard of care

Therapy	% patients	Dose per day	Mg/unit	Units/pack	AIP Cost/pack (DKK)	Reference
UDCA	95%	12mg/kg	250	100	137.90	Medicinpriser.dk
Cholestyramine (pediatric)	37.5%	4,000mg	4,000	50	194.35	Medicinpriser.dk
Cholestyramine (adult)		6,000mg				
Rifampicin (pediatric)	66%	10mg/kg	300	100	372.00	Medicinpriser.dk
Rifampicin (adult)		450mg				
Naltrexone	10%	2mg/kg	50	28	222.60	Medicinpriser.dk

Abbreviations: UDCA, ursodeoxycholic acid

8.5.3 PEBD costs

The cost of PEBD surgery and reoperations are assumed equivalent to Danish DRG: 06MP10: Større operationer på tyndtarm og tyktarm u. kompl. Bidiag (see Table 52). The proportion of patients with complications (re-operations, infection or bowel prolapse) was informed by Bjornland et al., 2020 [84]. The weighted average cost of PEBD and associated complications is DKK 170,656.

Table 52. Costs associated with PEBD surgery and complications

Description	Unit cost (DKK)	Proportion of patients*	Source
PEBD surgery	94,133	100%	Danish DRG_tasker 2021 06MP10: Større operationer på tyndtarm og tyktarm u. kompl. bidiag. 94133DKK
Re-operations	94,133	67%	06MP10: Større operationer på tyndtarm og tyktarm u. kompl. bidiag. 94133DKK
Treatment for infection	27,594	43%	Mand , 32 År (DT814I) Postoperativ intraabdominal infektion UNS, 18MA03 - Postoperative og posttraumatiske infektioner, u. kompl. Faktorer 2kontact days task 27594kr https://interaktivdrg.sundhedsdata.dk/
Surgery for bowel prolapse	22,789	7%	Mand , 32 År (DK638E)Prolapsus coli06MA14 - Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år 2 kontact days 22.789 https://interaktivdrg.sundhedsdata.dk/

Abbreviations: PEBD, partial external biliary diversion
*Of those receiving PEBDs

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8.5.4 Liver transplant costs

The cost of liver transplant is assumed equivalent to the cost reported in the 2021 Danish DRG tariffs (26MP06 Levertransplantation). The cost is applied to patients in the year of transplant (Table 53).

Table 53. Costs incurred in year of LTx

Type of cost	Cost (2021 DKK)	Reference
Transplant	910,271	Danish DRG tariffs 2021, 26MP06 Levertransplantation

No direct Danish evidence for post-LTx follow-up costs was found. Therefore Swedish evidence [85] of the two-years post-LTx costs was adapted to the Danish context by applying an exchange rate (Table 55). This Swedish source of post-LTx follow-up costs was previously accepted by the DMC in the assessment of patisiran for hereditary teransthyretin-mediated amyloidosis (hATTR) [86].

Table 54. Costs incurred in 2 years following LTx

Type of cost	Cost (2021 DKK)	Cost per cycle, years 1 and 2	Reference
Post-LTx cost	93,038	46,519	2016 Folkhalsomyndigheten (Swedish) report [85]: Hepatit B-vaccination som ett särskilt vaccinationsprogram. 70000 1st year + 40000 2nd year. Cost estimates converted from SEK to DKK and inflated

Abbreviations: LTx, liver transplant.

Table 55. Costs of immunosuppression

Therapy	Dose per day (mg/kg)	Mg/unit	Units/pack	Cost/pack (DKK)	Reference
Azathioprine	1	50	100	46	Medicinpriser.dk (Azathioprin Ratiopharm")
Tacrolimus	Month 0-3: 0.12	2	50	856	Medicinpriser.dk (Tacrimolus “Dailiport”)
	Month 3-6: 0.09				
	Month 6-9: 0.08				
	Month 9-12+: 0.07				
Prednisolone	Month 0-3: 15	5	100	38	Medicinpriser.dk (Prednisolon "DAK")
	Month 3-6: 7.5				

8.5.5 Adverse event costs

Costs of adverse events associated with odevixibat treatment (Table 42) are presented in Table 56. LTx complications are commonly reported in PFIC1, including diarrhoea and liver steatosis, resulting in poorer post-

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LTx outcomes in this population. The LTx complications reported in Table 43 were allocated the costs shown in Table 57.

Table 56. Adverse events costs

Adverse events	Cost per event (DKK)	Reference
Diarrhoea	125	assumed as AIP package price of loperamide from https://medicinpriser.dk/Default.aspx?id=15&vnr=154521 60x2mg Orifarm Generics
Vomiting	63	assumed as AIP package price of ondansetron https://medicinpriser.dk/Default.aspx?id=15&vnr=591441 10x4mg from 2care4
Abdominal pain	0	Assumption.
Upper respiratory infection	16	assumed as AIP package price of amoxicillin from https://medicinpriser.dk/Default.aspx?id=15&vnr=598949 30x500mg from Sandoz
Nasopharyngitis	16	assumed as AIP package price of amoxicillin from https://medicinpriser.dk/Default.aspx?id=15&vnr=598949 30x500mg from Sandoz
Pyrexia	8	assumed as AIP package price of paracetamol from https://medicinpriser.dk/Default.aspx?id=15&vnr=580984 20x500mg from Vitabalans

Table 57. List of LTx complications and summary of costs included in the cost- effectiveness model

LTx Complication	Cost per event (DKK)	Reference
Diarrhoea	5130	Danish DRG tariffs 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Liver steatosis	30893	Danish DRG tariffs 2021, Mand , 32 År (DK760A) Ikke-alkoholisk fedtdegeneration i leveren 07MA05 - Kronisk leversygdom uden komplikationer 2 kontaktdage takst 30.893 https://interaktivdrg.sundhedsdata.dk/
Stunted growth	0	Assumption.
Deafness	0	Assumption.
Pancreatitis	2610	Danish DRG tariffs 2021, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DK859: Akut pankreatitis UNS

8.5.6 Patient costs

Patient costs for travel and time have been included based on the Danish methods guideline [66]. Frequency of healthcare visits were based on results of the burden of illness (PICTURE) study [82]. It was assumed that each visit would take an average of 2 hours patient time including travel time. The value of patients' time was DKK 179 per hour, and travel expenses were assumed to be DKK 100 per roundtrip [66].

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8.6 Results

8.6.1 Base case overview

The key aspects of the base case cost-effectiveness model are presented in Table 58.

Table 58. Base case overview

Comparator	Standard care
Type of model	Markov model
Time horizon	Lifetime (up to age 100)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Literature-derived utilities
Included costs	Pharmaceutical costs Healthcare resources Adverse events Patient- and transportation costs
Dosage of pharmaceutical	Based on weight

8.6.2 Base case results

In the model base case where odevixibat is compared against standard care (off-label symptomatic medications prior to liver transplant), discounted results are presented in Table 59. Using a lifetime horizon (up to a maximum age 100), the incremental expected total life-year gain amounts to [redacted]). The discounted incremental costs of [redacted] and incremental QALYs [redacted] resulted in an incremental cost-effectiveness ratio (ICER) of [redacted] versus standard care.

Table 59. [redacted]

Per patient	Standard of Care	Odevixibat	Difference
Life years gained (undiscount	[redacted]		
Years with response			
Years with loss of response			
Years in PEBD with response			
Years in PEBD with loss of response			
Years in LTx			
Years in post-LTx			
Total life-years			
Life-years gained (discounted			
Years with response			
Years with loss of response			
Years in PEBD with response			
Years in PEBD with loss of response			
Years in LTx			
Years in post-LTx			
Total life-years			
QALYs (discounted)			

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Per patient	Standard of Care	Odevixibat	Difference
QALYs with response	[redacted]		
QALYs loss of response			
QALYs PEBD response			
QALYs PEBD no response			
QALYs LTx			
QALYs post-LTx			
QALY decrements			
Total QALYs			
Costs (DKK, discounted)			
Costs of odevixibat medication			
Costs of non-odevixibat medications			
Costs of odevixibat medication administration Initiation			
Healthcare resources			
Adverse event costs			
Patient costs (time and travel)			
Death costs			
Total costs			
Incremental results			
ICER			

8.7 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications, including details of how they varied in the model can be found in Appendix J – Probabilistic sensitivity analyses.

8.7.1 Deterministic sensitivity analyses

Univariate 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. The 10 most influential model parameters with regards to impact on range of impact on the base case ICER are presented in Table 60, and as a tornado diagram in Figure 29. A curve for the relationship between odevixibat medication price and ICER is presented in Figure 30.

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Table 60. One-way sensitivity analyses results

Parameter	ICER at lower value of parameter (DKK/QALY)	ICER at upper value of parameter (DKK/QALY)	% change from base case at lower value	% change from base case at upper value
Response to odevixibat - sBA & pruritus response – up-titrators	[redacted]			
Healthy PedsQL - emotional score (Kamath 2015)				
Disutility of stoma bag - ulcerative colitis				
Response to odevixibat - sBA & pruritus response - 40 µg/kg				
Healthy PedsQL - physical score (Kamath 2015)				
LTx mortality, post-LTx - pooled rate				
LTx mortality, in year of transplant - meta-analysis				
sBA≥118 PedsQL - emotional score (Kamath 2015)				
Annual loss of response (odevixibat)				
sBA≥118 PedsQL - physical score (Kamath 2015)				

Figure 29. Tornado diagram: One-way sensitivity analysis

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Figure 30. ICER (DKK/QALY) vs. odevixibat price curve for odevixibat for PFIC

A number of scenarios were considered in the deterministic sensitivity analyses exploring variations from the base model settings (Table 61). Important factors for estimating the ICER of treatment of PFIC patients with odevixibat include the time on treatment, dosing of odevixibat, source of utilities, and source of liver transplant related mortality. If treatment continues regardless of clinical response until surgery, this will significantly increase costs, as it will if patients are all treated with high dose odevixibat. Utilities from the PEDFIC1 trial were considered in the scenario analysis as PedsQL data were included as an exploratory endpoint in the PEDFIC1 study and 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.

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Table 61. Scenario analyses

Scenario	Incremental costs (DKK)	Incremental QALYs	ICER (DKK/QALY)	% change from base case ICER
Base case	[redacted]			
Time on treatment with odevixibat (treat until surgery)				
Annual loss of response to odevixibat 5%				
Annual loss of response to odevixibat 10%				
Odevixibat 40µg/kg dose				
Odevixibat 120µg/kg dose				
Response to SoC = 10%				
Time horizon halved (50 years)				
Utilities from PEDFIC 1				
Utilities from PEDFIC 2 (parent-proxy)				
Pruritus response endpoint from PEDFIC1				
LTx mortality from NHS report				
Parent proxy QoL				
Proportion of PFIC 1 = 50%				
Discount rate = 5%				
No discounting				

8.7.2 Probabilistic sensitivity analyses

A scatter plot of 2000 simulations, including a 95% confidence ellipse, is presented in Figure 31, with an associated cost-effectiveness acceptability curve presented in Figure 32. The full set of parameters included in the model, including details of distributional forms, are presented in Appendix J – Probabilistic sensitivity analyses.

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Figure 31. Cost-effectiveness plane

Figure 32. Cost-effectiveness acceptability curve

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9. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending odevixibat as the standard treatment for patients with PFIC in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of odevixibat in Denmark.

The budget impact model was linked through the Markov traces in the cost-effectiveness model, and therefore any changes in the settings of the cost-effectiveness model would affect the results of the budget impact model.

The analysis was developed by comparing the costs for the Danish healthcare system per year over five years in the scenario where odevixibat is recommended as standard treatment and the scenario where odevixibat is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios.

9.1 Number of patients

PFIC is an orphan disease with very few patients (see section 5). In Denmark, it is known that PFIC patients are treated by specialists in Copenhagen and Aarhus. KOLs have not precisely identified the number of PFIC patients in Denmark who would be eligible for odevixibat if previous treatment has not proven successful. The feedback which has been provided suggests that there may be approximately [redacted].

For the purpose of estimating the budget impact of the introduction of odevixibat, [redacted] Furthermore, the average age of a PFIC patient who would be eligible for treatment with odevixibat (e.g. has not yet had a liver transplant) has been assumed as 10. The estimated numbers of patients who would be treated with odevixibat under the scenarios where odevixibat is and is not introduced (Table 62, Table 63) are based on the assumption [redacted] of eligible patients would be treated with odevixibat in the following years.

Table 62. Number of eligible patients expected to be treated over the next five-year period if odevixibat is introduced

	2022	2023	2024	2025	2026
Odevixibat	[redacted]				
Standard Care					
Total number of patients					

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Table 63. Number of eligible patients expected to be treated over the next five-year period if odevixibat is NOT introduced

	2022	2023	2024	2025	2026
Odevixibat	[redacted]				
Standard Care					
Total number of patients					

9.2 Budget impact

The budget impact estimated below (Table 64) is based on non-discounted cost outputs (2021 DKK) from the cost-effectiveness model for five years, and the assumed eligible patients described above, as well as the assumed uptake of odevixibat for the treatment of eligible PFIC patients described above.

Table 64. Expected budget impact (2021 DKK) of recommending odevixibat for treatment of PFIC

	2022	2023	2024	2025	2026
Odevixibat is NOT recommended	[redacted]				
Odevixibat is recommended					
Budget impact of the recommendation					

10. Discussion on the submitted documentation

Progressive familial intrahepatic cholestasis is an orphan disease with severe debilitating life consequences. Due to the rarity of PFIC there is extremely limited clinical evidence available regarding the natural history of the disease and as a necessary consequence of the small number of patients, there is unavoidable uncertainty regarding the efficacy of treatment. The completed PEDFIC1 [9] and ongoing PEDFIC2 [11] trials provide the most comprehensive data available regarding efficacy of odevixibat for treatment of patients with PFIC. However, the evidence that is available is limited to patients with PFIC1 and PFIC2, with only a small number of individuals with other (even rarer) PFIC subtypes currently represented in the ongoing PEDFIC2 trial.

By offering an effective non-surgical treatment option, odevixibat has the potential to transform the lives of individuals with PFIC and their families/caregivers. However, as odevixibat is the first treatment licensed for treatment of PFIC [8], it is a limitation of this submission that there is no evidence of the relative efficacy of odevixibat with other active medicinal treatments for PFIC. Additionally, while data continues to be collected through ongoing long-term follow-up studies, the key trial comparing odevixibat with placebo (PEDFIC1) lasted only 24 weeks and the primary endpoint (at least a 70% reduction in sBA concentration from baseline or reaching a level ≤70µmol/L) was not long-term survival, and there is limited evidence of the annual rate of loss of response to odevixibat. While it is expected that clinical response to odevixibat will be able to delay and possibly even obviate the need for liver transplant, there is no direct evidence of this from the clinical studies. Further, it is

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uncertain how response and loss of response to odevixibat will be assessed in clinical practice in Denmark. The continued use of odevixibat beyond loss of response may have consequential economic impacts.

PFIC often initially affects young children for whom the primary clinical endpoints fail to fully indicate the benefits of treatment with odevixibat. Consequently, it is a real strength that PEDFIC studies have collected a substantial set of secondary endpoints which identify important evidence of the potential for odevixibat to improve the lives of both patients and their caregivers. Capturing endpoints such as patients' cognitive functioning, communication abilities, family relationships, sleep parameters and growth indicators strengthen the evidence base of the positive impacts that treatment with odevixibat can have on the lives of patients with PFIC.

To address the limitations in the lack of published clinical evidence for this orphan disease, Albireo is continuing to collect the following additional data to support the evidence package for odevixibat, alongside the current PEDFIC1, PEDFIC2 and NAPPED data:

- The "Odevixibat vs. External Control" (OvEC) study to compare clinical outcomes in odevixibat to comparable external controls (matched NAPPED data)
- Prospective, registry-based studies to investigate the long-term safety and efficacy of odevixibat in patients with PFIC.

The clinical pathway for PFIC patients reflected in the structure of the Markov model was KOL validated for Denmark. However, healthcare resource use data used in the model comes from a burden of illness study [82], and there is uncertainty regarding the accuracy of the resource use estimates for PFIC patients pre and post-surgery in Denmark.

The uncertainly regarding estimation of health state utilities is a limitation. Very few participants in the PEDFIC1 study reported PedsQL data which could be mapped to EQ-5D scores, and the data that did come from directly from patients (young children) was inconsistent. Consequently, utilities from the literature were used to inform health states of responders and non-responders to odevixibat prior to surgical intervention.

Acute and particularly long-term post liver-transplant mortality amongst PFIC patients are important factors affecting the expected cost-effectiveness of odevixibat. However, it is uncertain how well the post liver-transplant mortality data used in the economic model reflects post-liver transplant survival of PFIC patients in Denmark.

It is a weakness that the budget impact analysis is based on an uncertain number of PFIC patients who will be eligible for treatment with odevixibat in Denmark, as well as the current average weight of PFIC patients who have not yet had liver transplant surgery.

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13. References

[1] M. Gunaydin and A. Bozkurter Cil, 'Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment', *Hepatic Med. Evid. Res.*, vol. 10, pp. 95–104, Sep. 2018, doi: 10.2147/HMER.S137209.

[2] L. Pawlikowska *et al.*, 'Differences in presentation and progression between severe FIC1 and BSEP deficiencies', *J. Hepatol.*, vol. 53, no. 1, pp. 170–178, 2010, doi: 10.1016/j.jhep.2010.01.034.

[3] Albireo, 'Albireo UK Advisory Board Meeting. 3 March 2021. Meeting report'. 2021.

[4] T. Hori, J. H. Nguyen, and S. Uemoto, 'Progressive Familial Intrahepatic Cholestasis', *Hepatobiliary Pancreat Dis Int*, vol. 9, no. 6, pp. 570–578, 2010.

[5] D. van Wessel *et al.*, 'Genotype correlates with the natural history of severe bile salt export pump deficiency', *J. Hepatol.*, vol. 73, no. 1, pp. 84–93, 2020, [Online]. Available: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2005431889%0Ahttp://dx.doi.org/10.1016/j.jhep.2020.02.007.

[6] E. Gonzales and E. Jacquemin, 'Mutation specific drug therapy for progressive familial or benign recurrent intrahepatic cholestasis: A new tool in a near future?', *J. Hepatol.*, vol. 53, no. 2, pp. 385–387, 2010, doi: 10.1016/j.jhep.2010.03.012.

[7] E. Jacquemin, 'Progressive familial intrahepatic cholestasis', *Clin. Res. Hepatol. Gastroenterol.*, no. 36, pp. S26–S35, 2012.

[8] EMA, 'Bylvay SUMMARY OF PRODUCT CHARACTERISTICS'. 2021, Accessed: Oct. 11, 2021. [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/bylvay-epar-product-information_en.pdf.

[9] Albireo, 'A4250-005 Clinical Study Report A Double-Blind, Randomized, PlaceboControlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 1)'. 2020.

[10] R. J. Thompson *et al.*, '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', 2020.

[11] Albireo, 'A4250-008 Clinical Study Report: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2)'. 2020.

[12] R. Thompson *et al.*, '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 Richard', 2020, [Online]. Available: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02286068/full.

[13] Albireo, 'Data on File: Analysis of response to 120mcg dose in PEDFIC2 according to response to 40mcg

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www.medicinraadet.dk

dose in PEDFIC1'. 2021.

[14] D. B. E. Wessel *et al.*, 'Impact of Genotype, Serum Bile Acids, and Surgical Biliary Diversion on Native Liver Survival in FIC1 Deficiency', *Hepatology*, vol. 74, no. 2, pp. 892–906, Aug. 2021, doi: 10.1002/hep.31787.

[15] Children's Liver Disease Foundation, 'Progressive Familial Intrahepatic Cholestasis - A Guide'. 2018, [Online]. Available: https://childliverdisease.org/liver-information/childhood-liver-conditions/progressive-familial-intrahepatic-cholestasis/.

[16] B. M. Kamath *et al.*, 'Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome', *J. Pediatr.*, vol. 167, no. 2, pp. 390-396.e3, Aug. 2015, doi: 10.1016/J.JPEDS.2015.04.077.

[17] C. N. Ghent, J. R. Bloomer, and G. Klatskin, 'Elevations in skin tissue levels of bile acids in human cholestasis: relation to serum levels and to pruritus', *Gastroenterology*, vol. 73, no. 5, pp. 1125–1130, 1977, doi: 10.1016/s0016-5085(19)31870-0.

[18] A. Srivastava, 'Progressive familial intrahepatic cholestasis', *Journal of Clinical and Experimental Hepatology*, vol. 4, no. 1. pp. 25–36, 2014, doi: 10.1016/j.jceh.2013.10.005.

[19] A. Mehl, H. Bohorquez, M.-S. Serrano, G. Galliano, and T. W. Reichman, 'Liver transplantation and the management of progressive familial intrahepatic cholestasis in children', *World J. Transplant.*, vol. 6, no. 2, p. 278, 2016, doi: 10.5500/wjt.v6.i2.278.

[20] A. Davit-Spraul, E. Gonzales, C. Baussan, and E. Jacquemin, 'Progressive familial intrahepatic cholestasis', *Orphanet J. Rare Dis.*, vol. 4, no. 1, 2009, doi: 10.1186/1750-1172-4-1.

[21] E. Sticova, M. Jirsa, and J. Pawłowska, 'New Insights in Genetic Cholestasis: From Molecular Mechanisms to Clinical Implications', *Can. J. Gastroenterol. Hepatol.*, vol. 2018, pp. 1–12, Jul. 2018, doi: 10.1155/2018/2313675.

[22] Albireo, 'Confidential - Indications for liver transplantation of BSEP1, BSEP2, and FIC1 patients: data from NAPPED (file H1016)'. 2020.

[23] A. Baker, N. Kerkar, L. Todorova, B. M. Kamath, and R. H. J. Houwen, 'Systematic review of progressive familial intrahepatic cholestasis', *Clin. Res. Hepatol. Gastroenterol.*, vol. 43, no. 1, pp. 20–36, 2019.

[24] R. A. Morotti, F. J. Suchy, and M. S. Magid, 'Progressive familial intrahepatic cholestasis (PFIC) Type 1, 2, and 3: A review of the liver pathology findings', *Semin. Liver Dis.*, vol. 31, no. 1, pp. 3–10, 2011, doi: 10.1055/s-0031-1272831.

[25] H. Per, D. Arslan, H. Gümüş, A. Çoskun, and S. Kumandaş, 'Intracranial hemorrhages and late hemorrhagic disease associated cholestatic liver disease', *Neurol. Sci.*, vol. 34, no. 1, pp. 51–56, 2013, doi: 10.1007/s10072-012-0965-5.

[26] L. Ruiz-Casas *et al.*, 'Burden of illness of progressive familial intrahepatic cholestasis in the US, UK, France, and Germany: study rationale and protocol of the PICTURE study', *Expert Rev.*

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Pharmacoeconomics Outcomes Res., vol. 21, no. 2, pp. 247–253, 2021, doi: 10.1080/14737167.2021.1859371.

[27] N. M. Samra, S. Emad El Abrak, H. H. El Dash, M. El Said El Raziky, and M. A. El Sheikh, 'Evaluation of vitamin D status bone mineral density and dental health in children with cholestasis', *Clin. Res. Hepatol. Gastroenterol.*, vol. 42, no. 4, pp. 368–377, Sep. 2018, doi: 10.1016/j.clinre.2017.11.010.

[28] N. Ruth *et al.*, 'Long term outcome of children with PFIC -A single centre experience', *HEPATOLOGY - General Hepatology H-P-074*, vol. 66, no. April. pp. 793–794, 2018.

[29] D. van Wessel *et al.*, 'The natural course of FIC1 deficiency and BSEP deficiency: Initial results from the NAPPED-consortium (Natural course and Prognosis of PFIC and Effect of biliary Diversion): Poster Presentation: SAT-048', 2018.

[30] D. van Wessel, R. Thompson, T. Grammatikopoulos, and E. Al., 'Factors associated with the natural course of disease in patients with FIC1-deficiency: the NAPPED-consortium', *J. Pediatr. Gastroenterol. Nutr.*, pp. 688–689, 2019, [Online]. Available: https://www.researchgate.net/journal/1536-4801_Journal_of_pediatric_gastroenterology_and_nutrition.

[31] l J. Valamparampi, K. Rinaldhy, M. Reddy, N. Shanmugam, and M. Rela, 'Outcomes of Liver Transplantation for Pediatric Recipients With Progressive Familial Intrahepatic Cholestasis', *J. Clin. Exp. Hepatol.*, vol. 9, no. 3, pp. 422–423, 2019.

[32] S. Acar, B. Demir, H. Ayyildiz, and E. Al., 'Living donor liver transplantation for PFIC type 3', *J. Pediatr. Gastroenterol. Nutr.*, vol. 68, no. Supplement 1, p. 918, 2019, [Online]. Available: https://www.researchgate.net/journal/1536-4801_Journal_of_pediatric_gastroenterology_and_nutrition.

[33] A. Davit-Spraul *et al.*, 'ATP8B1 and ABCB11 Analysis in 62 children with normal gamma-glutamyl transferase Progressive Familial Intrahepatic Cholestasis (PFIC): Phenotypic differences between PFIC1 and PFIC2 and natural history', *Hepatology*, vol. 51, no. 5, pp. 1645–1655, 2010, doi: 10.1002/hep.23539.

[34] S. B. Schatz *et al.*, 'Phenotypic spectrum and diagnostic pitfalls of ABCB4 deficiency depending on age of onset', *Hepatol. Commun.*, vol. 2, no. 5, pp. 504–514, 2018, doi: 10.1002/hep4.1149.

[35] J. Valamparampil, N. Shanmugam, M. S. Reddy, and M. Rela, 'Liver transplantation in progressive familial intrahepatic cholestasis: outcome analysis from a single centre', *Transplantation*, vol. 102 (S5 Su, pp. 141–142, 2018.

[36] C. Wanty *et al.*, 'Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy', *Acta Gastroenterol. Belg.*, vol. 67, no. 4, pp. 313–319, 2004.

[37] K. Torfgard, C. Gwaltney, J. Paty, J. Mattsson, and P. Soni, 'Symptoms and daily impacts associated with progressive familial intrahepatic cholestasis and other pediatric cholestatic liver diseases: a qualitative study with patients and caregivers HP-088.', *Gen. Hepatol.*, vol. 67, no. sup 1, pp. S208-209, 2018.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

[38] S. Wassman *et al.*, 'Quality of Life in Patients With Progressive Familial Intrahepatic Cholestasis: No Difference Between Post-liver Transplantation and Post-partial External Biliary Diversion', *J. Pediatr. Gastroenterol. Nutr.*, vol. 67, no. 5, pp. 643–648, 2018, doi: 10.1097/MPG.0000000000002118.

[39] K. Yee, O. Moshkovich, S. Llewellyn, K. Benjamin, and N. Desai, 'Web-Based Survey of Itch Severity after Surgical Treatment of Progressive Familial Intrahepatic Cholestasis in Children and Adolescents', *Hepatology*, vol. 68, no. supplement 1, p. 1047A, 2018.

[40] A. Kwak *et al.*, 'Health related quality of life in children with progressive familial intrahepatic cholestasis after partial external biliary diversion', *Pediatr. Wspolczesna*, vol. 7, no. 3, pp. 201–204, 2005.

[41] S. Aydogdu *et al.*, 'Liver transplantation for progressive familial intrahepatic cholestasis: Clinical and histopathological findings, outcome and impact on growth', *Pediatr. Transplant.*, vol. 11, no. 6, pp. 634–640, 2007, doi: 10.1111/j.1399-3046.2007.00722.x.

[42] Albireo, 'Data on File: PFIC patient testimonials (with consents provided for use in NICE submission)'. 2021.

[43] Committee for Medicinal Products for Human Use (CHMP), 'Bylvay - Assessment Report', 2021. Accessed: Oct. 21, 2021. [Online]. Available: www.ema.europa.eu/en/documents/assessment-report/bylvay-epar-public-assessment-report_en.pdf.

[44] Children's Liver Disease Foundation, 'Progressive Familial Intrahepatic Cholestasis - Webpage'. 2019, Accessed: Apr. 28, 2020. [Online]. Available: https://childliverdisease.org/liver-information/childhood-liver-conditions/progressive-familial-intrahepatic-cholestasis/.

[45] European Association for the Study of the Liver, 'EASL Clinical Practice Guidelines: Management of cholestatic liver diseases', *J. Hepatol.*, vol. 51, no. 2, pp. 237–267, 2009, doi: 10.1016/j.jhep.2009.04.009.

[46] R. van Dijk, A. Kremer, W. Smit, and E. Al., 'Characterization and treatment of persistent hepatocellular secretory failure', *Liver Int.*, vol. 35, pp. 1479–88, 2015.

[47] G. V. Gregorio, C. S. Ball, A. P. Mowat, and G. Mieli-Vergani, 'Effect of rifampicin in the treatment of pruritus in hepatic cholestasis', *Arch. Dis. Child.*, vol. 69, no. 1, pp. 141–143, 1993, doi: 10.1136/adc.69.1.141.

[48] L. S. Pillarisetty and A. Sharma, 'Pregnancy Intrahepatic Cholestasis', *StatPearls*, pp. 1–8, 2020, [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/31855347.

[49] N. Schukfeh, M. Metzelder, C. Petersen, and E. Al., 'Normalization of serum bile acids after partial external biliary diversion indicates an excellent long-term outcome in children with progressive familial intrahepatic cholestasis', *J. Pediatr. Surg.*, vol. 47, pp. 501–505, 2012.

[50] H. Yang, R. J. Porte, H. J. Verkade, Z. J. De Langen, and J. B. F. Hulscher, 'Partial External Biliary Diversion in Children With Progressive Familial Intrahepatic Cholestasis and Alagille Disease', *J. Pediatr. Gastroenterol. Nutr.*, vol. 49, pp. 216–221, 2009, [Online]. Available:

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
www.medicinraadet.dk

https://www.researchgate.net/journal/1536-.

[51] M. Melter *et al.*, 'Progressive familial intrahepatic cholestasis: Partial biliary diversion normalizes serum lipids and improves growth in noncirrhotic patients', *Am. J. Gastroenterol.*, vol. 95, no. 12, pp. 3522–3528, 2000, doi: 10.1016/S0002-9270(00)02163-8.

[52] Albireo (& Open Health), 'Technical Report: Systematic Literature Review and Meta Analysis Update on the Effect of Partial External Biliary Diversion Surgery on Clinical and Biochemical Outcomes in Progressive Familial Intrahepatic Cholestasis'. 2021.

[53] H. J. Verkade *et al.*, 'Systematic Review and Meta-analysis: Partial External Biliary Diversion in Progressive Familial Intrahepatic Cholestasis', *J. Pediatr. Gastroenterol. Nutr.*, vol. 71, pp. 176–183, 2020, [Online]. Available: https://www.researchgate.net/journal/1536-4801_Journal_of_pediatric_gastroenterology_and_nutrition.

[54] L. N. Bull *et al.*, 'Outcomes of surgical management of familial intrahepatic cholestasis 1 and bile salt export protein deficiencies', *Hepatol. Commun.*, vol. 2, no. 5, pp. 515–528, 2018, doi: 10.1002/hep4.1168.

[55] K. S. Wang *et al.*, 'Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis', *Hepatology*, vol. 65, no. 5, pp. 1645–1654, May 2017, doi: 10.1002/hep.29019.

[56] N. M. Silva, M. A. Dos Santos, S. R. Rosado, C. M. Galvão, and H. M. Sonobe, 'Psychological aspects of patients with intestinal stoma: integrative review', *Rev. Lat. Am. Enfermagem*, vol. 25, p. e2950, 2017, doi: 10.1590/1518-8345.2231.2950.

[57] J. M. Stapelbroek, K. J. van Erpecum, L. W. J. Klomp, and R. H. J. Houwen, 'Liver disease associated with canalicular transport defects: Current and future therapies', *J. Hepatol.*, vol. 52, no. 2, pp. 258–271, 2010, doi: 10.1016/j.jhep.2009.11.012.

[58] W. R. Kim *et al.*, 'OPTN/SRTR 2017 Annual Data Report: Liver', *Am. J. Transplant.*, vol. 19, pp. 184–283, 2019, doi: 10.1111/ajt.15276.

[59] P. Lykavieris *et al.*, 'Progressive familial intrahepatic cholestasis type 1 and extrahepatic features: No catch-up of stature growth, exacerbation of diarrhea, and appearance of liver steatosis after liver transplantation', *Journal of Hepatology*, vol. 39, no. 3. pp. 447–452, 2003, doi: 10.1016/S0168-8278(03)00286-1.

[60] R. S. Venick *et al.*, 'One Thousand Pediatric Liver Transplants During Thirty Years: Lessons Learned', *J. Am. Coll. Surg.*, vol. 226, no. 4, pp. 355–366, Apr. 2018, doi: 10.1016/j.jamcollsurg.2017.12.042.

[61] NICE, 'Odevixibat for treating progressive familial intrahepatic cholestasis [ID1570] Committee Papers', 2021. Accessed: Oct. 21, 2021. [Online]. Available: https://www.nice.org.uk/guidance/indevelopment/gid-hst10043/documents.

[62] Albireo, 'Data on File: Response to FDA's Clinical Information Request #2 dated 22JAN2021'. 2021.

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www.medicinraadet.dk

[63] NICE, 'Obeticholic acid for treating primary biliary cholangitis STA [ID785] Committee papers', 2017. [Online]. Available: https://www.nice.org.uk/guidance/ta443/documents/committee-papers.

[64] NICE, 'Highly Specialised Technology Evaluation Inotersen for treating hereditary transthyretin-related amyloidosis [ID1242] Evaluation Report', p. 621, 2019, [Online]. Available: https://www.nice.org.uk/guidance/hst9/evidence/evaluation-consultation-committee-papers-pdf-6782713166.

[65] DMC Medicinrådet, 'Inotersen (Tegsedi)', 2020. https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/i-l/inotersen-tegsedi-arvelig-transthyretin-medieret-amyloidose-hattr (accessed Nov. 23, 2021).

[66] DMC Medicinrådet, 'The Danish Medicines Council methods guide for assessing new pharmaceuticals version 1.2', 2021. Accessed: Nov. 03, 2021. [Online]. Available: https://medicinraadet.dk/media/wq0dxny2/the_danish_medicines_council_methods_guide_for_assessing_new_pharmaceuticals_version_1-2_adlegacy.pdf.

[67] Finansministeriet, 'Dokumentationsnotat for den samfundsøkonomiske diskonteringsrente', 2021. Accessed: Nov. 02, 2021. [Online]. Available: https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf.

[68] Statistics Denmark, 'Life table (2 years tables 2019-2020) by life table, time, age and sex', 2021. https://www.statbank.dk/statbank5a/SelectVarVal/saveselections.asp.

[69] NHS Blood and Transplant, 'Annual Activity Report - Section 8', 2020.

[70] T. Hori *et al.*, 'Progressive familial intrahepatic cholestasis: A single-center experience of living-donor liver transplantation during two decades in Japan', *Clin. Transplant.*, vol. 25, no. 5, pp. 776–785, 2011, doi: 10.1111/j.1399-0012.2010.01368.x.

[71] J. Tinggaard *et al.*, 'The 2014 Danish references from birth to 20 years for height, weight and body mass index', *Acta Paediatr.*, vol. 103, no. 2, pp. 214–224, Feb. 2014, doi: 10.1111/APA.12468.

[72] Albireo (& Roboleo), 'Caregiver burden related to the care of children with rare and ultra-rare diseases: Targeted literature review'. 2021.

[73] A. Al-Uzri *et al.*, 'The impact of short stature on health-related quality of life in children with chronic kidney disease', *J. Pediatr.*, vol. 163, no. 3, pp. 736-741.e1, 2013, doi: 10.1016/j.jpeds.2013.03.016.

[74] K. A. Khan, S. Petrou, O. Rivero-Arias, S. J. Walters, and S. E. Boyle, 'Mapping EQ-5D utility scores from the PedsQL™ generic core scales', *Pharmacoeconomics*, vol. 32, no. 7, pp. 693–706, 2014, doi: 10.1007/s40273-014-0153-y.

[75] DMC Medicinrådet, 'Appendiks: Aldersjustering for sundhedsrelateret livskvalitet', 2021. Accessed: Nov. 04, 2021. [Online]. Available: www.medicinraadet.dk.

[76] T. Lambe *et al.*, 'Mapping the Paediatric Quality of Life Inventory (PedsQL™) Generic Core Scales onto

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www.medicinraadet.dk

the Child Health Utility Index–9 Dimension (CHU-9D) Score for Economic Evaluation in Children', *PharmacoEconomics 2017 364*, vol. 36, no. 4, pp. 451–465, Dec. 2017, doi: 10.1007/S40273-017-0600-7.

[77] K. O. Arseneau *et al.*, 'Do Patient Preferences Influence Decisions on Treatment for Patients With Steroid-Refractory Ulcerative Colitis?', *Clin. Gastroenterol. Hepatol.*, vol. 4, no. 9, pp. 1135–1142, 2006, doi: 10.1016/j.cgh.2006.05.003.

[78] S. P. Kini, L. K. DeLong, E. Veledar, A. M. McKenzie-Brown, M. Schaufele, and S. C. Chen, 'The Impact of Pruritus on Quality of Life', *Arch. Dermatol.*, vol. 147, no. 10, p. 1153, Oct. 2011, doi: 10.1001/archdermatol.2011.178.

[79] A. Parmar, S. M. Vandriel, and V. L. Ng, 'Health-related quality of life after pediatric liver transplantation: A systematic review', *Liver Transplant.*, vol. 23, no. 3, pp. 361–374, Mar. 2017, doi: 10.1002/lt.24696.

[80] M. C. Hornbrook *et al.*, 'Complications Among Colorectal Cancer Survivors', *Med. Care*, vol. 49, no. 3, pp. 321–326, Mar. 2011, doi: 10.1097/MLR.0b013e31820194c8.

[81] OECD, 'Dataset: 4. PPPs and exchange rates'. 2021, [Online]. Available: https://stats.oecd.org/Index.aspx?DataSetCode=PRICES_CPI.

[82] Albireo, 'Data on File: PICTURE study – interim results'. 2021.

[83] NICE, 'British National Formulary'. 2021, [Online]. Available: https://bnf.nice.org.uk.

[84] K. Bjornland *et al.*, 'Partial Biliary Diversion May Promote Long-Term Relief of Pruritus and Native Liver Survival in Children with Cholestatic Liver Diseases', *Eur. J. Pediatr. Surg.*, vol. 31, no. 4, pp. 341–346, 2021, doi: 10.1055/s-0040-1714657.

[85] Folkhälsomyndigheten (Sweden), 'Hepatit B-vaccination som ett särskilt vaccinationsprogram Hälsoekonomisk utvärdering', 2016.

[86] DMC Medicinrådet, 'Patisiran (Onpattro)', 2020. https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/m-p/patisiran-onpattro-arvelig-transthyretin-medieret-amyloidose-hattr (accessed Nov. 23, 2021).

[87] J. W. Varni, M. Seid, and C. A. Rode, 'The PedsQL: measurement model for the pediatric quality of life inventory', *Med. Care*, vol. 37, no. 2, pp. 126–139, Feb. 1999, doi: 10.1097/00005650-199902000-00003.

[88] Mapi Research Trust and J. W. Varni, 'Pediatric Quality of Life Inventory™ (PedsQL™) SCALING AND SCORING OF THE', 2017. Accessed: Nov. 08, 2021. [Online]. Available: https://eprovide.mapi-trust.org/.

[89] Albireo, 'A4250-003 Clinical Study Report V3.0. An Exploratory Phase II Study to Demonstrate the Safety and Efficacy of A4250 in Children with Cholestatic Pruritus'. 2020.

[90] Albireo, 'Data on File: EMA Day 90 Response to Question 153 (PEDFIC2 updated efficacy and safety data - December 2020 cut-off)'. 2021.

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[91] Albireo, 'Patient- and Observer-Reported Outcome Pruritus Measures: Summary of Measurement Characteristics. Evidence Dossier. Odevixibat Progressive Familial Intrahepatic Cholestasis Development Programme. Draft 1.0.' 2020.

[92] C. Gwaltney, C. Ivanescu, L. Karlsson, N. Warholic, and P. Horn, 'Validation of the PRUCISION© Caregiver-Reported Pruritus Measure Using Data From the Phase 3, Randomised PEDFIC 1 Trial in Paediatric Patients With Progressive Familial Intrahepatic Cholestasis. Paper presented at: WCPGHAN: 6th World Congress of Pediatric'. 2021.

[93] D. L. Patrick *et al.*, 'Content validity - Establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: Part 2 - Assessing respondent understanding', *Value Heal.*, vol. 14, no. 8, pp. 978–988, 2011, doi: 10.1016/j.jval.2011.06.013.

[94] D. L. Patrick *et al.*, 'Content validity - Establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: Part 1 - Eliciting concepts for a new PRO instru', *Value Heal.*, vol. 14, no. 8, pp. 967–977, 2011, doi: 10.1016/j.jval.2011.06.014.

[95] FDA and HHS, 'Guidance for Industry Use in Medical Product Development to Support Labeling Claims Guidance for Industry', *Clin. Fed. Regist.*, no. December, pp. 1–39, 2009.

[96] Albireo, 'Odevixibat Common Technical Document Module 2.5 Clinical Overview'. 2020.

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14. Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

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). The adverse events search was combined with the clinical search.

All of the clinical database searches were conducted on 25th March 2021. The following databases were searched, and date spans of the database searches were:

- MEDLINE ALL (including MEDLINE daily, MEDLINE ePub ahead of print, MEDLINE (R) In-Process & Other Non-Indexed Citations) (via Ovid.com) 1946 to 24th March 2021 (see Search Strategy in Table 66)
- Embase (via Ovid.com) 1974 to 24th March 2021 (see Search Strategy in Table 67)
- The Cochrane Library databases (via the Wiley online platform) (see Search Strategy in Table 68):
    - Cochrane Database of Systematic Reviews (CDSR) Issue 3 of 12, March 2021
    - Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3 of 12, March 2021
- Centre for Reviews and Dissemination database (via york.ac.uk/crd) (see Search Strategy in Table 69):
    - Database of Abstracts of Reviews of Effects (DARE) Database inception to 25th March 2021 (no date limits applied)
    - NHS Economic Evaluation Database (NHS EED) Database inception to 25th March 2021 (no date limits applied)
    - Health Technology Assessment database (HTA database) Database inception to 25th March 2021 (no date limits applied)
- Additional grey literature was searched from a number of conference series (see Search Strategy in Table 70):
    - ISPOR meetings (2017 – 2021)
    - American Association for the Study of Liver Diseases (AASLD) (2017-2020)
    - The International Liver Congress, European Association for the Study of the Liver (EASL) (2017-2020)
    - North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting (NASPGHAN) (2017-2020)
- 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; ww.who.int/ictrp/en/) were searched to identify ongoing studies or results that may not have been published (see Search Strategy in Table 71):
- Searches were also conducted of a number of HTA agencies' websites (see Search Strategy in Table 72)

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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.

Search strategy

The inclusion and exclusion criteria used in the clinical review are as presented in Table 65.

Table 65. Eligibility criteria used in the clinical review

	Inclusion	Exclusion
Study design	Randomised controlled trials Non-randomised controlled studies, including case-control and controlled prospective studies Non-controlled studies will be included if there is a lack of availability of the above study designs	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.
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	Any other population
Intervention	Odevixibat (A 4250, A4250) Surgery (including partial external biliary diversion and internal ileal exclusion) Liver transplant Ursodeoxycholic acid Rifampicin/rifampin	Any other treatment
Comparators	Any or no treatment	No restriction
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	Any other outcomes

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	Inclusion	Exclusion
	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	
Geographical location	No restriction	No restriction
Language	No restriction	No restriction
Publication date	No restriction; any study date	No restriction

The complete search strategies, including all the search terms are presented in Table 66, Table 67, Table 68, Table 69, and Table 70.

Table 66. Search terms for clinical SLR in MEDLINE (via Ovid)

Number	Search Term	Number of hits
1	exp intrahepatic cholestasis/ and (benign* or progress* or famil*).mp.	2387
2	(((famil* or progress* or benign* or recurrent or chronic) adj4 intrahepatic cholest*) or ((gamma-GT or gammaGT or greenland or (progress* adj4 famil*) or (benign adj4 recurrent)) adj4 cholest*) or PFIC* or Byler* disease* or byler* syndrome* or ((FIC1 or Familial intrahepatic cholestasis 1) adj4 deficien*) or BRIC or ((bile salt export pump or BSEP) adj4 deficien*) or ((MDR3 or multidrug resistance 3) adj4 deficien*) or ((TJP or tight junction protein) adj4 deficien*) or ((ATP8B1 or ABCB11 or ABCB4 or TJP2 or NR1H4 or MYO5B) adj10 cholest*)).mp.	1867
3	1 or 2	3622
4	(Odevixibat or A 4250 or A4250 or (inhibit* adj10 bile adj10 acid) or IBAT* or ASBT*).mp.	2360
5	ursodeoxycholic acid/ or ((alpha adj3 beta adj3 dihydroxycholanic acid) or actigall or adursal or arsacol or bilifalk or cgs 21240 or cgs21240 or cholacid or cholid ursan or cholit ursan or cholofalk or deoxyursocholic acid or de ursil or delursan or desoxil or destolit or deursil or estazor or litoff or litursol or peptarom or pramur or udihep or UDCA or urdafalk or urdox or urosomix or ursacholic acid or ursacol or ursilon or ursilon retard or urso or ursogal or urso-ratiopharm or ursobil or ursobilane or ursobilin or ursochol or ursod* or ursolite or ursofalk or ursolin or ursolisin or ursolit or ursolvan or ursomedica or ursopol or ursosan or ursultec or norursodeoxycholic acid or norUDCA or 724l30y2qr).mp.	7008
6	exp Biliary Tract Surgical Procedures/ or (((Diversion* or drainage* or bypass* or operation* or reoperation* or reconstruct*) and (cholesta* or hepatic* or bile or bili* or nasobiliary)) or (ile* adj3 (exclusion or bypass)) or transplant* or surg* or cholecyst* or anastomos* or PEBD or PIBD or ileocolostom* or ileostom* or ostom* or conduit*).mp.	3864018

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Number	Search Term	Number of hits
7	Rifampin/ or (ba 41 166 or ba 41166 or ba 41166e or ba41166 or ba41166e or benemycin or doloresum or eremfat or finamicina or kalrifam or l 5103 or lositril or manorifcin or medifam or nsc 113916 or nsc 113926 or orifam or prolung or ramfin or ramicin or rhymactan or rifa or rifacilin or rifadin or rifadine or rifagen or rifaldin or rifamax or rifampicin* or rifampin or rifampycin or rifapiam or rifarad or rifasynt or rifcap or rifcin or rifodex or rifoldin or rimactan or rimactane or rimapen or rimpacin or rimpin or rimycin or ripin or ripolin or rofact or sinerdol or tubocin or tuborin or vjt6j7r4tr or 13292-46-1).mp.	31169
8	or/4-7	3900035
9	3 and 8	1302

Table 67. Search terms for clinical SLR in Embase (via Ovid)

Number	Search Term	Number of hits
1	intrahepatic cholestasis/ and (benign* or progress* or famil*).mp.	1996
2	(((famil* or progress* or benign* or recurrent or chronic) adj4 intrahepatic cholest*) or ((gamma-GT or gammaGT or greenland or (progress* adj4 famil*) or (benign adj4 recurrent)) adj4 cholest*) or PFIC* or Byler* disease* or byler* syndrome* or ((FIC1 or Familial intrahepatic cholestasis 1) adj4 deficien*) or BRIC or ((bile salt export pump or BSEP) adj4 deficien*) or ((MDR3 or multidrug resistance 3) adj4 deficien*) or ((TJP or tight junction protein) adj4 deficien*) or ((ATP8B1 or ABCB11 or ABCB4 or TJP2 or NR1H4 or MYO5B) adj10 cholest*)).mp.	2900
3	1 or 2	3592
4	Odevixibat/ or (odevixibat or A 4250 or A4250 or (inhibit* adj10 bile adj10 acid) or IBAT* or ASBT*).mp.	3419
5	ursodeoxycholic acid/ or ((alpha adj3 beta adj3 dihydroxycholanic acid) or actigall or adursal or arsacol or bilifalk or cgs 21240 or cgs21240 or cholacid or cholid ursan or cholit ursan or cholofalk or deoxyursocholic acid or de ursil or delursan or desoxil or destolit or deursil or estazor or litoff or litursol or peptarom or pramur or udihep or UDCA or urdafalk or urdox or urosomix or ursacholic acid or ursacol or ursilon or ursilon retard or urso or ursogal or urso-ratiopharm or ursobil or ursobilane or ursobilin or ursochol or ursod* or ursolite or ursofalk or ursolin or ursolisin or ursolit or ursolvan or ursomedica or ursopol or ursosan or ursultec or norursodeoxycholic acid or norUDCA or 724l30y2qr).mp.	16364
6	exp Biliary Tract surgery/ or (((Diversion* or drainage* or bypass* or operation* or reoperation* or reconstruct*) and (cholesta* or hepatic* or bile or bili* or nasobiliary)) or (ile* adj3 (exclusion or bypass)) or transplant* or surg* or cholecyst* or anastomos* or PEBD or PIBD or ileocolostom* or ileostom* or ostom* or conduit*).mp.	5085697
7	Rifampicin/ or (ba 41 166 or ba 41166 or ba 41166e or ba41166 or ba41166e or benemycin or doloresum or eremfat or finamicina or kalrifam or l 5103 or lositril or manorifcin or medifam or nsc 113916 or nsc 113926 or orifam or prolung or ramfin or ramicin or rhymactan or rifa or rifacilin or rifadin or rifadine or rifagen or rifaldin or rifamax or rifampicin* or rifampin or rifampycin or rifapiam or rifarad or rifasynt or rifcap or rifcin or rifodex or rifoldin or rimactan or rimactane or rimapen or rimpacin or rimpin or rimycin or ripin or ripolin or rofact or sinerdol or tubocin or tuborin or vjt6j7r4tr or 13292-46-1).mp.	95900
8	or/4-7	5179643
9	3 and 8	1521

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Table 68. Search terms for clinical SLR in The Cochrane Library (via Wiley online platform)

Number	Search Term	Number of hits
#1	[mh "intrahepatic cholestasis"] and (benign* or progress* or famil*):ti,ab,kw	68
#2	(((famil* or progress* or benign* or recurrent or chronic) NEAR/4 intrahepatic cholest*) or ((gamma-GT or gammaGT or greenland or (progress* NEAR/4 famil*) or (benign NEAR/4 recurrent)) NEAR/4 cholest*) or PFIC* or Byler* disease* or byler* syndrome* or ((FIC1 or "Familial intrahepatic cholestasis 1") NEAR/4 deficien*) or BRIC or ((bile salt export pump or BSEP) NEAR/4 deficien*) or ((MDR3 or "multidrug resistance 3") NEAR/4 deficien*) or ((TJP or tight junction protein) NEAR/4 deficien*) or ((ATP8B1 or ABCB11 or ABCB4 or TJP2 or NR1H4 or MYO5B) NEAR/10 cholest*)):ti,ab,kw	384
#3	#1 or #2	449
#4	(Odevixibat or A 4250 or A4250 or (inhibit* NEAR/10 bile NEAR/10 acid) or IBAT* or ASBT*):ti,ab,kw	272
#5	[mh ^"ursodeoxycholic acid"] or ((alpha NEAR/3 beta NEAR/3 dihydroxycholanic acid) or actigall or adursal or arsacol or bilifalk or cgs 21240 or cgs21240 or cholacid or cholid ursan or cholit ursan or cholofalk or deoxyursocholic acid or de ursil or delursan or desoxil or destolit or deursil or estazor or litoff or litursol or peptarom or pramur or udihep or UDCA or urdafalk or urdox or urosomix or ursacholic acid or ursacol or ursilon or ursilon retard or urso or ursogal or urso-ratiopharm or ursobil or ursobilane or ursobilin or ursochol or ursod* or ursolite or ursofalk or ursolin or ursolisin or ursolit or ursolvan or ursomedica or ursopol or ursosan or ursultec or norursodeoxycholic acid or norUDCA or 724l30y2qr):ti,ab,kw	1516
#6	[mh "Biliary Tract Surgical Procedures"] or (((Diversion* or drainage* or bypass* or operation* or reoperation* or reconstruct*) and (cholesta* or hepatic* or bile or bili* or nasobiliary)) or (ile* NEAR/3 (exclusion or bypass)) or transplant* or surg* or cholecyst* or anastomos* or PEBD or PIBD or ileocolostom* or ileostom* or ostom* or conduit*):ti,ab,kw	288589
#7	[mh ^"Rifampin"] or ("ba 41 166" or "ba 41166" or "ba 41166e" or "ba41166" or "ba41166e" or benemycin or doloresum or eremfat or finamicina or kalrifam or "l 5103" or lositril or manorifcin or medifam or "nsc 113916" or "nsc 113926" or orifam or prolung or ramfin or ramicin or rhymactan or rifa or rifacilin or rifadin or rifadine or rifagen or rifaldin or rifamax or rifampicin* or rifampin or rifampycin or rifapiam or rifarad or rifasynt or rifcap or rifcin or rifodex or rifoldin or rimactan or rimactane or rimapen or rimpacin or rimpin or rimycin or ripin or ripolin or rofact or sinerdol or tubocin or tuborin or "vjt6j7r4tr" or "13292-46-1"):ti,ab,kw	2538
#8	Or #4-#7	292311
#9	#3 and #8	104

Cochrane Database of Systematic Reviews Issue 3 of 12, March 2021 (n=8), Cochrane Central Register of Controlled Trials Issue 3 of 12, March 2021 (n=96)

Table 69. Search terms for clinical SLR in the Database of Abstract Reviews of Effects, NHS Economic Evaluation Database, HTA Database search terms (via York.ac.uk/crd interface)

Number	Search Term	Number of hits
1	cholestasis or cholestatic or PFIC or Byler disease or byler syndrome or Bylers disease or bylers syndrome or Byler's disease or byler's syndrome or FIC1 or BRIC or bile salt export pump deficiency or MDR3 or multidrug resistance 3 or TJP or tight junction protein	85

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Table 70. Grey literature search strategy

	Access	Search strategy	Included
ISPOR (all meetings) **2021** **2020** **2019** **2018** **2017**	2021 2020 2019 2018 2017: https://www.ispor.org/heor-resources/presentations-database/search	In the search bar searched for: Cholestasis Cholestatic Byler Bylers Byler's PFIC BRIC Bile salt export pump BSEP MDR3 Multidrug resistance 3 Tight junction protein TJP Deduplicated: 4 Reviewed each abstract for inclusion	1 (clinical and quality of life SLRs)
American Association for the Study of Liver Diseases (AASLD) **2020** **2019** **2018** **2017**	2020: https://aasldpubs.onlinelibrary.wiley.com/toc/15273350/2020/72/S1 2019: https://aasldpubs.onlinelibrary.wiley.com/toc/15273350/2019/70/S1 2018: https://aasldpubs.onlinelibrary.wiley.com/toc/15273350/2018/68/S1 2017: https://aasldpubs.onlinelibrary.wiley.com/toc/15273350/2017/66/S1	In each PDF CtrlF on the page for: Cholesta Byler, bylers, byler's, PFIC BRIC Bile salt export pump BSEP MDR3 Multidrug resistance 3 Tight junction protein TJP Reviewed each abstract containing one of these terms for inclusion Hits 2020: Oral 13, posters 77 2019: Oral 20, posters 87 2018: Oral 25, posters 79 2017: Oral 19, posters 84	0
The International Liver Congress, European Association for the Study of the Liver (EASL) **2020** **2019** **2018** **2017**	2020 https://easl.eu/wp-content/uploads/2020/12/digital-ilc-2020-abstract.pdf 2019 https://easl.eu/wp-content/uploads/2020/12/EASL-ILC2019-AbstractBook.pdf 2018 https://www.journal-of-hepatology.eu/issue/S0168-8278(18)X0004-X 2017	In each PDF CtrlF on the page for: Familial cholesta Progressive cholesta Benign cholesta Recurrent cholesta Chronic cholesta Intrahepatic cholesta Byler, bylers, byler's, PFIC BRIC Bile salt export pump BSEP MDR3 Multidrug resistance 3 Tight junction protein TJP Reviewed each abstract containing one of these terms for inclusion	0

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	Access	Search strategy	Included
	https://www.journal-of-hepatology.eu/issue/S0168-8278(17)X0002-0	Hits 2020: 31 2019: 22 2018: 26 2017: 14	
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting (NASPGHAN) **2020** **2019** **2018** **2017**	2020 https://journals.lww.com/jpgn/Citation/2020/11001/NASPGHAN_Annual_Meeting_Abstracts.1.aspx 2019 https://journals.lww.com/jpgn/toc/2019/11002 2018 https://journals.lww.com/jpgn/toc/2018/11001 2017 https://journals.lww.com/jpgn/toc/2017/11002	In each PDF CtrlF on the page for: Familial cholesta Progressive cholesta Benign cholesta Recurrent cholesta Chronic cholesta Intrahepatic cholesta Byler, bylers, byler's, PFIC BRIC Bile salt export pump BSEP MDR3 Multidrug resistance 3 Tight junction protein TJP Reviewed each abstract containing one of these terms for inclusion Hits 2020: 8 2019: 6 2018: 7 2017: 10	0

Table 71. Search for recent and ongoing clinical trials

Source	Search strategy	Included
Clinicaltrials.gov	progressive intrahepatic cholestasis: 19 progressive familial intrahepatic cholestasis: 16 familial intrahepatic cholestasis: 18 benign recurrent intrahepatic cholestasis: 1 PFIC1: 15 PFIC2: 15 PFIC3: 18 BRIC: 1 byler disease: 1 byler syndrome: 4 Deduplicated: 23	0 No results available from any of the 23 records
Clinicaltrialsregister.eu	intrahepatic cholestasis: 19 PFIC: 9 BRIC: 0 Byler: 0 Bylers: 0 Byler's: 0 Deduplicated: 19 3 with results in a relevant population:	0 Unable to access results pages for all 3 stating "with results"

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Source	Search strategy	Included
	https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000906-20/GB/ https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-003833-14/GB/ https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-001157-32/SE/	
WHO International Clinical Trials Registry Platform (ICTRP): https://apps.who.int/trialsearch/	intrahepatic cholestasis: PFIC: BRIC: byler: bylers: byler's:	0 Multiple attempts, unable to search ("The requested URL was rejected")

Table 72. HTA agency websites

Source	Search strategy	Included
National Institute for Health and Care Excellence (NICE) (via https://www.nice.org.uk/)	intrahepatic cholestasis: 3 PFIC: 0 BRIC: 0 byler: 0 bylers: 0 byler's: 0	0
Scottish Medicines Consortium (SMC) (via https://www.scottishmedicines.org.uk/)	intrahepatic cholestasis: 0 PFIC: 0 BRIC: 0 byler: 0 bylers: 0 byler's: 0	0
All Wales Medicines Strategy Group (AWMSG) (via http://www.awmsg.org/)	intrahepatic cholestasis: 1 PFIC: 0 BRIC: 0 byler: 0 bylers: 0 byler's: 0	0

SLRs were included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract (first pass) for inclusion using the eligibility criteria. Disagreements were discussed and a third reviewer involved if required.

Full text copies of all potentially relevant records were then obtained and evaluated in more detail (second pass) against the eligibility criteria. This assessment was also undertaken by two independent reviewers, with disagreements discussed and a third reviewer involved if required.

Data was extracted by one reviewer and checked by a second.

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Systematic selection of studies

The PRISMA flow diagram of Figure 33 presents the flow of studies identified through the clinical SLR.

Figure 33. Clinical SLR PRISMA

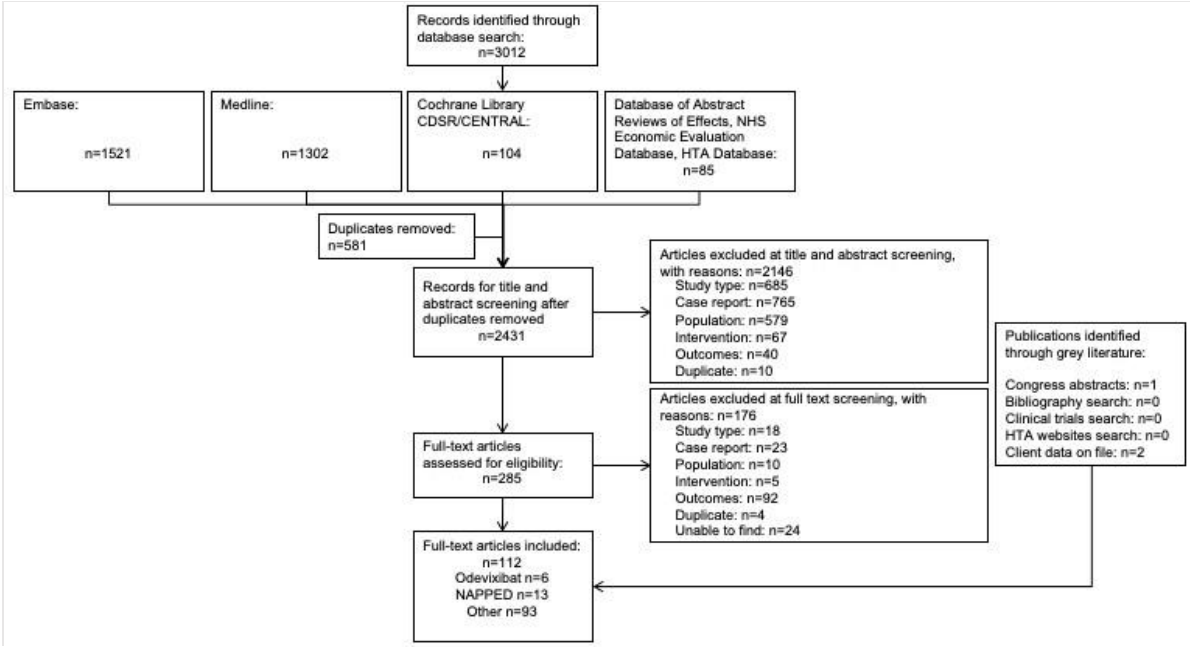

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Table 73. Overview of the odevixibat references included in the global SLR

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
A4250-003 Phase 2	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
A4250-003 Phase 2	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
PEDFIC1	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 PEDFIC1 Study. Value in Health. 2021;24(5):S1
PEDFIC1	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 PEDFIC1, 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 PEDFIC2, 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

Table 74. Overview of the NAPPED study references included in the global SLR

Study name (acronym)	Citation
NAPPED	van Wessel DB, Thompson RJ, Gonzales E, Jankowska I, Shneider BL, Sokal E, Grammatikopoulos T et al. Impact of Genotype, Serum Bile Acids, and Surgical Biliary Diversion on Native Liver Survival in FIC1 Deficiency. Hepatology. 2021
NAPPED	van Wessel DB, Thompson RJ, Gonzales E, Jankowska I, Sokal E, Grammatikopoulos T, Kadaristiana A, Jacquemin E, Spraul A, Lipiński P, Czubkowski P et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. Journal of hepatology. 2020 Jul 1;73(1):84-93.
NAPPED	Felzen A, van Wessel D, Thompson RJ, Gonzales EM, Jankowska I, Shneider BL, Sokal E, Grammatikopoulos T, Kadaristiana A, Jacquemin E, Spraul A et al. The presence of a truncating mutation in ABCB11 abrogates the beneficial effect of a residual function mutation on the course of severe bile salt export pump deficiency. Hepatology. 2020;72(S1):884A-886A
NAPPED	Felzen A, van Wessel D, Thompson RJ, Gonzales EM, Jankowska I, Sokal E, Grammatikopoulos T, Kadaristiana A, Jacquemin E, Spraul A et al. The phenotype of compound heterozygous BSEP deficiency patients is determined by the combined residual function of the two ABCB11 mutations: results from the NAPPED consortium. Journal of Hepatology. 2020;73(S1):S536-S537
NAPPED	van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E et al. The natural course of FIC1 deficiency and BSEP deficiency: Initial results from the NAPPED-consortium (NAtural course and prognosis of PFIC and effect of biliary diversion). Journal of Pediatric Gastroenterology and Nutrition. 2018;66(S2):650-652
NAPPED	van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E et al. The natural course of FIC1 deficiency and BSEP deficiency: Initial results from the NAPPED-consortium (Natural course and Prognosis of PFIC and Effect of biliary Diversion). Journal of Hepatology. 2018 Apr;68(S1):S626-7.
NAPPED	van Wessel D, Thompson RJ, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E et al. The Natural Course of FIC1 Deficiency: Results from the Napped-Consortium. Hepatology. 2018;68(S1):1051A-1052A
NAPPED	van Wessel D, Thompson RJ, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E et al. The natural course of BSEP deficiency: Results from the global napped-consortium. Hepatology. 2018;68(S1):117A-118A
NAPPED	van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipiński P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E et al. Predicting long-term outcome after surgical biliary diversion in Bsep-deficiency patients: Results from the NAPPED consortium. Journal of Hepatology. 2019 Apr 1;70(S1):e121
NAPPED	van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipiński P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E et al. Predicting long-term outcome after surgical biliary diversion in BSEP-deficiency patients: Results from the NAPPED consortium. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):702-703

Study name (acronym)	Citation
NAPPED	van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipiński P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E et al. Factors associated with the natural course of disease in patients with FIC1-deficiency: The NAPPED-consortium. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):688-689
NAPPED	van Wesssel D, Thompson RJ, Gonzales EM, Jankowska I, Sokal E et al. Genotype phenotype relationships in patients with relatively mild mutations in ABCB11: results from the napped consortium. Hepatology. 2019:70(S1):48A-49A
NAPPED	van Wessel D, Thompson RJ, Gonzales EM, Jankowska I, Shneider BL, Sokal E, Grammatikopoulos T, Kadaristiana A, Jacquemin E, Spraul A et al. Native liver survival in patients with FIC1 deficiency: Impact of genotype, serum bile acid concentrations and surgical biliary diversion. Hepatology. 2020;72(S1):878A-880A

Table 75. Overview of the references concerning other comparators included in the global SLR

Reference	Intervention	Study design
Gregorio GV, Ball CS, Mowat AP, Mieli-Vergani G. Effect of rifampicin in the treatment of pruritus in hepatic cholestasis. Archives of disease in childhood. 1993 Jul 1;69(1):141-3.	Rifampicin	Non-controlled: retrospective
Morris AL, Bukauskas K, Sada RE, Shneider BL. Byler disease: early natural history. Journal of pediatric gastroenterology and nutrition. 2015 Apr 1;60(4):460-6.	Rifampicin, UDCA	Non-controlled: retrospective
Schatz SB, Jüngst C, Keitel-Anselmo V, Kubitz R, Becker C, Gerner P, Pfister ED, Goldschmidt I, Junge N, Wenning D, Gehring S. Phenotypic spectrum and diagnostic pitfalls of ABCB4 deficiency depending on age of onset. Hepatology communications. 2018 May 1;2(5):504-14.	Rifampicin, UDCA, liver transplant	Non-controlled: retrospective
Whitington PF, Freese DK, Alonso EM, Schwarzenberg SJ, Sharp HL. Clinical and biochemical findings in progressive familial intrahepatic cholestasis. Journal of pediatric gastroenterology and nutrition. 1994 Feb 1;18(2):134-41.	Rifampicin, UDCA, liver transplant, surgery	Non-controlled: retrospective

Reference	Intervention	Study design
Agarwal S, Lal BB, Rawat D, Rastogi A, Bharathy KG, Alam S. Progressive familial intrahepatic cholestasis (PFIC) in Indian children: clinical spectrum and outcome. Journal of clinical and experimental hepatology. 2016 Sep 1;6(3):203-8.	UDCA (and UDCA combination treatments including rifampicin), surgery	Non-controlled: retrospective
Colombo C, Vajro P, Degiorgio D, Coviello DA, Costantino L, Tornillo L, Motta V, Consonni D, Maggiore G, SIGENP Study Group for Genetic Cholestasis. Clinical features and genotype-phenotype correlations in children with progressive familial intrahepatic cholestasis type 3 related to ABCB4 mutations. Journal of pediatric gastroenterology and nutrition. 2011 Jan 1;52(1):73-83.	UDCA, liver transplant	Non-controlled: retrospective
Davit-Spraul A, Fabre M, Branchereau S, Baussan C, Gonzales E, Stieger B, Bernard O, Jacquemin E. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. Hepatology. 2010 May;51(5):1645-55.	UDCA, liver transplant, surgery	Non-controlled: retrospective
Dinler GÖ, Koçak NU, Özen HA, Yüce AY, Gürakan FI. Ursodeoxycholic acid treatment in children with Byler disease. Pediatrics International. 1999 Dec;41(6):662-5.	UDCA	Non-controlled: prospective
Englert C, Grabhorn E, Richter A, Rogiers X, Burdelski M, Ganschow R. Liver transplantation in children with progressive familial intrahepatic cholestasis. Transplantation. 2007 Nov 27;84(10):1361-3.	UDCA, liver transplant, surgery	Non-controlled: retrospective
Gordo-Gilart R, Andueza S, Hierro L, Martínez-Fernández P, D'Agostino D, Jara P, Alvarez L. Functional analysis of ABCB4 mutations relates clinical outcomes of progressive familial intrahepatic cholestasis type 3 to the degree of MDR3 floppase activity. Gut. 2015 Jan 1;64(1):147-55.	UDCA	Non-controlled: retrospective
Ismail H, Kaliciński P, Markiewicz M, Jankowska I, Pawłowska J, Kluge P, Eliadou E, Kamiński A, Szymczak M, Drewniak T, Revillon Y. Treatment of progressive familial intrahepatic cholestasis: liver transplantation or partial external biliary diversion. Pediatric transplantation. 1999 Aug;3(3):219-24.	UDCA	Non-controlled: retrospective
Jacquemin E, Bernard O, Hadchouel M, Cresteil D, De Vree JM, Paul M, Elferink RP, Bosma PJ, Sokal EM, Sturm E, Burdelski M. The wide spectrum of multidrug resistance 3 deficiency: from neonatal cholestasis to cirrhosis of adulthood. Gastroenterology. 2001 May 1;120(6):1448-58.	UDCA	Non-controlled: retrospective

Reference	Intervention	Study design
Jacquemin E, Hermans D, Myara A, Habes D, Debray D, Hadchouel M, Sokal EM, Bernard O. Ursodeoxycholic acid therapy in pediatric patients with progressive familial intrahepatic cholestasis. Hepatology. 1997 Mar;25(3):519-23.	UDCA	Non-controlled: prospective
Khabou B, Mahjoub B, Barbu V, Balhoudi N, Wardani A, Sfar MT, Fakhfakh F. Phenotypic variability in Tunisian PFIC3 patients harboring a complex genotype with a differential clinical outcome of UDCA treatment. Clinica Chimica Acta. 2018 Nov 1;486:122-8.	UDCA	Non-controlled: NR
Lee WS, Chai PF, Looi LM. Progressive familial intrahepatic cholestasis in Malaysian patients—a report of five cases. Med J Malaysia. 2009 Sep 1;64(3):216-9.	UDCA (with other treatments)	Non-controlled: retrospective
Socha P, Nowicka G, Jankowska I, Rujner J, Pawłowska J, Socha J. Apolipoprotein E polymorphism in Alagille syndrome and progressive familial intrahepatic cholestasis. Digestive diseases and sciences. 2000 Apr;45(4):675-9.	UDCA	Non-controlled: retrospective
Soler DM, Del Valle AI, Fernandez-Lube D, Shneider BL. Cross-sectional analysis of progressive familial intrahepatic cholestasis in Puerto Rican children. Puerto Rico health sciences journal. 2016 Nov 14;35(4):220-3.	UDCA	Non-controlled: NR
Varma S, Revencu N, Stephenne X, Scheers I, Smets F, Beleza-Meireles A, Reding R, Roskams T, Sokal EM. Retargeting of bile salt export pump and favorable outcome in children with progressive familial intrahepatic cholestasis type 2. Hepatology. 2015 Jul;62(1):198-206.	UDCA, liver transplant, surgery	Non-controlled: retrospective
Varma S, Stephenne X, Revencu N, Scheers I, Reding R, Smets F, Sokal E. Predictive factors of response to non-transplant treatment strategies in progressive familial intrahepatic cholestasis type II: 669. Hepatology. 2014 Oct;60:524A-525A.	UDCA, surgery	Non-controlled: retrospective
Wanty C, Joomye R, Van Hoorebeek N, Paul K, Otte JB, Reding R, Sokal EM. Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy. Acta gastro-enterologica Belgica. 2004 Oct 1;67(4):313-9.	UDCA, liver transplant, surgery	Non-controlled: retrospective
Zhang J, Liu LL, Gong JY, Hao CZ, Qiu YL, Lu Y, Feng JY, Li JQ, Li ZD, Wang MX, Xing QH. TJP2 hepatobiliary disorders: Novel variants and clinical diversity. Human mutation. 2020 Feb;41(2):502-11.	UDCA	Non-controlled: retrospective
Acar S, Demir B, Ayyildiz H, Polat KY, Kanmaz T, Akyildiz M, Arikan C. Living donor liver transplantation for PFIC type 3. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):918	Liver transplant	Non-controlled: retrospective

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Reference	Intervention	Study design
Almehaidib A. Progressive familial intrahepatic cholestasis in Saudi Arabia. Archives of Disease in Childhood. 2014;99:A282	Liver transplant	Non-controlled: retrospective
Almehaidib A, Alshahrani A, Banemai M, Alsaleem K, Aldekhail W. Progressive familial intrahepatic cholestasis at tertiary care centre in Saudi Arabia. Hepatology International. 2015;9(1):S119.	Liver transplant	Non-controlled: retrospective
Aydogdu S, Cakir M, Arikan C, Tumgor G, Yuksekkaya HA, Yilmaz F, Kilic M. Liver transplantation for progressive familial intrahepatic cholestasis: clinical and histopathological findings, outcome and impact on growth. Pediatric transplantation. 2007 Sep;11(6):634-40.	Liver transplant	Non-controlled: retrospective
Bassas A, Chehab M, Hebby H, Al Shahed M, Al Husseini H, Al Zahrani A, Wali S. Living related liver transplantation in 13 cases of progressive familial intrahepatic cholestasis. Transplantation proceedings 2003 Dec 1;35(8):3003-3005	Liver transplant	Non-controlled: NR
Bull LN, Pawlikowska L, Strautnieks S, Jankowska I, Czubkowski P, Dodge JL, Emerick K, Wanty C, Wali S, Blanchard S, Lacaille F. Outcomes of surgical management of familial intrahepatic cholestasis 1 and bile salt export protein deficiencies. Hepatology communications. 2018 May;2(5):515-28.	Liver transplant, surgery	Non-controlled: retrospective
Cutillo L, Najimi M, Smets F, Janssen M, Reding R, De Goyet JD, Sokal EM. Safety of living-related liver transplantation for progressive familial intrahepatic cholestasis. Pediatric transplantation. 2006 Aug;10(5):570-4.	Liver transplant	Non-controlled: retrospective
Dehghani SM, Honar N, Inaloo S, Gholami S, Kazemi K, Bahador A, Haghighat M, Malek-Hosseini SA. Neuromuscular complication after liver transplant in children: a single-center experience. Exp Clin Transplant. 2010 Mar 1;8(1):9-13.	Liver transplant	Non-controlled: prospective
Djurberg H, Facharzt WP, Joseph D, Tjan D, Zuleika M, Ferns S, Rasheed A, Evans DA, Bassas A. Anesthesia care for living-related liver transplantation for infants and children with end-stage liver disease: report of our initial experience. Journal of clinical anesthesia. 2002 Dec 1;14(8):564-70.	Liver transplant	Non-controlled: NR
Egawa H, Yorifuji T, Sumazaki R, Kimura A, Hasegawa M, Tanaka K. Intractable diarrhea after liver transplantation for Byler's disease: successful treatment with bile adsorptive resin. Liver transplantation. 2002 Aug;8(8):714-6.	Liver transplant	Non-controlled: NR
Emond JC, Whitington PF. Selective surgical management of progressive familial intrahepatic cholestasis (Byler's disease). Journal of pediatric surgery. 1995 Dec 1;30(12):1635-41.	Liver transplant, surgery	Non-controlled: retrospective

Reference	Intervention	Study design
Ghaffar TY, El Naghi S, Youssef A, El Adawy M, Moafy M, Sattar MA, Gamal M, Allam A, Hegazy N, Maksoud HA, Mokhtar A. Living Related Liver Transplantation (LRLT) for Progressive Familial Intrahepatic Cholestasis Type III (PFIC III) Children: A Single Center Experience. Hepatology. 2017 Oct 1;66(S1):892A	Liver transplant	Non-controlled: NR
Gridelli B, Spada M, Petz W, Bertani A, Lucianetti A, Colledan M, Altobelli M, Alberti D, Guizzetti M, Riva S, Melzi ML. Split-liver transplantation eliminates the need for living-donor liver transplantation in children with end-stage cholestatic liver disease. Transplantation. 2003 Apr 27;75(8):1197-203.	Liver transplant	Non-controlled: retrospective
Herbst SM, Vermehren J, Kurz A, Kowalzyk Z, Loskarn S, Melter M, Hehr U. From gallstones to liver transplantation-Long term follow-up and success of liver transplantation in patients with familial intrahepatic cholestasis: Is there an association between genotype and outcome? Medizinische Genetik. 2013;25(1):178	Liver transplant	Non-controlled: retrospective
Hertel P, Goodrich N, Thompson R, Bull L, Ye W, Bass L, Bozic M, Heubi J, Murray K et al. A cross-sectional multi-center analysis of clinical features of progressive familial intrahepatic cholestasis (PFIC)-initial results of the children logic protocol. Journal of Pediatric Gastroenterology and Nutrition. 2017;65(S2):S58-S59	Liver transplant, surgery	Non-controlled: prospective
Hori T, Egawa H, Miyagawa-Hayashino A, Yorifuji T, Yonekawa Y, Nguyen JH, Uemoto S. Living-donor liver transplantation for progressive familial intrahepatic cholestasis. World journal of surgery. 2011 Feb;35(2):393-402	Liver transplant	Non-controlled: NR
Hori T, Egawa H, Takada Y, Ueda M, Oike F, Ogura Y, Sakamoto S, Kasahara M, Ogawa K, Miyagawa-Hayashino A, Yonekawa Y. Progressive familial intrahepatic cholestasis: a single-center experience of living-donor liver transplantation during two decades in Japan. Clinical transplantation. 2011 Sep;25(5):776-85.	Liver transplant	Non-controlled: NR
Jericho HS, Kaurs E, Boverhof R, Knisely A, Shneider BL, Verkade HJ, Whitington PF. Bile acid pool dynamics in progressive familial intrahepatic cholestasis with partial external bile diversion. Journal of pediatric gastroenterology and nutrition. 2015 Mar;60(3):368-374.	Liver transplant, surgery	Non-controlled: prospective
Jericho H, Westfall E, Knisely A, Verkade H, Whitington P. Bile Salt Kinetics in Children with Genetic Cholestasis and Bile Diversion Therapy: 35. Hepatology. 2012 Oct;56: 208A-209A.	Liver transplant, surgery	Non-controlled: prospective
Karakayali H, Aktas S, Ozcay F, Moray G, Torgay A, Haberal M. Long term outcomes in liver transplantation for progressive familial intrahepatic cholestasis. Liver Transplantation. 2011;17:S126	Liver transplant	Non-controlled: retrospective

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Reference	Intervention	Study design
Karakayali H, Aktas S, Ozcay F, Moray G, Torgay A, Haberal M. Long term outcomes in liver transplantation for progressive familial intrahepatic cholestasis. Pediatric Transplantation. 2011;15:86	Liver transplant	Non-controlled: retrospective
Khan IA, Al-Shaqrani MA, Arain ZB, Al-Hebbi HA, Wali SH, Bassas AF. One hundred and thirty-seven living donor pediatric liver transplants at Riyadh Military Hospital. Saudi Med J. 2009;30(3):403-8.	Liver transplant	Non-controlled: retrospective
Kirimlioglu S, Bull L, Joseph N, Kakar S, Bove K, Ferrell L, Ince U, Kim G. Hepatocellular carcinoma in patients with MDR3 deficiency. Modern Pathology. Conference: 108th Annual Meeting of the United States and Canadian Academy of Pathology, USCAP. 2019;32(3):.	Liver transplant	Non-controlled: retrospective
Kirino I, Hori T, Egawa H, Miyagawa-Hashimoto A, Yorifuji T, Yonekawa Y, Uemoto, S. Living-donor liver transplantation for progressive familial intrahepatic cholestasis. Liver Transplantation. 2014;20:S343	Liver transplant	Non-controlled: retrospective
Liu Y, Sun LY, Zhu ZJ, Wei L, Qu W, Zeng ZG. Liver transplantation for progressive familial intrahepatic cholestasis. Annals of transplantation. 2018;23:666-673.	Liver transplant	Non-controlled: retrospective
Miyagawa-Hayashino A, Egawa H, Yorifuji T, Hasegawa M, Haga H, Tsuruyama T, Wen MC, Sumazaki R, Manabe T, Uemoto S. Allograft steatohepatitis in progressive familial intrahepatic cholestasis type 1 after living donor liver transplantation. Liver Transplantation. 2009 Jun;15(6):610-8.	Liver transplant	Non-controlled: retrospective
Okamoto T, Sonoda M, Ogawa E, Ito S, Togawa T, Hayashi H, Okajima H, Uemoto S. Long-term outcomes of living-donor liver transplantation for progressive familial intrahepatic cholestasis type 1. Journal of Pediatric Gastroenterology and Nutrition. 2021 Mar 1;72(3):425-9.	Liver transplant	Non-controlled: retrospective
Polat E, Zeytun M, Kilic M, Doganay L, Arikan C. Outcome of children with PFIC after living donor liver transplantation. Journal of Pediatric Gastroenterology and Nutrition. 2017;64(S1):647.	Liver transplant	Non-controlled: retrospective
Siebold L, Dick AA, Thompson R, Maggiore G, Jacquemin E, Jaffe R, Strautnieks S, Grammatikopoulos T, Horslen S, Whitington PF, Shneider BL. Recurrent low gamma-glutamyl transpeptidase cholestasis following liver transplantation for bile salt export pump (BSEP) disease (posttransplant recurrent BSEP disease). Liver transplantation. 2010 Jul;16(7):856-63.	Liver transplant	Non-controlled: retrospective

Reference	Intervention	Study design
Soubrane OL, Gauthier F, DeVictor D, Bernard OL, Valayer J, Houssin DI, Chapuis Y. Orthotopic liver transplantation for Byler disease. Transplantation. 1990 Nov 1;50(5):804-6.	Liver transplant	Non-controlled: retrospective
Torri E, Lucianetti A, Pinelli D, Corno V, Guizzetti M, Maldini G, Zambelli M, Bertani A, Melzi ML, Alberti D, Doffria E. Orthotopic liver transplantation for Byler's disease. Transplantation proceedings 2005 Mar 1;37(2):1149-1150	Liver transplant	Non-controlled: NR
Valamparampil JJ, Rinaldhy K, Reddy MS, Shanmugam N, Rela M. Outcomes of Liver Transplantation for Pediatric Recipients With Progressive Familial Intrahepatic Cholestasis. Journal of Clinical and Experimental Hepatology. 2019;9(3):422-423	Liver transplant	Non-controlled: retrospective
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(5S1):141-142.	Liver transplant	Non-controlled: retrospective
Vuong P, Lee LY, Brubaker A, Than P, Gallo A, Esquivel C, Bonham CA. Long-term outcomes of pediatric liver transplantation for progressive familial intrahepatic cholestasis. Transplantation. 2020 Sep 1;104(S3):S557.	Liver transplant	Non-controlled: retrospective
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.	Liver transplant, surgery	Non-randomised controlled: prospective
Yee K, Moshkovich O, Llewellyn S, Benjamin K, Desai NK. A Web-Based Survey of Itch Severity after Surgical Treatment of Progressive Familial Intrahepatic Cholestasis in Children and Adolescents. Hepatology. 2018 Oct 1;68(S1):1047A.	Liver transplant, surgery	Non-controlled: cross-sectional study
Arnell H, Bergdahl S, Papadogiannakis N, Nemeth A, Fischler B. Preoperative observations and short-term outcome after partial external biliary diversion in 13 patients with progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2008 Jul 1;43(7):1312-20.	Surgery	Non-controlled: NR
Arnell H, Fischler B, Bergdahl S, Schnell PO, Jacobsson H, Nemeth A. Hepatobiliary scintigraphy during cholestatic and noncholestatic periods in patients with progressive familial intrahepatic cholestasis after partial external biliary diversion. Journal of pediatric surgery. 2011 Mar 1;46(3):467-72.	Surgery	Non-controlled: prospective

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Reference	Intervention	Study design
Arnell H, Papadogiannakis N, Zemack H, Knisely AS, Németh A, Fischler B. Follow-up in children with progressive familial intrahepatic cholestasis after partial external biliary diversion. Journal of pediatric gastroenterology and nutrition. 2010 Oct 1;51(4):494-9.	Surgery	Non-controlled: prospective
Bjørnland K, Hukkinen M, Gatzinsky V, Arnell H, Pakarinen MP, Almaas R, Svensson JF. Partial Biliary Diversion May Promote Long-Term Relief of Pruritus and Native Liver Survival in Children with Cholestatic Liver Diseases. European Journal of Pediatric Surgery. 2020 Jul 24.	Surgery	Non-controlled: retrospective
Cheema HA, Prakash A, Cheema R. Partial internal biliary diversion improves clinical, biochemical and histological parameters in progressive, familial intrahepatic cholestasis: A study of 21 patients. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S336	Surgery	Non-controlled: prospective
Chen L, Xiao H, Ren XH, Li L. Long-term outcomes after cholecystocolostomy for progressive familial intrahepatic cholestasis. Hepatology Research. 2018 Dec;48(13):1163-71.	Surgery	Non-controlled: retrospective
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.	Surgery	Non-controlled: retrospective
Emerick KM, Elias MS, Melin-Aldana H, Strautnieks S, Thompson RJ, Bull LN, Knisely AS, Whitington PF, Green RM. Bile composition in Alagille syndrome and PFIC patients having partial external biliary diversion. BMC gastroenterology. 2008 Dec;8(1):47.	Surgery	Non-controlled: prospective
Erginel B, Soysal FG, Durmaz O, Celik A, Salman T. Long-term outcomes of six patients after partial internal biliary diversion for progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2018 Mar 1;53(3):468-71.	Surgery	Non-controlled: retrospective
Fischler B, Papadogiannakis N, Nemeth A. Clinical aspects on neonatal cholestasis based on observations at a Swedish tertiary referral centre. Acta Pædiatrica. 2001 Feb;90(2):171-8.	Surgery	Non-controlled: retrospective
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;36(5):603-610.	Surgery	Non-controlled: prospective

Reference	Intervention	Study design
Gunaydin M, Tander B, Demirel D, Caltepe G, Kalayci AG, Eren E, Bicakcı U, Rizalar R, Ariturk E, Bernay F. Different techniques for biliary diversion in progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2016 Mar 1;51(3):386-9.	Surgery	Non-controlled: NR
Halaweish I, Chwals WJ. Long-term outcome after partial external biliary diversion for progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2010 May 1;45(5):934-7.	Surgery	Non-controlled: retrospective
Hollands CM, Rivera-Pedrogo FJ, Gonzalez-Vallina R, Loret-de-Mola O, Nahmad M, Burnweit CA. Ileal exclusion for Byler's disease: an alternative surgical approach with promising early results for pruritus. Journal of pediatric surgery. 1998 Feb 1;33(2):220-4.	Surgery	Non-controlled: NR
Jankowska I, Czubkowski P, Wierzbicka A, Pawlowska J, Kalicinski P, Socha P. Influence of partial external biliary diversion on the lipid profile in children with progressive familial intrahepatic cholestasis. Journal of pediatric gastroenterology and nutrition. 2016 Dec 1;63(6):598-602.	Surgery	Non-controlled: prospective
Jankowska I, Czubkowski P, Kalicinski P, Ismail H, Kowalski A, Ryzko J, Pawlowska J. Ileal exclusion in children with progressive familial intrahepatic cholestasis. Journal of pediatric gastroenterology and nutrition. 2014 Jan 1;58(1):92-5.	Surgery	Non-controlled: NR
Jankowska I, Pawlowska J, Ismail H, Teisseyre M, Cielecka-Kuszyk J, Strautnieks S, Kalicinski P, Ryzko J. Ileal exclusion in children with progressive familial intrahepatic cholestasis-own experience. Journal of Pediatric Gastroenterology and Nutrition. 2011;52:E59-E60.	Surgery	Non-controlled: NR
Kaliciński PJ, Ismail H, Jankowska I, Kamiński A, Pawłowska J, Drewniak T, Markiewicz M, Szymczak M. Surgical treatment of progressive familial intrahepatic cholestasis: comparison of partial external biliary diversion and ileal bypass. European journal of pediatric surgery. 2003 Oct;13(5):307-11.	Surgery	Non-controlled: retrospective
Lemoine C, Bhardwaj T, Bass LM, Superina RA. Outcomes following partial external biliary diversion in patients with progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2017 Feb 1;52(2):268-72.	Surgery	Non-controlled: retrospective
Li Q, Chong C, Sun R, Yin T, Huang T, Diao M, Li L. Long-term outcome following cholecystocolostomy in 41 patients with progressive familial intrahepatic cholestasis. Pediatric Surgery International. 2021 Mar 2:1-8.	Surgery	Non-controlled: retrospective

Reference	Intervention	Study design
Liu T, Wang RX, Han J, Qiu YL, Borchers CH, Ling V, Wang JS. Changes in plasma bile acid profiles after partial internal biliary diversion in PFIC2 patients. Annals of translational medicine. 2020 Mar;8(5).	Surgery	Non-controlled: retrospective (for the outcomes with >5 patients)
Magnusson M, Gälman C, Fischler B, Beijer E, Arnell H, Németh A, Eggertsen G. The impact of serum bile acid levels on the mRNA expression of pro-and anticoagulant proteins in liver tissue: PO443-TUE. Journal of Thrombosis and Haemostasis. 2015 Jun;13:667.	Surgery	Non-controlled: prospective
Magnusson M, Gälman C, Fischler B, Beijer E, Arnell H, Németh A, Eggertsen G. The impact of serum bile acid levels on the mRNA expression of pro-and anticoagulant proteins in liver tissue. Journal of Pediatric Gastroenterology and Nutrition. 2016;62:601.	Surgery	Non-controlled: prospective
Melter M, Rodeck B, Kardorff R, Hoyer PF, Petersen C, Ballauff A, Brodehl J. Progressive familial intrahepatic cholestasis: partial biliary diversion normalizes serum lipids and improves growth in noncirrhotic patients. The American journal of gastroenterology. 2000 Dec 1;95(12):3522-8.	Surgery	Non-controlled: prospective
Ng VL, Ryckman FC, Porta G, Miura IK, de Carvalho E, Servidoni MF, Bezerra JA, Balistreri WF. Long-term outcome after partial external biliary diversion for intractable pruritus in patients with intrahepatic cholestasis. Journal of pediatric gastroenterology and nutrition. 2000 Feb 1;30(2):152-6.	Surgery	Non-controlled: retrospective
Ramachandran P, Shanmugam NP, Al Sinani S, Shanmugam V, Srinivas S, Sathiyasekaran M, Tamilvanan V, Rela M. Outcome of partial internal biliary diversion for intractable pruritus in children with cholestatic liver disease. Pediatric surgery international. 2014 Oct;30(10):1045-9.	Surgery	Non-controlled: retrospective
Schukfeh N, Metzelder ML, Petersen C, Reismann M, Pfister ED, Ure BM, Kuebler JF. Normalization of serum bile acids after partial external biliary diversion indicates an excellent long-term outcome in children with progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2012 Mar 1;47(3):501-5.	Surgery	Non-controlled: retrospective
Squires JE, Celik N, Morris A, Soltys K, Mazariegos G, Shneider B, Squires RH. Clinical variability following partial external biliary diversion in familial intrahepatic cholestasis 1 deficiency. Hepatology. 2016;64(1S1):277A	Surgery	Non-controlled: retrospective

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Reference	Intervention	Study design
Squires JE, Celik N, Morris A, Soltys K, Mazariegos G, Shneider B, Squires RH. Clinical variability after partial external biliary diversion in familial intrahepatic cholestasis 1 deficiency. Journal of pediatric gastroenterology and nutrition. 2017 Mar 1;64(3):425-30.	Surgery	Non-controlled: retrospective
Squires, JE, Squires R, Celik N, Morris A, Soltys K, Mazariegos G, Shneider B. Clinical variability folllowing partial external biliary diversion in familial intrahepatic cholestasis 1 deficiency. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S195	Surgery	Non-controlled: retrospective
Szymanska S, Cielecka-Kuszyk J, Grajkowska W, Lipiriski P, Jankowska I, Pronicki M. Long-term follow-up in children with progressive familial intrahepatic cholestasis type 2 after partial external biliary diversion with focus on histopathological changes. Virchows Archiv. 2018;473(S1):s125.	Surgery	Non-controlled: retrospective
Van Vaisberg V, Tannuri AC, Lima FR, Tannuri U. Ileal exclusion for pruritus treatment in children with progressive familial intrahepatic cholestasis and other cholestatic diseases. Journal of pediatric surgery. 2020 Jul 1;55(7):1385-91.	Surgery	Non-controlled: retrospective
Wang KS, Shneider BL, Azen CG, Arnon R, Bass LM et al. Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis: A retrospective, multi-institutional study. Hepatology. 2014;60:523A	Surgery	Non-controlled: retrospective
Wang KS, Tiao G, Bass LM, Hertel PM, Mogul D, Kerkar N, Clifton M, Azen C, Bull L, Rosenthal P, Stewart D. Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. Hepatology. 2017 May;65(5):1645-54.	Surgery	Non-controlled: retrospective
Yakar T, Demir M, Gokturk HS, Kanat AG, Parlakgumus A, Ozer B, Serin E. Nasobiliary drainage for benign recurrent intrahepatic cholestasis in patients refractory to standard therapy. Clinical and Investigative Medicine. 2016;39(6):.	Surgery	Non-controlled: retrospective
Yang H, Porte RJ, Verkade HJ, De Langen ZJ, Hulscher JB. Partial external biliary diversion in children with progressive familial intrahepatic cholestasis and Alagille disease. Journal of pediatric gastroenterology and nutrition. 2009 Aug 1;49(2):216-21.	Surgery	Non-controlled: retrospective

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Table 76. Overview of study design for studies included in the technology assessment/analysis

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
PEDFIC1 **A4250-005** **Phase 3**	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 Types 1 and 2 (PFIC1 and PFIC2)	Double-blind, Randomised-controlled-trial	Children with PFIC1 & PFIC2	Odevixibat vs. Placebo (n=62)	Proportion of patients experiencing at least a 70% reduction in serum bile acid concentration from baseline to end of treatment or reaching a level ≤70 µmol/L over the 24-week treatment period. Proportion of positive pruritus assessments at the patient level over the 24-week treatment period.	To evaluate the effect of odevixibat on serum alanine aminotransferase (ALT) concentration, growth, sleep disturbance, and the need for surgical treatment (biliary diversion or liver transplantation) over the 24-week treatment period To assess the safety and tolerability of repeated daily doses of odevixibat for 24 weeks.
PEDFIC2 **A4250-008** **Phase 3**	To investigate the long-term efficacy and safety of a 120 µg/kg/day daily dose of odevixibat in patients with PFIC	Phase 3, multi-centre, open-label extension study	Children with PFIC1 & PFIC2	Odevixibat (target n=120, recruitment ongoing)	The efficacy of treatment with odevixibat was primarily assessed by serial measurements of serum bile acids and evaluation of itching (Albireo PRO) and scratching (Albireo ObsRO) conducted twice daily in the morning (AM score, evaluating night time itching/scratching) and at bedtime (PM score, evaluating daytime itching/scratching) as recorded by the patient and caregiver in the eDiary. Seventy-two weeks with an option to continue in the	Additional efficacy assessments included serial evaluation of growth (height, weight and body mass index [BMI] z-scores), sleep parameters (including tiredness and number of awakenings) as assessed by items in the Albireo PRO and ObsRO, quality of life (QoL), PedsQL, GIC and GIS, liver function tests (ALT, aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], and total bilirubin), other parameters of hepatic health (Paediatric End-stage Liver Disease/and Model for End-stage Liver Disease [PELD/MELD], AST to platelet ratio

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
					extension period, which allows patients to continue on study drug until the drug is commercially available.	index [APRI] and FIB-4 scores), and number of patients undergoing biliary diversion surgery or liver transplantation

Excluded references

Table 77: Table of studies excluded at the full text review stage from the clinical SLR (n=176)

Reference	Reason for exclusion
1st National Meeting of the Liver Transplantation Society of India (LTSICON) 2018 AIIMS. Journal of Clinical and Experimental Hepatology;9(3):283-446 https://www.sciencedirect.com/journal/journal-of-clinical-and-experimental-hepatology/vol/9/issue/3 Valamparampil JJ, Rinaldhy K, Reddy MS, Shanmugam N, Rela M. Outcomes of Liver Transplantation for Pediatric Recipients With Progressive Familial Intrahepatic Cholestasis. Journal of Clinical and Experimental Hepatology. 2019;9(3):422-423 (included)	Duplicate
Gordo-Gilart R, Andueza S, Hierro L, Martínez-Fernández P, D'Agostino D, Jara P, Alvarez L. Functional analysis of ABCB4 mutations relates clinical outcomes of progressive familial intrahepatic cholestasis type 3 to the degree of MDR3 floppase activity. Gut. 2015 Jan 1;64(1):147-55.	Duplicate
Khan IA, Al-Shaqrani MA, Arain ZB, Al-Hebbi HA, Wali SH, Bassas AF. One hundred and thirty-seven living donor pediatric liver transplants at Riyadh Military Hospital. Saudi Med J. 2009;30(3):403-8.	Duplicate
van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipiński P, Czubkowski P, Gonzales E, Jacquemin E, Spraul A, Sokal E. Predicting long-term outcome after surgical biliary diversion in Bsep-deficiency patients: Results from the NAPPED consortium. J Hepatol. 2019 Apr 1;70(S1):e121.	Duplicate
Busachi C, Scagliarini G, Lambertini F, Cavalli G. Benign recurrent intrahepatic cholestasis: reconstruction from biopsy of the small bile ducts. Bollettino della Societa italiana di biologia sperimentale. 1975 Sep 15;51(17):1050-4.	Unable to find
Chaabouni M, Bahloul S, Romdhane B, Saleh B, Chouchene C, Zroud N, Kammoun T, Karray A. Epidemiological, etiological and evolutionary aspects of children cirrhosis in a developing country: experience of the pediatric department of SFAX University hospital, Tunisia. La Tunisie medicale. 2007 Sep 1;85(9):738-43.	Unable to find

Reference	Reason for exclusion
Chapman KA, Mew NA, Duckworth C, Kaufman S, Fishbein T, Yazigi N. Outcomes of liver transplants for inherited metabolic disorders over the last 15 years. Molecular Genetics and Metabolism. 2018 Mar 1;123(3):36	Unable to find
Dinler G, Koçak N, Yüce AY, Gürakan F, Ozen HA. Ursodeoxycholic acid therapy in children with cholestatic liver disease. The Turkish journal of pediatrics. 1999 Jan 1;41(1):91-8.	Unable to find
Euctr, F. R. 2018. A study to determine if A4250 is safe and can be used to treat children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2. Available from: http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-002338-21-FR	Unable to find
Euctr, N. L. 2018. A study to determine if A4250 is safe and can be used to treat children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-002338-21-NL	Unable to find
Fracchia M, Ferraris R, Petrarulo M, Secreto P, Dunn T, Galatola G. Effect of ursodeoxycholic acid on the masses of biliary lipids and alkaline phosphatase within the gallbladder in chronic cholestatic liver disease. European Journal of Gastroenterology and Hepatology. 1992;4(10):843-8.	Unable to find
Golovanova EV, Petrakov, AV. Diagnosis and treatment of intrahepatic cholestasis in chronic diseases of the liver. [Russian]. Terapevticheskii Arkhiv. 2011;83(2):33-39.	Unable to find
Gouffier E, Coste T, Rautureau J. Recurrent benign cholestasis. [French] La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris. La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris. 1974;50(19):1289-1292.	Unable to find
Jankowska I, Pawlowska J, Ismail H, Kalicinski P. Retrospective evaluation of different methods of treatment in children with progressive familial intrahepatic cholestasis. [Polish]. Pediatria Polska. 2001;76(1):13-19.	Unable to find
International Clinical Trials Registry Platform. A study to assess the safety and efficacy of rifampicin for progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC). Available from: http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000017823	Unable to find
Kertész T, Balázs M. Surgical Aspects of Chronic Intrahepatic Cholestasis. Acta chirurgica Academiae Scientiarum Hungaricae. 1968;9(3):279-86.	Unable to find
Kotalova R, Sticova E, Jirsa M. Progressive familial intrahepatic cholestasis type 2 -paediatric patients followed at the Paediatric Clinic of the 2nd Medical Faculty, University Hospital Motol, Prague. [Slovak] Gastroenterologia y Hepatologia. 2015;69(6):547-553	Unable to find
Kwak A, Dabrowska M, Jankowska I. Health related quality of life in children with progressive familial intrahepatic cholestasis after partial external biliray diversion. [Polish]. Pediatria Wspolczesna. 2005;7(3):201-204	Unable to find
Li XF, Gong JY, Wang JS. Non-transplant surgical intervention in progressive familial intrahepatic cholestasis. Zhonghua er ke za zhi= Chinese journal of pediatrics. 2018 May 2;56(5):392-5.	Unable to find
Lovisetto P, Raviolo P, Rizzetto M, Marchi L, Actis GC, Verme G. Benign recurrent intrahepatic cholestasis. A clinico-pathologic study. La Ricerca in clinica e in laboratorio. 1990 Jan;20(1):19-27.	Unable to find
Lyson-Wojciechowska G, Jankowska I Pawlowska J, Socha J, Skawinski W. Thickness and optical density of the second metacarpal bone in the differential diagnosis of children with progressive familial intrahepatic cholestasis. [Polish] Pediatria Polska. 2003;78(4):281-288	Unable to find

Reference	Reason for exclusion
Nicolau-Raducu RE, Eleborg L, Damian D, Nicolau-Raducu M. Hemodynamic changes during liver transplantation in different liver diseases. Hemodynamic changes during liver transplantation in different liver diseases. Romanian Journal of Gastroenterology. 2001;10(3):211-217.	Unable to find
Razemon-Pinta M, Lecomte-Houcke M, Mary JP, Loreille GA. Byler's disease (familial fibrogenic cholestasis in children). Apropos of 7 cases. Pediatrie. 1988 Jan 1;43(4):361-70.	Unable to find
Robson SC, Kahn D, Gordon P, Jacobs P. A cost-to-benefit analysis of blood products used during the initiation of an orthotopic liver transplantation programme. South African journal of surgery. Suid-Afrikaanse tydskrif vir chirurgie. 1995 Dec 1;33(4):154-8.	Unable to find
Schweizer WP, Matthews JB, Baer HU, Nudelmann LI, Triller J, Halter F, Gertsch P, Blumgart LH. Combined surgical and interventional radiological approach for complex benign biliary tract obstruction. Journal of British Surgery. 1991 May;78(5):559-63.	Unable to find
Steig B, Juijn JA, Bull LN, Houwen RH, Tygstrup N. Recurrent familial intrahepatic cholestasis in the Faroe Islands. [Danish]. Ugeskrift for laeger. 1999;161(35):4871-4874	Unable to find
Sturm E, Latta A, Rogiers X, Malago M, Burdelski M. Byler's disease (progressive familial intrahepatic cholestasis. PFIC)-Clinical findings, diagnostic strategies and therapy. Verdauungskrankheiten. 1996;14:17-21.	Unable to find
Zant R, Melter M, Schlitt HJ, Loss M, Ameres M, Knoppke B, Kunkel J. High levels of procalcitonin in the early phase after pediatric liver transplantation indicate poor postoperative outcome. Hepato-gastroenterology. 2014 Jul 1;61(133):1344-9.	Unable to find
Dalgic A, Ozcay F, Arslan G, Emiroglu R, Sozen H, Moray G, Karakayali H, Bilgin N, Haberal M. Living-related liver transplantation in pediatric patients. Transplantation proceedings 2005 Sep 1;37(7):3133-3136	Case report (<5)
de Vries E, Mazzetti M, Takkenberg B, Mostafavi N, Bikker H, Marzioni M, de Veer R, van Der Meer A, Doukas M, Verheij J, Beuers U. Carriers of ABCB4 gene variants show a mild clinical course, but impaired quality of life and limited risk for cholangiocarcinoma. Liver International. 2020 Dec;40(12):3042-50.	Case report (<5)
Evason K, Bove K, Knisely A, Rhee S, Rosenthal P, Miethke A, Ferrell L, Kim G. Morphological Findings in Progressive Familial Cholestasis 2 (PFIC2): Correlation With Genetic and Immunohistochemical Studies.: 13. Pediatric & Developmental Pathology. 2009 Jul;12(4):317	Case report (<5)
Fang LJ, Wang XH, Knisely AS, Yu H, Lu Y, Liu LY, Wang JS. Chinese children with chronic intrahepatic cholestasis and high γ-glutamyl transpeptidase: clinical features and association with ABCB4 mutations. Journal of pediatric gastroenterology and nutrition. 2012 Aug 1;55(2):150-6.	Case report (<5)
Fang L, Wang X, Zhu Q, Wang J. ABCB4 gene mutations in chinese children with chronic intrahepatic cholestasis and high gamma glutamyltransferase. Hepatology International. 2011;5(1):322	Case report (<5)
Fredericks EM, Dore-Stites D, Calderon SY, Well A, Eder SJ, Magee JC, Lopez MJ. Relationship between sleep problems and health-related quality of life among pediatric liver transplant recipients. Liver Transplantation. 2012 Jun;18(6):707-15.	Case report (<5)
Gencoglu EA, Karakayali H, Moray G, Aktas A, Haberal M. Evaluation of pediatric liver transplant recipients using quantitative hepatobiliary scintigraphy: 25 years in renal transplantation. Transplantation proceedings. 2002;34(6):2160-2162	Case report (<5)
Kang HJ, Hong SA, Oh SH, Kim KM, Yoo HW, Kim GH, Yu E. Progressive Familial Intrahepatic Cholestasis in Korea: A Clinicopathological Study of Five Patients. Journal of pathology and translational medicine. 2019 Jul;53(4):253-260.	Case report (<5)
Karthikeyan P, Davenport M, Knisely A, Thompson R, Bansal S. Biliary diversion in children with intractable pruritus-A single centre experience. Hepatology. 2013 Oct;58(4):804A-805A	Case report (<5)

Reference	Reason for exclusion
Kaur S, Sharma D, Wadhwa N, Gupta S, Chowdhary SK, Sibal A. Therapeutic interventions in progressive familial intrahepatic cholestasis: experience from a tertiary care centre in north India. The Indian Journal of Pediatrics. 2012 Feb;79(2):270-3.	Case report (<5)
Kondo S, Hashimoto T, Suzuki T, Nakamura T, Shimizu Y. Living related liver transplantation in two Byler disease families. Transplantation proceedings. 2000;32(7):2185-2186	Case report (<5)
Lee SJ, Kim JE, Choe BH, Seo AN, Bae HI, Hwang SK. Early diagnosis of ABCB11 spectrum liver disorders by next generation sequencing. Pediatric gastroenterology, hepatology & nutrition. 2017 Jun;20(2):114-123	Case report (<5)
Lee WS, Chai PF, Boey CC, Looi LM. Aetiology and outcome of neonatal cholestasis in Malaysia. Singapore medical journal. 2010;51(5):434-9.	Case report (<5)
Muiesan P, Jassem W, Girlanda R, Steinberg R, Vilca-Melendez H, Mieli-Vergani G, Dhawan A, Rela M, Heaton N. Segmental liver transplantation from non-heart beating donors—an early experience with implications for the future. American journal of transplantation. 2006 May;6(5p1):1012-6.	Case report (<5)
Odièvre MM, Gautier M, Hadchouel M, Alagille D. Severe familial intrahepatic cholestasis. Archives of disease in childhood. 1973 Oct 1;48(10):806-12.	Case report (<5)
Pinelli D, Giovanelli M, Vicario E, Sala F, Rubicondo C, Mangili A, Zambelli MF, Amaduzzi A, Colledan M. Outcome of reno-portal bypass in liver transplantation with non tumorous portal vein thrombosis. Transplant international. 2019 Oct 1;32(S2):63	Case report (<5)
Stapelbroek JM, van Erpecum KJ, Klomp LW, Venneman NG, Schwartz TP, van Berge Henegouwen GP, Devlin J, van Nieuwkerk CM, Knisely AS, Houwen RH. Nasobiliary drainage induces long-lasting remission in benign recurrent intrahepatic cholestasis. Hepatology. 2006 Jan;43(1):51-3.	Case report (<5)
Tygstrup N, Steig BÁ, Juijn JA, Bull LN, Houwen RH. Recurrent familial intrahepatic cholestasis in the Faeroe Islands. Phenotypic heterogeneity but genetic homogeneity. Hepatology. 1999 Feb;29(2):506-8.	Case report (<5)
Vajro P, Celentano L, Manguso F, Vallone G, Lenta S, Mandato C, Di Cosmo N, Capuano G, Staiano A, D'Arienzo A. Per-rectal portal scintigraphy is complementary to ultrasonography and endoscopy in the assessment of portal hypertension in children with chronic cholestasis. Journal of Nuclear Medicine. 2004 Oct 1;45(10):1705-11.	Case report (<5)
van der Woerd WL, Kokke FT, van der Zee DC, Houwen RH. Total biliary diversion as a treatment option for patients with progressive familial intrahepatic cholestasis and Alagille syndrome. Journal of pediatric surgery. 2015 Nov 1;50(11):1846-9.	Case report (<5)
Vij M, Shanmugam NP, Reddy MS, Sankaranarayanan S, Rela M. Paediatric hepatocellular carcinoma in tight junction protein 2 (TJP2) deficiency. Virchows Archiv. 2017 Nov;471(5):679-83.	Case report (<5)
Wei CS, Becher N, Blechingberg J, Ott P, Vogel I, Gronbaek H. New tight junction protein 2 variant causing progressive familial intrahepatic cholestasis type 4 in adults: A case report. World journal of gastroenterology. 2020;26(8):550-561	Case report (<5)
Zhelev C, Panteleeva E. Pre-and postoperative care of pediatric liver recipients: the bulgarian experience.: Abstract# 301. Pediatric Transplantation. 2009 Apr;13:118-9. Available from: https://recherche-pediatrique.hug.ch/sites/recherche_pediatrique/files/documents/abstract-transpante.pdf	Case report (<5)
Baker A, Kerkar N, Kamath BM, Houwen RH. Sytematic review of the epidemiology and burden of disease of progressive familial intrahepatic cholestasis (PFIC): A genetic disease associated with liver failure in children. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S330-S331	Study design
Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RH. Systematic review of progressive familial intrahepatic cholestasis. Clinics and research in hepatology and gastroenterology. 2019 Feb 1;43(1):20-36.	Study design

Reference	Reason for exclusion
Baussan C, Cresteil D, Gonzales E, Raynaud N, Dumont M, Bernard O, Hadchouel M, Jacquemin E. Genetic cholestatic liver diseases: the example of progressive familial intrahepatic cholestasis and related disorders. Act Gastro-Enterologica Belgica. 2004 Apr 1;67:179-83.	Study design
Catzola A, Vajro P. Management options for cholestatic liver disease in children. Expert review of gastroenterology & hepatology. 2017 Nov 2;11(11):1019-30.	Study design
Davis AR, Rosenthal P, Newman TB. Nontransplant surgical interventions in progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2009 Apr 1;44(4):821-7.	Study design
Davis AR, Rosenthal P, Newman TB. Nontransplant surgical interventions in progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2009 Apr 1;44(4):821-7.	Study design** Reference above came from Ovid databases, this one York – should have been a duplicate
Hori T, Nguyen JH, Uemoto S. Progressive familial intrahepatic cholestasis. Hepatobiliary and Pancreatic Diseases International. 2010;9(6):570-578	Study design
Khurana S, Singh P. Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials. Liver International. 2006 Oct;26(8):943-8.	Study design
Knisely AS, Houwen RH. Liver steatosis and diarrhea after liver transplantation for progressive familial intrahepatic cholestasis type 1: can biliary diversion solve these problems?. Journal of Pediatric Gastroenterology and Nutrition. 2021 Mar 1;72(3):341-2. Available from: https://journals.lww.com/jpgn/Citation/2021/03000/Liver_Steatosis_and_Diarrhea_After_Liver.1.aspx	Study design
Lipinski P, Jankowska I. [Progressive familial intrahepatic cholestasis type 3]. Medycyna Wieku Rozwojowego. 2018;22(4):385-389	Study design
Mehl A, Bohorquez H, Serrano MS, Galliano G, Reichman TW. Liver transplantation and the management of progressive familial intrahepatic cholestasis in children. World journal of transplantation. 2016 Jun 24;6(2):278-90.	Study design
Nguyen MP, Jain V, Iansante V, Mitry RR, Filippi C, Dhawan A. Clinical application of hepatocyte transplantation: current status, applicability, limitations, and future outlook. Expert review of gastroenterology & hepatology. 2020 Mar 3;14(3):185-96.	Study design
Palmeira CM, Rolo AP. Mitochondrially-mediated toxicity of bile acids. Toxicology. 2004 Oct 15;203(1-3):1-5.	Study design
Richter A, Ganschow R. Deficiency of BSEP in PFIC with hepatocellular malignancy [2]. Pediatric Transplantation. 2006;10(5):646	Study design
Tandon P, Rowe BH, Vandermeer B, Bain VG. The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. American Journal of Gastroenterology. 2007 Jul 1;102(7):1528-36.	Study design

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Reference	Reason for exclusion
Verkade HJ, Thompson RJ, Arnell H, Fischler B, Gillberg PG, Mattsson JP, Torfgård K, Lindström E. Systematic literature review of the effect of partial external biliary diversion surgery on clinical and biochemical outcomes in progressive familial intrahepatic cholestasis patients. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(S1):S209-S210	Study design
Verkade HJ, Thompson RJ, Arnell H, Fischler B, Gillberg PG, Mattsson JP, Torfgård K, Lindström E. Systematic review and meta-analysis: partial external biliary diversion in progressive familial intrahepatic cholestasis. Journal of Pediatric Gastroenterology and Nutrition. 2020 Aug 1;71(2):176-83.	Study design
Verkade HJ, Thompson RJ, Arnell H, Fischler B, Gillberg PG, Mattsson JP, Torfgård K, Lindström E, Soni PN. Systematic literature review of the effect of partial external biliary diversion surgery on clinical and biochemical outcomes in progressive familial intrahepatic cholestasis patients. Journal of Pediatric Gastroenterology and Nutrition. 2018;66(S2):818-819.	Study design
Alfieri S, Carriero C, Caprino P, Di Giorgio A, Sgadari A, Crucitti F, Doglietto GB. Avoiding early postoperative complications in liver surgery. A multivariate analysis of 254 patients consecutively observed. Digestive and Liver Disease. 2001 May 1;33(4):341-6.	Population
Avena A, Puggelli S, Morris M, Cerny A, Andrade AR, Pareti E, Bihl F, Cassatella D, Moix I, Merlo E, Rougemont AL. ABCB4 variants in adult patients with cholestatic disease are frequent and underdiagnosed. Digestive and Liver Disease. 2021 Mar 1;53(3):329-44.	Population
Gottschalk E, Schwarz H. Therapeutic problems in bile duct atresia. [German] Zentralblatt fur Chirurgie. 1986;111(8):461-468.	Population
Gumrich, H.; Krumme, H.; Nadler, K.; Ewald, P. [Transhepatic endless drainage according to Goetze-Dick in stenoses of the intrahepatic and extrahepatic bile ducts (author's transl)]. Zentralblatt fur Chirurgie. 1980;105(3):154-61.	Population
Hao CZ, Luan W, Li JQ, Gong JY, Qiu YL, Lu Y et al. Biallelic complete loss-of-function ZFYVE19 mutations: Congenital hepatic fibrosis, sclerosing cholangiopathy, and high-GGT cholestasis. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):726	Population
Jacquemin E, Setchell KD, O'connell NC, Bernard O. A new cause of progressive intrahepatic cholestasis: 3β-hydroxy-C27-steroid dehydrogenase/isomerase deficiency. The Journal of pediatrics. 1994 Sep 1;125(3):379-84.	Population
Mazzetti M, de Vries E, Takkenberg B, Mostafavi N, Bikker H, Marzioni M, de Veer R, Van der Meer A, Doukas M, Verheij J, Beuers U. Heterozygous carriers of ABCB4 mutations show a mild clinical course, but impaired quality of life and limited risk for cholangiocarcinoma–a cohort study. Journal of Hepatology. 2020 Aug 1;73(S1):S86.	Population
Poley JW, Lekkerkerker MN, Metselaar HJ, Kuipers EJ, Bruno MJ. Clinical outcome of progressive stenting in patients with anastomotic strictures after orthotopic liver transplantation. Endoscopy. 2013 Jul;45(7):567-70.	Population
Poupon R, Arrive L, Rosmorduc O. The cholangiographic features of severe forms of ABCB4/MDR3 deficiency-associated cholangiopathy in adults. Gastroenterologie clinique et biologique. 2010 Aug 1;34(6-7):380-7.	Population
Shagrani MA, Barr M, Broering DC. ABCB11 mutations diagnosed by next generation sequencing (NGS): Phenotypic correlation and the role of NGS in personalized medicine. Journal of Pediatric Gastroenterology and Nutrition. 2017;64(S1):717-718	Population
Hoerning A, Raub S, Dechêne A, Brosch MN, Kathemann S, Hoyer PF, Gerner P. Diversity of disorders causing neonatal cholestasis–the experience of a tertiary pediatric center in Germany. Frontiers in pediatrics. 2014;2:65.	Intervention

Reference	Reason for exclusion
Li L, Lu Y, Gong J, Zhao J, Qiu Y, Abuduxikuer K, Wang N, Wang J. ATP8B1 and ABCB11 mutations in Chinese patients with normal gamma-glutamyl transferase cholestasis: Phenotypic differences between progressive familial intrahepatic cholestasis type 1 and 2. Hepatology International. 2017;11(1S1):S180.	Intervention
Lu FT, Wu JF, Hsu HY, Ni YH, Chang MH, Chao CI, Chen HL. γ-Glutamyl transpeptidase level as a screening marker among diverse etiologies of infantile intrahepatic cholestasis. Journal of pediatric gastroenterology and nutrition. 2014 Dec 1;59(6):695-701.	Intervention
Srivastava A, Ravindranath A, Mathias A, Sen Sarma M, Poddar U, Yachha SK. Prevalence, precipitants and predictors of hepatic encephalopathy in children with chronic liver disease. Hepatology. 2019;70(S1):468A-469A.	Intervention
Thompson R, Kelly D, Miethke A, Rajwal S, Soufi N, Jankowska I, Mack C, Lachaux A, Jaecklin T, Vig P, Wardle A. Serum bile acid control in long-term maralixibat-treated patients is associated with native liver survival in children with progressive familial intrahepatic cholestasis due to bile salt export pump deficiency. Journal of Hepatology. 2020 Aug 1;73:S120.	Intervention
[Cholic acid: assessment according to section 35a (paragraph 1, sentence 10) Social Code Book V (dossier assessment)]	Outcomes
Al Mehaidib A, Al Shahrani A. Progressive familial intrahepatic cholestasis in arabs. Journal of Hepatology. 2013;58:S555-S556.	Outcomes
Al-Lawati TT, George M, Al-Lawati FA. Pattern of liver diseases in Oman. Annals of tropical paediatrics. 2009 Sep 1;29(3):183-9.	Outcomes
Al-Marzoug A, Al-Marzoug H, Al-Zaben A, Al-Rumayyan A. Neurological complications among pediatric postliver transplant in king abdulaziz medical city-riyadh. Saudi Journal of Gastroenterology. 2016;22(S7):S7-S8.	Outcomes
Alkhalil F, Bitar R, Azaz A, Almuraikhi N, Natouri H, Miqdady M. Overseas liver transplantation in children; One centre experience. Journal of Pediatric Gastroenterology and Nutrition. 2017;64(S1):715.	Outcomes
Alkhalil F, Bitar R, Azaz A, Natouri H, Almuraikhi N, Miqdady M. Growth and bone health in children following liver transplantation. Journal of Pediatric Gastroenterology and Nutrition. 2017;64(S1):714.	Outcomes
Alqabandi W, Thomas E, Buhamrah E. Pediatric liver transplantation for metabolic liver disease in Kuwait. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S129.	Outcomes
Bachina P, Okokon E, Sherwood R, Dhawan A. Prospective Evaluation of a Biomarker in Assessing Renal Function and Its Cost Effectiveness in Children before and after Liver Transplantation. Liver Transplantation. 2010;16(S1):S71.	Outcomes
Bahador A, Salahi H, Nikeghbalian S, Dehghani SM, Dehghani M, Kakaei F, Kazemi K, Rajaei E, Gholami S, Malek-Hosseini SA. Pediatric liver transplantation in Iran: a 9-year experience. Transplantation Proceedings. 2009 Sep 1;41(7):2864-2867.	Outcomes
Baig MA, Dogar AW, Shams Z, Ali AH. Successful journey of 100 living donor of liver transplant from stumbling to incline in remote area of Pakistan; beginning of New Era. Hepatology International. 2020;14(S1):S229.	Outcomes
Barr M, Kumar K, Hassan AA, Al Bogami D, Burkholder J, Shagrani MA, Algoufi T, Szonyi L. Bloodstream infections in children after living related liver transplantation. One center experience. Journal of Pediatric Gastroenterology and Nutrition. 2016;62:647.	Outcomes
Basso M, Subramaniam P, Tredger JM, Verma A, Heaton N, Rela M, Mieli-Vergani G, Dhawan A. Sirolimus as renal and immunological rescue agent in pediatric liver transplant recipients. Hepatology. 2010;52:1031A.	Outcomes

Reference	Reason for exclusion
Basso MS, Subramaniam P, Tredger M, Verma A, Heaton N, Mieli-Vergani G, Dhawan A. Sirolimus as renal and immunological rescue agent in pediatric liver transplant recipients. Pediatric Transplantation. 2011;15:136.	Outcomes
Basturk A, Yılmaz A, Sayar E, Dinçhan A, Aliosmanoğlu İ, Erbiş H, Aydınlı B, Artan R. Pediatric Liver Transplantation: Our Experiences. The Eurasian journal of medicine. 2016 Oct;48(3):209-212.	Outcomes
Cantez MS, Onal Z, Guller D, Ekici F, Gulluoglu M, Soysal FG, Ozden I, Ugurcan OD. Diverse mutations and different clinical outcomes in children with progressive intrahepatic cholestasis. Journal of Pediatric Gastroenterology and Nutrition. 2018;66(S2):723.	Outcomes
Carlier M, Van Obbergh LJ, Veyckemans F, De Kock M, De Beys CC, Lavenne-Pardonge E, Moulin D, Otte JB. Hemostasis in children undergoing liver transplantation. Seminars in thrombosis and hemostasis.1993 Jan 1;19(3):218-222.	Outcomes
Cherian TP, Shanmugam N, Varghese J, Bharathan A, Rajkumar A, Reddy SM, Venugopal K, Narasimhan G, Kaliamoorthy I, Rela M. Paediatric liver transplantation in south india: Outcomes and lessons learnt from the first 50 cases. Journal of Clinical and Experimental Hepatology. 2013 Mar 1;3(1):S113-4.	Outcomes
Choi Y, Yi NJ, Hong G, Kim H, Park MS, Suh S, You T, Lee H, Lee KW, Suh KS. The Pitfall in Familial Living Donor Liver Transplantation for Metabolic Disorders. Liver Transplantation. 2013;19(6):S269.	Outcomes
Choi Y, Yi NJ, Kim H, Park MS, Suh SW, Yoo T, Lee H, Lee KW, Suh KS. The pitfall in familial living donor liver transplantation for metabolic disorders. Hpb. 2014;16(S2):572.	Outcomes
Cicak Novak M, Babic K, Maric A, Saratlija M, Novak M, Vukovic J. Pediatric liver transplantation: present state in Croatia. Intensive Care Medicine. 2011 Nov 1;37:S440	Outcomes
Colak M, Altay A, Bozbulut NE, Dalgic B, Fidan I, Ozkan S, Bozdayi G. Investigation of malignancy associated with EBV (Epstein-barr virus) in paediatric patients with liver transplant. Journal of Clinical Virology. 2016;82(S1):S142.	Outcomes
Colombo C, Vajro P, Degiorgio D, Tornillo L, Motta V, Zancan L, Iorio R, D'antiga L, Maggiore G. Role of ABCB4 gene in progressive familial intrahepatic cholestasis type 3 (PFIC-3): final report of an Italian multicenter study. Journal of Pediatric Gastroenterology and Nutrition. 2010 Jun 1;50:E47-E48	Outcomes
Dalgic A, Ozen O, Yüksel O, Demirogulari B, Sozen H. Surcigal Outcome of Pediatric Liver Transplantation: Gazi University/Ankara-Turkey Experience. Transplantation. 2016;100(5S1):245.	Outcomes
Darius T, Rivera J, Lai Q, Fusaro F, De Magnee C, Ciccarelli O, Janssen M, Lerut J, Reding R. A Plea for Surgical Redo as First Therapeutic Option for Anastomotic Biliary Complications after Pediatric Liver Transplantation. Transplantation. 2012 Nov 27;94(10S):27.	Outcomes
Darius T, Rivera J, Lai Q, Fusaro F, de Magnée C, Ciccarelli O, Janssen M, Lerut J, Reding R. Anastomotic Biliary Complications after Pediatric Liver Transplantation: A Plea for Surgical Redo as First Therapeutic Option. American Journal of Transplantation. 2012;12:342.	Outcomes
Davit-Spraul A, Gendrot C, Parfait B, Jacquemin E, Bacq Y, Poupon R, Hillaire S, Belabbas K, Housset C, Baussan C, Barbu V. Sequence variations of ABCB4 gene in the French cohort of hereditary cholestasis and cholelithiasis. Hepatology. 2010;52:348A-349A.	Outcomes
De Magnee C, Bourdeaux C, De Dobbeleer F, Janssen M, Menten R, Clapuyt P, Reding R. Impact of pre-transplant liver hemodynamics and portal reconstruction techniques on post-transplant portal vein complications in pediatric liver transplantation: a retrospective analysis in 197 recipients. Annals of surgery. 2011 Jul 1;254(1):55-61.	Outcomes

Reference	Reason for exclusion
Degtyareva A, Puchkova A, Pykov M, Filippova E, Ivanec T. Outcome of the children after liver transplantation. Pediatric Transplantation. 2015;19:118.	Outcomes
Degtyareva A, Puchkova A, Albegova M, Pykov M, Pavlushkina L. Outcome of children after liver transplantation: experience at a children hospital. Pediatric Transplantation. 2011;15:48.	Outcomes
Dehghani SM, Bahador A, Gholami S, Nikeghbalian S, Salahi H, Imanieh MH, Haghighat M, Davari HR, Serati Z, Mehrabani D, Malek-Hosseini SA. Pediatric liver transplantation in Iran: Evaluation of the first 50 cases. Pediatric transplantation. 2007 May;11(3):256-60.	Outcomes
Dehghani SM, Shahramian I, Bazi A, Mofrad MM, Mardani S. Evaluation of underlying liver disease and its severity in children referred for liver transplant: A single-center report from Nemazee Hospital of Shiraz. Experimental and Clinical transplantation. 2020;18(7):803-807.	Outcomes
El Fakiri K, Bourouhouat A, Ait Sab I, Sbihi M. Cholestasis neonatal and infant: Marrakech University Hospital Experience. [French]. Journal de Pediatrie et de Puericulture. 2016;29(3):139-143	Outcomes
Fernandez C, Navarro M, Alonso A, Hierro L, Camarena C, Paloma J. Growth hormone in children with Chronic Renal insufficiency and liver transplant: 3-years experience. Pediatric Transplantation. 2009;13:112. Available from: https://recherche-pediatrique.hug.ch/sites/recherche_pediatrique/files/documents/abstract-transpante.pdf	Outcomes
Fernandez C, Navarro M, Espinosa L, Pena A, Garcia C, Melgosa M. Final height in children with chronic kidney disease (CKD) and liver transplant treated with growth hormone. Pediatric Nephrology. 2013;28(9):1894.	Outcomes
Flores CD, Yangyang RY, Miloh TA, Goss J, Brandt ML. Surgical outcomes in Alagille syndrome and PFIC: A single institution's 20-year experience. Journal of pediatric surgery. 2018 May 1;53(5):976-9.	Outcomes
Folvik G, Hilde O, Helge GO. Benign recurrent intrahepatic cholestasis: review and long-term follow-up of five cases. Scandinavian journal of gastroenterology. 2012 Apr 1;47(4):482-8.	Outcomes
Gautier S, Tsirulnikova O, Kurabekova R, Tsirulnikova I, Gichkun O, Shevchenko O. Pediatric living donor liver transplantation: correlation plasma level of transforming growth factor beta-1 with tacrolimus dosage but not with its concentration. Transplantation. 2016;100(7):S575	Outcomes
Gautier S, Shevchenko O, Tsirulnikova O, Gichkun O, Kuncevich N. Correlation between plasma levels of homocysteine and sCD40L In pediatric living donor liver transplantation. Pediatric Transplantation. 2013;17:99.	Outcomes
Gautier SV, Tsirulnikova OM, Ammosov AA, Gichkun OE, Pitshulina ME, Kuncevich NV, Shevchenko OP. Pediatric living donors liver transplantation: soluble CD40 ligand as an early predictor of graft dysfunction. Transplantation. 2010 Jul 27;90:853.	Outcomes
Geramizadeh B, Baghernezhad M, Salehi H, Nikeghbalian S, Shamsaeefar A, Kazemi K, Malekhosseini SA. Clinicopathological Discrepancies in the Diagnosis of Hepatocellular Carcinoma in Explanted Livers, A Single Center Study on More Than 1500 Transplanted Livers. Hepatitis Monthly. 2017 Oct 1;17(10):e11836.	Outcomes
Grimaldi C, Guettier C, Gonzales E, Angelico R, Saffioti MC, Guerin F, Spada M, Branchereau S. Outcome of HCC on Chronic Liver Disease in Children: A Multicenter Series. Pediatric Blood & Cancer. 2018;65(S2):S359.	Outcomes
Hayat BBH, Reda BBR, Amel HHA, Rachida BBR. The inborn error of primary bile acid synthesis: Report of 10 cases from Algeria. Journal of Inherited Metabolic Disease. 2019;42(S1):218	Outcomes

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Reference	Reason for exclusion
Ho CM, Wu YM, Ho MC, Hu RH, Lee PH. Isolated increase of serum alkaline phosphatase after liver transplantation: Risk factors and outcome analysis. Liver Transplantation. 2012;18:S115.	Outcomes
Hudert C, Mueller S, Luck W, Weber K, Laass M, Henning S, Bufler P. Mycophenolate motefil monotherapy in paediatric primary liver transplant patients. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):936.	Outcomes
Iakobadze Z, Yilmaz C. Reduced-size left lateral sector grafts for infants weighing less than 10 kilograms. International Journal of Surgery. 2020 Mar 1;75:S3.	Outcomes
Kanmaz T, Yankol Y, Karatas C, Mecit N, Orug T, Durmaz O, Acarli K, Kalayoglu M. Pediatric living donor liver transplantation: a single center study of 42 consecutive cases. Pediatric Transplantation. 2011;15:48-9.	Outcomes
Kanmaz T, Yankol Y, Mecit N, Durmaz Ö, Acarli K, Kalayoglu M. Pediatric liver transplantation: a single center study of 100 consecutive patients. Pediatric Transplantation. 2013;17:101.	Outcomes
Kanmaz T, Yankol Y, Mecit N, Durmaz O, Acarli K, Kalayoğlu M. Pediatric liver transplant: a single-center study of 100 consecutive patients. Exp Clin Transplant. 2014 Feb 1;12(1):41-5.	Outcomes
Karkra S, Mohan N, Goyal D, Dhaliwal M, Raghunathan V, Rastogi A, Goja S, Bhangui P, Ramchandra S, Vohra V, Soin S. Living related liver transplantation as a cure for metabolic disorders with or without liver injury: Etiology, timing, selection criteria, specific issues and outcome. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S342.	Outcomes
Khan I, Al-Zharani AA, Arain Z, Hebbi H, Wali S, Bassas A. One hundred and fifty pediatric liver transplants at Riyadh military hospital. Liver Transplantation. 2009;15:S260.	Outcomes
Kizilcan S, Karakoyun M, Turan C, Aydogdu S. Survival after liver transplantation in metabolic diseases and congenital liver diseases. Journal of Pediatric Gastroenterology and Nutrition. 2016;62:634	Outcomes
Kurabekova R, Tsirulnikova I, Olefirenko G, Gichkun O, Mozheyko N, Tsirulnikova O, Shevchenko O, Gautier S. Transforming growth factor beta 1 blood level relates with liver disease etiology and fibrosis severity in pediatric liver recipients. Transplantation. 2016 Jul 1;100(7S1):S574	Outcomes
Leiskau C, Samuel S, Pfister ED, Junge N, Laue T, Mutschler F, Goldschmidt I, Beneke J, Stupak J, Schrem H, Baumann U. Low dose steroids do make a difference-failure to thrive after pediatric liver Transplantation. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):949.	Outcomes
Lind RC, Hoekstra-Weebers JE, Verkade HJ, Porte RJ, Hulscher JB. Quality of life in children after a partial external biliary diversion for progressive familial intrahepatic cholestasis or Alagille's disease. Journal of Pediatric Gastroenterology and Nutrition. 2010;50:E155.	Outcomes
Lipinski P, Jurkiewicz D, Ciara E, Ploski R, Socha P, Jankowska I. Next-generation sequencing in diagnostic approach to cholestatic liver disease-one-centre experience. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):828.	Outcomes
Meena BL, Khanna R, Sharma CB, Rawat D, Alam S. Ductal paucity in childhood: Spectrum, profile and outcome. Hepatology International. 2017;11(1S1):S366.	Outcomes
Mohan N, Karkra S, Dhaliwal M, Raghunathan V, Goyal D et al. Pediatric living donor liver transplants in India- Experience of the first double century. Indian Journal of Gastroenterology. 2016;35(S1):A75.	Outcomes
Mohan N, Karkra S, Goyal D, Dhaliwal M, Raghunathan V, Sharma J, Rastogi A, Goja S, Bhangui P, Ramachandra S, Vohra V. Liver Transplantation for Inherited Metabolic Disorders-Etiology, Timing, Selection Criteria, Specific Issues and Outcome. Transplantation. 2016;100(5S1):S108	Outcomes

Reference	Reason for exclusion
Müller G, Veyckemans F, Carlier M, Van Obbergh LJ, De Kock M, Sokal EM, Otte JB. Anaesthetic considerations in progressive familial intrahepatic cholestasis (Byler's disease). Canadian journal of anaesthesia. 1995 Dec 1;42(12):1126-33.	Outcomes
Mussini C, Gonzales E, Redon MJ, Branchereau S, Martelli H, Jacquemin E, Guettier C. Pediatric hepatocellular carcinoma of common type: Morphologic and immunophenotypic characterization of a monocentric series of 13 cases. Virchows Archiv. 2013;463(2):120.	Outcomes
Navaratne, S.; Ljutikov, A.; Sellars, M.; Kane, P.; Dhawan, A.; Heaton, N.; Karani, J. B. Non-invasive measures that guide the indication, pathology and outcome of percutaneous biliary intervention in paediatric transplantation. CardioVascular and Interventional Radiology. 2013;36:S258	Outcomes
Naveh Y, Bassan L, Rosenthal E, Berkowitz D, Jaffe M, Mandel H, Berant M. Progressive familial intrahepatic cholestasis among the Arab population in Israel. Journal of pediatric gastroenterology and nutrition. 1997;24(5):548-54.	Outcomes
NCT. This Study Will Investigate the Efficacy and Safety of A4250 in Children With PFIC 1 or 2. Available from: https://clinicaltrials.gov/show/NCT03566238	Outcomes
Nemati H, Kazemi K, Mokarram AT. Neurological Complications associated with Pediatric Liver Transplant in Namazi Hospital: One-Year Follow-Up. International Journal Of Organ Transplantation Medicine. 2019;10(1):30-35.	Outcomes
Nikeghbalian S, Kakaei F, Kazemi K, Shamsaeefar A, Sanei B, Ghaffaripour S, Salahi H, Bahador A, Janghorban P, Malekhosseini SA. Biliary complications following living donor liver transplantation: comparison of bilioenteric with duct-to-duct anastomosis. Transplantation. 2010;90:799.	Outcomes
Nikeghbalian S, Malekhosseini SA, Kazemi K, Arasteh P, Eghlimi H, Shamsaeefar A, Nikoupour H, Gholami S, Dehghani M, Dehghani SM, Bahador A. The largest single center report on pediatric liver transplantation: experiences and lessons learned. Annals of Surgery. 2021 Feb 1;273(2):e70-2.	Outcomes
Nikeghbalian S, Nejatollahi SM, Salahi H, Bahador A, Dehghani SM, Kazemi K, Dehghani M, Kakaei F, Ghaffaripour S, Sattari H, Gholami S. Experience of living donor liver transplantation in Iran: a single-center report. Transplantation proceedings. 2009;41(7):2868-2871.	Outcomes
Ozdogan E, Doganay L, Can D, Arikan C. Disease Course and Treatment Response of Eosinophilic Gastrointestinal Diseases in Children With Liver Transplantation: Long-Term Follow-Up. American Journal of Gastroenterology. 2021;116(1):188-97.	Outcomes
Palaniappan K, Shrivastav M, Shanmugam N, Rajalingam R, Perumalla R, Narashiman G, Rela M. Monogenic Liver Diseases-Liver Transplantation As Gene Therapy. Liver Transplantation. 2014;20:S208.	Outcomes
Parra DA, Peters S, Amaral J. Findings in percutaneous transhepatic cholecysto-cholangiography in neonates and young infants presenting with conjugated hyperbilirubinemia. Pediatric Radiology. 2017;47(S2):S358.	Outcomes
Pei J, Wang Z, Shen C, Zhang Q, Li J. Liver transplantation for the treatment of children with inherited metabolic liver diseases: single center experience. Transplantation. 2020;104(S3):S549. Available from: https://journals.lww.com/transplantjournal/Citation/2020/09003/LIVER_TRANSPLANTATION_FOR_THE_TREATMENT_OF.811.aspx	Outcomes
Rai A, Mohan N, Karkra S, Goyal D, Dhaliwal M, Raghunathan V, Rastogi A, Goja S, Bhangui P, Srinivasan T, Vohra V, Soin A. LRLTas a cure for metabolic disorders with or without liver injury-Etiology, timing, selection criteria, specific issues and outcome. Indian Journal of Gastroenterology. 2016;35(S1):A75.	Outcomes
Reding R, Bourdeaux C, Gras J, Evrard V, Buts JP, Carlier M, Ciccarelli O, Clapuyt P, de Clety SC, De Kock M, Hermans D. The paediatric liver transplantation program at the Université catholique de Louvain. Acta gastro-enterologica Belgica. 2004 Apr 1;67(2):176-8.	Outcomes

Reference	Reason for exclusion
Rela M, Reddy M, Khoula HH, Al-Busafi S, Al Harthi N, Al Kindi A, Tawfiq T, Kancherla R. A model for provision of liver transplantation services on a nation-wide basis-a novel approach by the Omani health care system. Transplantation. 2016;100(7):S805-S806.	Outcomes
Revillon Y, Michel JL, Lacaille F, Sauvat F, Farges O, Belghiti J, Rengeval A, Jouvet P, Sayegh N, Sarnacki S, Jan D. Living-related liver transplantation in children: the 'Parisian'strategy to safely increase organ availability. Journal of pediatric surgery. 1999 May 1;34(5):851-3.	Outcomes
Rivera J, Darius T, Fusaro F, De Magnee C, Ciccarelli O, Lerut J, Janssen M, Reding R. Biliary complications in pediatric liver transplantation: A 18 year single center experience in 429 cases. Transplant International. 2011;24:350.	Outcomes
Ruth N, Sharif K, McGovern-Weijers A, Hartley J, Van Mourik I, Kelly D, Gupte, G. Long term outcome of children with PFIC-A single centre experience. Journal of Pediatric Gastroenterology and Nutrition. 2018;66(S2):793-794.	Outcomes
Serradilla J, Bueno A, Andrés AM, Sánchez-Galán A, Encinas JL, Nuño J, Hierro L, Hernández-Oliveros F, López-Santamaría M. 200 living donor liver transplantation in children: outcomes and results according to indication for transplantation and graft type. Transplantation. 2020 Sep 1;104(S3):S506.	Outcomes
Sherif AE, Badawy MT, Aziz AM, Osman M, Abdeldaym H, Kasahara M, Tanaka K, Abou El-Ella K. Surgical challenges toward better outcomes of pediatric living donor liver transplantation: experience of the first egyptian pediatric liver transplant center. Transplant International. 2017;30(S2):539.	Outcomes
Shevchenko O, Kurabekova R, Tsirulnikova I, Olefirenko G, Gichkun O, Tsirulnikova O, Gautier S. Prognostic value of TGF-B1 plasma level at pediatric living donor liver transplantation. Clinical Chemistry and Laboratory Medicine. 2017 Jun 1;55(S1):S377.	Outcomes
Shevchenko OP, Pitshulina ME, Gichkun OE, Kuncevich NV, Ammosov AA, Tsirulnikova OM, Gautier SV. Plasma levels of soluble CD30 and neopterin in pediatric living donors liver transplantation. Transplantation. 2010;90:1071.	Outcomes
Sun LY, Zhu ZJ, Lin Wei L Qu W, Zeng ZG, Liu Y, He EH, Zhang L et al. Pediatric liver transplantation for metabolic disease. Transplantation. 2019;103(8S1):245-246.	Outcomes
Sun LY, Zhu ZJ, Wei L, Qu W, Zeng ZG, Liu Y, He EH, Zhang L, Jiang YZ, Li XY, He YF. Pediatric liver transplantation for metabolic disease. Pediatric Transplantation. 2019;23(S1):.	Outcomes
Thejeal RF. Clinical Profile Of A Group Of Iraqi Children With Transplanted Liver. Systematic Reviews in Pharmacy. 2021;12(1):276-81.	Outcomes
Thomas Cherian P, Shanmugam N, Verghese J, Rajakumar A, Reddy MS, Venugopal K, Narasimhan G, Kaliamoorthy, I, Rela M. Paediatric liver transplantation in south India: Outcomes and lessons learnt from the first 50 cases. Liver Transplantation. 2013;19(6):S106.	Outcomes
Thomas AM, Korula S, Thomas L, Sridhar S, Mathai J, Hephzibah J. Neonatal cholestasis syndrome: Aetiological spectrum and outcome analysis - Single center study. Journal of Clinical and Diagnostic Research. 2019;13(11):SC01-SC04.	Outcomes
Varma S, Revencu N, Stéphenne X, Scheers I, Smets F, Beleza-Meireles A, De Magnee C, Reding R, Roskams T, Sokal E. Retargeting of bile salt export pump (BSEP) and criteria of favourable outcome in children with progressive familial intrahepatic cholestasis type II (PFIC-II). Journal of Hepatology. 2015;62:S818-S819.	Outcomes
Vij M, Safwan M, Shanmugam NP, Rela M. Liver pathology in severe multidrug resistant 3 protein deficiency: a series of 10 pediatric cases. Annals of diagnostic pathology. 2015;19(5):277-82.	Outcomes
Vimalesvaran S, Nevus L, Deheragoda M, Samyn M, Melendez H, Heaton N, Dhawan A. Allograft histology and biopsychosocial health 10 years after liver transplantation in children. Transplantation. 2019;103(8):92.	Outcomes

Reference	Reason for exclusion
Vimalesvaran S, Nevus L, Deheragoda M, Samyn M, Melendez H, Heaton N, Dhawan A. Allograft histology and biopsychosocial health 10 years after liver transplantation in children. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(S1):975.	Outcomes
Yadav S, Bharadia L, Gupta A. Progressive familial intrahepatic cholestasis: An emerging cause of neonatal cholestasis in young infants. Hepatology International. 2018;12 (2):S286	Outcomes
Zahmatkeshan M, Haghighat M, Imanieh M, Geramizadeh B, Dehghani S. PFIC the first report from South Iran. Journal of Pediatric Gastroenterology and Nutrition. 2010;50:E166.	Outcomes

Quality assessment

The literature search adhered to the highest standards for conducting and reporting. A critical appraisal of the randomised controlled trials found in the SLR is presented in Table 78, and a critical appraisal of the NAPPED and other observational studies in the SLR is presented in Table 79. Critical appraisals were not conducted of 93 surgery, liver transplant, UDCA and rifampicin studies which were non-controlled.

Table 78: Critical appraisal of randomised controlled trials in the clinical SLR

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 had been completed)	Demographic characteristics were generally similar across the study groups in Cohort 1 and Cohort 2
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.				

Table 79. Critical appraisal of the NAPPED study and observational studies in the SLR

Study name	**NAPPED**		**Baumann 2017, Sturm 2017, Sturm 2017, CSR (Odevixibat Phase 2)**	
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 the cohort recruited in an acceptable way?	Yes	Patient data were obtained from the global NAPPED database	Yes	Aimed to evaluate pediatric patients with pruritus from cholestatic liver disease, including PFIC and other diseases. No unexpected eligibility criteria. Recruited from 6 centres.

Study name	NAPPED		Baumann 2017, Sturm 2017, Sturm 2017, CSR (Odevixibat Phase 2)	
Was the exposure accurately measured to minimise bias?[1]	Yes	Full details were reported in the papers	Yes	Full details in CSR including subgroup analysis of PFIC types
Was the outcome accurately measured to minimise bias?	Yes	Objective measurements were evaluated	Yes	Objective measurements were evaluated
Have the authors identified all important confounding factors?	Yes	Most of the NAPPED studies evaluate outcomes by type of mutation	Yes	PFIC types grouped, baseline variation in VAS-itch score noted
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Many of the NAPPED studies have compared outcomes by the type of mutation, and also other baseline characteristics	Yes	Subgroup analysis of PFIC types.
Was the follow-up of patients complete?	Yes	All individuals were included in the analysis within this group of studies (retrospective analyses of data from a database)	Yes	All individuals were included in the analysis
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	The full papers present effect sizes, confidence intervals, and p values (where appropriate to do so). Given that CIs were not wide, we are confident in these results	Not clear	P values for change from baseline data were not reported

Note: Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study

[1] For this review, this criterion considers how PFIC and/or mutations were described

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Unpublished data

Table 80. List of relevant unpublished studies

Primary data source	Study name (acronym)	Description	Population	Intervention	Comparator	Status
Clinical study report: A4250-003	A4250-003 Phase 2	Single arm, single and multiple dosing open-label dose-escalating study	Paediatric cholestasis n=24	Odevixibat	None	Completed
Clinical study report: A4250-005	A4250-005 PEDFIC1 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 PEDFIC2 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) Target 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

The data-on file used for this submission were full study reports from PEDFIC1 and were developed to support regulatory submissions to EMA/FDA. The data and analysis therefore adherers to the most stringent quality criteria.

Publication of a manuscript presenting results from PEDFIC1 is planned for Q2 2022.

15. Appendix B – Main characteristics of included studies

Table 81. Main characteristics of PEDFIC1

Trial name: A4250-005: A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC1)	**NCT number: NCT03659916**
Objective	Primary: 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 Types 1 and 2 (PFIC1 and PFIC2), as determined by the following: • Proportion of patients experiencing at least a 70% reduction in serum bile acid concentration from baseline to end of treatment or reaching a level ≤70 µmol/L. • Proportion of positive pruritus assessments at the patient level over the 24-week treatment period. Secondary: • To evaluate the effect of odevixibat on serum alanine aminotransferase (ALT) concentration, growth, sleep disturbance, and the need for surgical treatment (biliary diversion or liver transplantation). • To assess the safety and tolerability of repeated daily doses of odevixibat for 24 weeks.
Publications – title, author, journal, year	Publication of a manuscript presenting results from PEDFIC1 is planned for Q1-Q2 2022.
Study type and design	Study A4250-005 was a double blind, randomised, placebo controlled, multicentre, Phase 3 study to investigate the efficacy and safety of odevixibat at doses of 40 µg/kg/day and 120 µg/kg/day administered once daily compared to placebo in paediatric patients with PFIC1 and PFIC2. The study included up to an 8-week screening period, a 24-week treatment period, and a 4-week follow-up period. Screening procedures included medical and surgical history, concomitant medications, genetic confirmation for PFIC, physical examination, vital signs, and laboratory assessments, including serum bile acids, haematology, chemistry, coagulation profile, and fat-soluble vitamin levels. At the first visit during screening, patients and/or their caregivers were provided an electronic diary (eDiary) to record patient reported (patients ≥8 years of age) and observer reported (caregivers for all patients) outcome items from the Albireo Patient-Reported Outcome (PRO) and Observer-Reported Outcome (ObsRO) instruments for evaluation of pruritus (itching and scratching, respectively) and sleep disturbance; data were to be entered twice daily. After completion of the screening period, eligible patients 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 matching placebo. Randomisation was stratified according to PFIC type (Types 1 and 2) and age (6 months to 5 years, 6 to 12 years, and 13 to ≤18 years). During the treatment period, patients returned to the clinic at Weeks 4, 8, 12, 18, 22, and 24 (End of Treatment). Assessments conducted on the day of

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	randomisation (Day 0) and at the on-treatment visits included physical examinations, vital signs, laboratory assessments (haematology, chemistry, international normalised ratio [INR], serum bile acids, vitamin A, vitamin E, 25 hydroxy vitamin D, urine pregnancy testing, and urinalysis), abdominal ultrasound, quality of life (QoL) assessments (Pediatric Quality of Life questionnaire [PedsQL] and global symptom relief based on the Global Impression of Symptoms (GIS) and Global Impression of Change [GIC] instruments), Fibroscan®, and review of concomitant medications and adverse events (AEs). Following this 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.
Sample size (n)	Planned: Approximately 60 to 70 patients were planned to be enrolled to obtain 20 evaluable patients in each treatment group. Analysed: 62 patients were randomised into the study: 20, 23 and 19 patients were randomised to receive placebo and odevixibat 40 and 120 µg/kg/day, respectively. All randomised patients received their assigned treatment.
Main inclusion and exclusion criteria	Key Inclusion Criteria: • A male or female participant with a clinical diagnosis of PFIC Type 1 or 2 and with a body weight above 5 kg • Participant must have clinical genetic confirmation of PFIC-1 or PFIC-2 • Participant must have elevated serum bile acid (s-BA) concentration • Participant must have history of significant pruritus and a caregiver reported observed scratching in the eDiary • Participant and/or legal guardian must sign informed consent (and assent) as appropriate. • Participants will be expected to have a consistent caregiver(s) for the duration of the study • Caregivers and age-appropriate participants (≥8 years of age) must be willing and able to use an eDiary device as required by the study Key Exclusion Criteria: • Participant with pathologic variations of the ABCB11 gene that predict complete absence of the bile salt export pump (BSEP) protein • Participant with past medical history or ongoing presence of other types of liver disease including, but not limited to, the following: 1. Biliary atresia of any kind 2. Benign recurrent intrahepatic cholestasis, indicated by any history of normal s BAs 3. Suspected or proven liver cancer or metastasis to the liver on imaging studies 4. Histopathology on liver biopsy that is suggestive of alternate non-PFIC related etiology of cholestasis • Participant with past medical history or ongoing chronic diarrhea • Any participant with suspected or confirmed cancers except for basal cell carcinoma

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	• Participant 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 • Participant with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period • Participant has had a liver transplant or a liver transplant is planned within 6 months of randomization • Decompensated liver disease • Participant suffers from uncontrolled, recalcitrant pruritic condition other than PFIC • Participant who has been previously treated with an IBAT inhibitor whose pruritus has not responded to treatment
Intervention	42 patients randomised to receive once daily odevixibat (23 and 19 patients to 40 and 120 µg/kg/day, respectively)
Comparator(s)	20 randomised to receive once daily placebo.
Follow-up time	24 weeks with the possibility to continue treatment with odevixibat 120 µg/kg/day in the open label extension study 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 (noncompliance/inability to travel to the site).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The primary efficacy endpoints were region based: **EU and Rest of World** • 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. o 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 Figure 13 and section 9.4.1.4 below). o Completed twice daily by the caregiver The secondary efficacy endpoints were region based: **EU and Rest of World** • Proportion of positive pruritus assessments at the subject level over the 24-week Treatment Period.

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	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.
Method of analysis	**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 nonpositive 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.
Subgroup 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 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),

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	• 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. 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.
Other relevant information	

Table 82. Main characteristics of PEDFIC2

Trial name: A4250-008: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC2)	**NCT number: NCT03659916**
Objective	To investigate the long-term efficacy and safety of a 120 µg/kg/day daily dose of odevixibat in patients with PFIC
Publications – title, author, journal, year	The PEDFIC2 trial is ongoing and there are no publications.
Study type and design	Phase 3, multi-centre, open-label extension study
Sample size (n)	N=120 (N=69 as of the data cut-off of 15 July 2020)
Main inclusion and exclusion criteria	Inclusion Criteria Cohort 1: 1. Completion of the 24-week Treatment Period of Study A4250-005 or withdrawn from Study A4250-005 due to patient/caregiver judgment of intolerable symptoms after completing at least 12 weeks of treatment 2. Signed informed consent and assent as appropriate 3. Patients expected to have a consistent caregiver for the duration of the study 4. Caregivers (and age appropriate patients) must be willing and able to use an eDiary device as required by the study Inclusion Criteria Cohort 2: 1. A male or female patient with a clinical diagnosis of PFIC and with a body weight ≥5 kg 2. Patient must have clinical genetic confirmation of PFIC 3. Patient must have elevated serum bile acid levels 4. Patient must have history of significant pruritus 5. Age appropriate patients are expected to have a consistent caregiver for the duration of the study

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Trial name: A4250-008: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC2)	NCT number: NCT03659916
	6. Caregivers and age-appropriate patients (≥8 years of age) must be willing and able to use an eDiary device as required by the study Exclusion Criteria Cohort 1: 1. Decompensated liver disease: coagulopathy, history, or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy 2. Sexually active males and females who are not using a reliable contraceptive method with ≤1% failure rate (such as hormonal contraception, intra-uterine device, or complete abstinence) throughout the duration of the study and 90 days thereafter 3. Patients not compliant with treatment in study A4250-005 4. 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 participating in or completing the study Exclusion Criteria Cohort 2: 1. Known pathologic variations of the ABCB11 gene that have been demonstrated to result in complete absence of the BSEP protein 2. Patient with past medical history or ongoing presence of other types of liver disease including, but not limited to, the following: a. Biliary atresia of any kind b. Benign recurrent intrahepatic cholestasis, indicated by any history of normal serum bile acids c. Suspected or proven liver cancer or metastasis to the liver on imaging studies d. Histopathology on liver biopsy is suggestive of alternate non-PFIC related etiology of cholestasis 3. Patient with past medical history or ongoing chronic (i.e., >3 months) diarrhoea 4. Any patient with suspected or confirmed cancers except for basal cell carcinoma 5. Patient has had a liver transplant, or a liver transplant is planned within 6 months of the Screening/Inclusion Visit 6. Decompensated liver disease 7. Patient suffers from uncontrolled, recalcitrant pruritic condition other than PFIC 8. Patient previously treated with an IBAT inhibitor and whose pruritus did not respond to treatment 9. Sexually active males and females who are not using a reliable contraceptive method with ≤1% failure rate (such as hormonal contraception, intra-uterine device, or complete abstinence) throughout the duration of the study and 90 days thereafter
Intervention	120 µg/kg/day daily dose of odevixibat

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Trial name: A4250-008: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC2)	NCT number: NCT03659916
Comparator(s)	NA
Follow-up time	72 weeks
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Primary outcomes:** **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:** **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 biliary diversion (BD) • Number of patients listed for liver transplant (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
Method of analysis	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

Trial name: A4250-008: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC2)	NCT number: NCT03659916
	urinalysis) and concomitant medication. Analyses will be performed using the full analysis set.
Subgroup analyses	Subgroup analyses are 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. Descriptive summary statistics are provided for the following parameters, along with forest plots: • The proportion of positive pruritus assessments at the patient level over the 24-week treatment period (primary endpoint) • Serum bile acid (primary endpoint) • Laboratory parameters of serum bile acid, ALT, and growth (secondary/exploratory endpoints)
Other relevant information	

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16. Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 83. Baseline characteristics of patients in studies used for the analysis of efficacy and safety

	PEDFIC1		PEDFIC2 (Open-label extension study)			
			Cohort 1 (From PEDFIC1)			Cohort 2 Treatment naive
	Placebo (n=20)	Odevixibat (n=42)	Odevixibat 120 µg/kg/day (Placebo from PEDFIC1) (n=19)	Odevixibat 120 µg/kg/day (40 µg/kg/day from PEDFIC1) (n=19)	Odevixibat 120 µg/kg/day (120 µg/kg/day From PEDFIC1) (n=15)	Odevixibat 120 µg/kg/day (n=16)
Age (years)	4.48 (0.6 – 15.9)	4.48 (0.6 – 15.9)	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)	54.8	54.8	36.8	52.6	53.3	56.3
PFIC type, n (%)	Type 1: 12 (28.6) Type 2: 30 (71.4)	Type 1: 12 (28.6) Type 2: 30 (71.4)	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 (µmol/L)	252.1 (36 – 605)	252.1 (36 – 605)	270.79 (11 – 528)	104.89 (1 – 327)	155.87 (2.5 – 439)	221.53 (10.5 – 465)
Pruritus (0-4 scale)	3.00 (2.0 – 4.0)	3.00 (2.0 – 4.0)				
UDCA, n (%)	32 (76.2)	32 (76.2)	17 (89.5)	14 (73.7)	9 (60.0)	13 (81.3)
Rifampicin, n (%)	24 (57.1)	24 (57.1)	17 (89.5)	8 (42.1)	7 (46.7)	7 (43.8)
ALT and range (U/L)	110.2 (16.0 – 798)	110.2 (16.0 – 798)	71.26 (14 – 231)	74.42 (9 – 352)	73.20 (14 – 239)	69.75 (14 – 231)
Total bilirubin and range (mg/dl)	3.18 (0.2 – 18.6)	3.18 (0.2 – 18.6)	53.34 (3.3 - 39.3)	22.55 (2.5 – 12.6)	37.35 (2.2 – 10.4)	41.48 (11.2 – 19.2)

Abbreviations: ALT, alanine aminotransferase; UDCA, ursodeoxycholic acid
Figures presented are means (range) or n (%)
Sources: A4250-005 CSR [9]; Thompson 2020 [10]; PEDFIC2 CSR [11]; Thompson et al, 2020 [12]

Comparability of patients across studies

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).

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 PEDFIC1, 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.

Comparability of the study populations with Danish patients eligible for treatment

It is expected that incident PFIC patients would begin treatment with odevixibat at the time when PFIC is diagnosed, and that the average age of PFIC diagnosis would closely align with the average age of patients at enrolment into the PEDFIC1 trial. However, the initial Danish patient group may include patients who have a higher average age at the point that odevixibat is available compared to when their PFIC was identified, and therefore may have a higher average age than that of the patients at the beginning of the PEDFIC1 trial.

17. Appendix D – Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

The definition of each included outcome measure is provided in Table 84. The same definitions were used across the included studies. The table also provides a description of how the validity and clinical relevance of the outcomes has been investigated.

Table 84. Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Serum bile acids	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.	Reduction in serum bile acids is the primary response endpoint for approval of odevixibat by the EMA [43]	Reduction in sBA can be correlated with increase in native liver survival [29], [30] and is considered the main response clinical criteria for the efficacy of treatment with odevixibat determining treatment continuation.
Pruritus	Proportion of positive pruritus assessments at the subject level over the 24-week Treatment Period. o Positive pruritus assessment defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the Albireo ObsRO instrument.	Validity of Pruritus and Sleep Analysis outcome measures have been investigated (see Appendix M – Patient- and observer-reported outcome measures for pruritus)	Greater than a fall of one point in the mean score is considered clinically meaningful.

Outcome measure	Definition	Validity	Clinical relevance
	o Completed twice daily by the caregiver		
Sleep Analysis	Change in Sleep Parameters from Baseline Over the 24-Week Treatment Period – Albireo ObsRO Instrument	Validity of Pruritus and Sleep Analysis outcome measures have been investigated (see Appendix M – Patient- and observer-reported outcome measures for pruritus)	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.
Growth Analysis	Growth is measured as height and body weight using a certified weight scale at the time points specified in the Schedules of Assessments Body mass index is calculated as weight (kg)/height (m2). Change in growth parameters is assessed using linear growth deficit (weight, height, and body mass index [BMI] for age) compared with a standard growth curve (Z-score, standard deviation [SD] from the 50th percentile).	The validity of growth measurement has not been specifically assessed. BMI, weight and height are fundamental measures of childhood development.	Growth is of a key marker of childhood development.
Hepatic Analysis	The Paediatric End-stage Liver Disease (PELD) score is calculated for patients < 12 years of age. For patients ≥ 12 years, the Model for End-stage Liver Disease (MELD) score is calculated. For patients reaching their twelfth birthday while on study, both PELD and	The validity of clinical measures of hepatic health status have been assessed. Haseli N, Hassanzadeh J, Dehghani SM, Bahador A, Malek Hosseini SA. Long-term survival and its related factors in pediatric liver transplant	Paediatric end-stage liver disease (PELD) and model for end-stage liver disease (MELD) scores are used to estimate relative disease severity and the probability for survival of patients awaiting liver transplantation [Haseli 2013; Olthoff 2004]. APRI score: The APRI score is a way to assess fibrosis of the liver. The lower the APRI score (< 0.5), the greater the negative predictive value (and ability to rule out cirrhosis) and the higher the value (> 1.5) the

Outcome measure	Definition	Validity	Clinical relevance
	MELD scores are calculated at the first visit after the twelfth birthday; for subsequent visits only the MELD score is determined. The PELD score is based on the following test results: albumin, bilirubin, INR, growth failure [based on gender, height, and weight], and age at study visits; this score can range across negative (e.g. from -10) and positive (e.g. 50) values. The MELD score is based on the following laboratory test results: serum creatinine, bilirubin, INR, and serum sodium and ranges from 6 (low level of illness) to 40 (gravely ill). Fibroscan, a specialized ultrasound of the liver measuring fibrosis and steatosis, is performed at study sites with the ability per institution standard practice. Markers of fibrosis, AST to platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores, were also calculated.	recipients of shiraz transplant center, shiraz, iran in 2012. *Hepat Mon.* 2013;13(7):e10257. Olthoff KM, Brown RS, Jr., Delmonico FL, et al. Summary report of a national conference: Evolving concepts in liver allocation in the MELD and PELD era. December 8, 2003, Washington, DC, USA. *Liver Transpl.* 2004;10(10 Suppl 2):A6-22. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med. 2013;158(11):807-820. Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53(3):726-736. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-1325.	greater the positive predictive value (and ability to rule in cirrhosis) [Chou 2013; Lin 2011]. FIB-4 score: The FIB-4 score estimates the amount of scarring in the liver. A FIB-4 score < 1.45 has a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 > 3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis [Sterling 2006].

Outcome measure	Definition	Validity	Clinical relevance
PedsQL	Caregivers and patients (if applicable), were to complete the PedsQL (Version 4.0), an instrument designed to assess QoL in children and adolescents. The PedsQL is designed to examine problems within 4 functional domains: physical, emotional, social, and school (Varni, 1999) [87]. Different versions of the PedsQL were used depending on the age of the child: patient- and parent-report core modules for 5 to 7 year-olds, 8 to 12 year-olds, and 13 to 18 year-olds; and a parent-report core module for toddlers (2 to 4 years old). The caregiver was also asked to complete the PedsQL Family Impact Module designed to measure the impact of paediatric chronic health conditions on parents and the family.	Scoring scales for the PedsQL was based on the publication by Mapi Research Trust (2017) [88]	Quality of life measurement (e.g. as assessed by use for the PedsQL measure) is relevant to assess the overall wellbeing of pediatric patients, as well as for estimation of cost-effectiveness of treatments in a cost-utility framework.
Global Impression of Change and Global Impression of Symptoms	Patients (≥8 years of age), caregivers, and clinicians completed the GIC and GIS measures. The GIS items were used to assess itch (patient version, PGIS), scratching (caregiver [CaGIS] and clinician [CGIS] versions), and	PGIC and PGIS measures have not been formally validated in the context of patients with PFIC.	Global Impression of Change and Global Impression of Symptoms measures may provide a top-level indication of any changes in patients' health which may be attributable to treatment.

Outcome measure	Definition	Validity	Clinical relevance
	sleep (all versions) in the past week. The questions in this assessment were assessed on a 5-point scale: 1 – none, 2 – a little/mild, 3 – medium/moderate, 4 – bad/severe, and 5 – very bad/very severe. The GIC items were used to assess change in itch (patient version, PGIC), scratching (caregiver [CaGIC] and clinician [CGIC] versions), and sleep (all versions) since starting the study drug. The GIC was assessed on a 7-point scale:1 – very much better, 2 – much/moderately better, 3 – a little better, 4 – no change, 5 – a little worse, 6 – much/moderately worse, and 7 – very much worse. Caregivers and clinicians were to complete the GIC and GIS for all patients; those patients ≥8 years of age were to complete the PGIC and PGIS.		

Results per study

Table 85. Detailed results of PEDFIC1 (NCT03566238)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Analysis of Number (%) of Patients Experiencing at Least a 70% Reduction in Fasting Serum Bile Acid Concentration from Baseline to End of Treatment or Reaching a Level <=70 µmol/L after 24 Weeks of Treatment	Odevixibat (all doses)	42	14 (33.3%) (19.57, 49.55)	Unadjusted: 0.333 Adjusted: 0.307	Unadjusted: (0.0861, 0.4955) Adjusted: (0.1260, 0.4879)	One-Sided Unadjusted: 0.0015 One-Sided Adjusted: NR	NR	NR	NR	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. Miettinen-Nurminen (score) confidence interval (CI) adjusting stratification factors	PEDFIC1 CSR (Table 19, 14.2.1.1.1)
	Placebo	20	0 (0%) (0.00, 16.84)								
	Odevixibat 40 µg/kg	23	10 (43.5%) (23.19, 65.51)	Unadjusted: 0.435 Adjusted: 0.441	Unadjusted: (0.2195, 0.6551) Adjusted: (-0.0050, 0.4380)	One-Sided Unadjusted: 0.0003 One-Sided Adjusted: 0.0015	NR	NR	NR		
	Placebo	20	0 (0%) (0.00, 16.84)								
	Odevixibat 120 µg/kg	19	4 (21.1%) (6.05, 45.57)	Unadjusted: 0.211 Adjusted: 0.216	Unadjusted: (0.0210, 0.4557) Adjusted: (0.2361, 0.6464)	One-Sided Unadjusted: 0.0174 One-Sided Adjusted: 0.0174	NR	NR	NR		
	Placebo	20	0 (0%) (0.00, 16.84)								
Proportion of Positive Pruritus Assessments (AM and PM Scores Combined) at the Patient Level over the 24-Week Treatment Period –	Odevixibat (all doses)	42	Mean: 53.51 (5.006) LS Mean: 55.08 (7.639)	LS Mean Difference (SE): 24.97 (8.240)	(8.45, 41.49)	One-Sided Unadjusted: 0.0019 One-Sided Adjusted: NR	NR	NR	NR	The analysis was based on an ANCOVA model with rounded AM and PM baseline scores as covariates, and treatment group and stratification	PEDFIC1 CSR (Table 20, 14.2.1.2.1)
	Placebo	20	Mean: 28.74 (5.209)								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Albireo ObsRO Instrument (SE)			LS Mean: 30.10 (9.119)							factors (PFIC type and age category) as fixed effects.	
	Odevixibat 40 µg/kg	23	Mean: 58.31 (6.205) LS Mean: 58.34 (8.580)	LS Mean Difference (SE): 28.23 (9.182)	(9.83, 46.64)	One-Sided Unadjusted: 0.0016 One-Sided Adjusted: 0.0019	NR	NR	NR		
	Placebo	20	Mean: 28.74 (5.209) LS Mean: 30.10 (9.119)								
	Odevixibat 120 µg/kg	19	Mean: 47.69 (8.110) LS Mean: 51.81 (9.459)	LS Mean Difference (SE): 21.71 (9.892)	(1.87, 41.54)	One-Sided Unadjusted p-value 0.0163 One-Sided Adjusted: 0.0163	NR	NR	NR		
	Placebo	20	Mean: 28.74 (5.209) LS Mean: 30.10 (9.119)								
Analysis of Number (%) of Patients Achieving Positive Pruritus Assessment for More Than 50% of	Odevixibat (all doses)	42	26 (61.9%)	0.320*	0.1062-0.5331	NR	Odds ratio: 6.21	1.539-27.429**	0.0016***	ANCOVA model with rounded AM and PM baseline scores as covariates, and treatment group	PEDFIC1 CSR (Table 25, 14.2.2.9.1)
	Placebo	20	4 (20.0%)								
	Odevixibat 40 µg/kg	23	17 (73.9%)	0.467*	0.2290-0.7045	NR	Odds ratio: 16.22		0.0002***		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
the Time during 24-Week Treatment Period - Albireo ObsRO Instrument (AM and PM Scores)	Placebo	20	4 (20.0%)					2.540-106.320**		and stratification factors (PFIC type and age) as fixed effects. *Proportion Difference Adjusting for Stratification Factors, Miettinen-Nurminen CI is reported. **Exact CI is reported based on Vollset, Hirji, and Elashoff. ***95% CI based on the Cochran-Mantel-Haenszel test adjusting for stratification factors.	
	Odevixibat 120 µg/kg	19	9 (47.4%)	0.287*	0.0344-0.5401	NR	Odds ratio: 3.14	0.718-18.700**	0.0391***		
	Placebo	20	4 (20.0%)								
Summary of Change from Baseline in Sleep Parameters by Week 21-24 Interval - Albireo ObsRO Instrument Percentage of Days with Help Falling Asleep (SE)	Odevixibat (all doses)	35	-42.99 (8.570)	NR	NR	NR	NR	NR	NR	Differences not reported in CSR	PEDFIC1 CSR (Table 14.2.2.6.1)
	Placebo	14	-3.19 (2.890)								
	Odevixibat 40 µg/kg	19	-51.75 (9.857)	NR	NR	NR	NR	NR	NR		
	Placebo	14	-3.19 (2.890)								
	Odevixibat 120 µg/kg	16	-32.58 (14.573)	NR	NR	NR	NR	NR	NR		
	Placebo	14	-3.19 (2.890)								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Summary of Change from Baseline in Sleep Parameters by Week 21-24 Interval - Albireo ObsRO Instrument Percentage of Days Requiring Soothing (SE)	Odevixibat (all doses)	35	-43.88 (8.288)	NR	NR	NR	NR	NR	NR	Differences not reported in CSR	PEDFIC1 CSR (Table 14.2.2.6.1)
	Placebo	14	-7.64 (6.182)								
	Odevixibat 40 µg/kg	19	-51.48 (10.323)	NR	NR	NR	NR	NR	NR		
	Placebo	14	-7.64 (6.182)								
	Odevixibat 120 µg/kg	16	-34.87 (13.369)	NR	NR	NR	NR	NR	NR		
	Placebo	14	-7.64 (6.182)								
Summary of Change from Baseline in Sleep Parameters by Week 21-24 Interval - Albireo ObsRO Instrument Percentage of Days Sleeping with Caregiver (SE)	Odevixibat (all doses)	35	-41.94 (7.841)	NR	NR	NR	NR	NR	NR	Differences not reported in CSR	PEDFIC1 CSR (Table 14.2.2.6.1)
	Placebo	14	-5.45 (4.844)								
	Odevixibat 40 µg/kg	19	-49.35 (10.466)	NR	NR	NR	NR	NR	NR		
	Placebo	14	-5.45 (4.844)								
	Odevixibat 120 µg/kg	16	-33.14 (11.801)	NR	NR	NR	NR	NR	NR		
	Placebo	14	-5.45 (4.844)								
Summary of Change from Baseline to Week 24 in Growth Parameters Weight (z-score) (SE)	Odevixibat (all doses)	33	Mean: 0.22 (0.080) LS Mean: 0.16 (0.084)	LS Mean Difference: 0.18 (0.129)	(-0.08, 0.44)	One-Sided Unadjusted: 0.0848	NR	NR	NR	The analysis was based on a mixed model for repeated measures (MMRM) with baseline growth data as a covariate, and treatment	PEDFIC1 CSR (Table 14.2.2.3.1)
	Placebo	12	Mean: 0.10 (0.102)								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
			LS Mean: -0.02 (0.120)							group, visit, treatment-by-visit interaction, treatment-by-baseline interaction and stratification factors (Progressive Familial Intrahepatic Cholestasis (PFIC) type and age category) as fixed effects using observed data.	
	Odevixibat 40 µg/kg	18	Mean: 0.29 (0.106) LS Mean: 0.26 (0.105)	LS Mean Difference: 0.28 (0.144)	(-0.01, 0.57)	One-Sided Unadjusted: 0.0277	NR	NR	NR		
	Placebo	12	Mean: 0.10 (0.102) LS Mean: -0.02 (0.120)								
	Odevixibat 120 µg/kg	15	Mean: 0.15 (0.124) LS Mean: 0.05 (0.113)	LS Mean Difference: 0.08 (0.149)	(-0.22, 0.37)	One-Sided Unadjusted: 0.3037	NR	NR	NR		
	Placebo	12	Mean: 0.10 (0.102) LS Mean: -0.02 (0.120)								
Summary of Change from Baseline to Week 24 in Growth Parameters	Odevixibat (all doses)	32	Mean: 0.03 (0.093) LS Mean: 0.01 (0.107)	LS Mean Difference: 0.24 (0.144)	(-0.05, 0.53)	One-Sided Unadjusted: 0.0516	NR	NR	NR	The analysis was based on a mixed model for repeated measures (MMRM) with baseline growth data as a	PEDFIC1 CSR (Table 14.2.2.3.1)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Height (z-score) (SE)										covariate, and treatment group, visit, treatment-by-visit interaction, treatment-by-baseline interaction and stratification factors (Progressive Familial Intrahepatic Cholestasis (PFIC) type and age category) as fixed effects using observed data.	
	Placebo	12	Mean: -0.16 (0.104) LS Mean: -0.22 (0.142)								
	Odevixibat 40 µg/kg	17	Mean: 0.05 (0.105) LS Mean: 0.10 (0.128)	LS Mean Difference: 0.32 (0.163)	(0.00, 0.65)	One-Sided Unadjusted: 0.0255	NR	NR	NR		
	Placebo	12	Mean: -0.16 (0.104) LS Mean: -0.22 (0.142)								
	Odevixibat 120 µg/kg	15	Mean: 0.00 (0.163) LS Mean: -0.07 (0.138)	LS Mean Difference: 0.15 (0.165)	(-0.18, 0.48)	One-Sided Unadjusted: 0.1804	NR	NR	NR		
	Placebo	12	Mean: -0.16 (0.104) LS Mean: -0.22 (0.142)								
Change from Baseline in Serum	Odevixibat (all doses)	32	Mean (SE)	LS Mean Difference	(-45.08, 15.40)	0.1645	NR	NR	NR	The analysis was based on a mixed	

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Alanine Aminotransferase (ALT) from Baseline to Week 24 (U/L) (SE)			-26.7 (13.98) LS Mean (SE) -21.38 (11.999)	(SE) -14.84 (15.047)						model for repeated measures (MMRM) with baseline serum alanine aminotransferase data as a covariate, and treatment group, visit, treatment-by-visit interaction, treatment-by-baseline interaction and stratification factors (Progressive Familial Intrahepatic Cholestasis (PFIC) type and age category) as fixed effects using observed data.	PEDFIC1 CSR (Table 14.2.2.2.1
	Placebo	11	Mean (SE) 3.7 (4.95) LS Mean (SE) -6.55 (16.333)								
	Odevixibat 40 µg/kg	17	Mean (SE) -27.9 (17.97) LS Mean (SE) -21.35 (13.907)	LS Mean Difference (SE) -14.81 (16.625)	(-48.27, 18.65)	0.1888	NR	NR	NR		
	Placebo	11	Mean (SE) 3.7 (4.95) LS Mean (SE) -6.55 (16.333)								
	Odevixibat 120 µg/kg	15	Mean (SE) -25.3 (22.47) LS Mean (SE) -21.41 (14.690)	LS Mean Difference (SE) -14.87 (17.252)	(-49.61, 19.88)	0.1967	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
	Placebo	11	Mean (SE) 3.7 (4.95) LS Mean (SE) -6.55 (16.333)								
Change from Baseline in Total Bilirubin from Baseline to Week 24 (mg/dL) (SE)	Odevixibat (all doses)	32	-1.266 (0.4633)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.6)
	Placebo	11	-0.563 (0.8876)								
	Odevixibat 40 µg/kg	17	-1.385 (0.5396)	NR	NR	NR	NR	NR	NR		
	Placebo	11	-0.563 (0.8876)								
	Odevixibat 120 µg/kg	15	-1.132 (0.7965)	NR	NR	NR	NR	NR	NR		
	Placebo	11	-0.563 (0.8876)								
Change from Baseline in Gamma Glutamyl Transferase (GGT) from Baseline to Week 24 (U/L) (SE)	Odevixibat (all doses)	32	-2.2 (0.95)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.6)
	Placebo	11	1.5 (0.99)								
	Odevixibat 40 µg/kg	17	-3.4 (1.58)	NR	NR	NR	NR	NR	NR		
	Placebo	11	1.5 (0.99)								
	Odevixibat 120 µg/kg	15	-0.8 (0.91)	NR	NR	NR	NR	NR	NR		
	Placebo	11	1.5 (0.99)								
Parent Reported Change from Baseline to Week 24 in Total Score of Pediatric Quality of	Odevixibat (all doses)	22	7.76 (4.440)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.1)
	Placebo	10	0.48 (5.065)								
	Odevixibat 40 µg/kg	13	5.51 (5.093)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Life Inventory (PedsQL) (SE)	Placebo	10	0.48 (5.065)								
	Odevixibat 120 µg/kg	9	11.00 (8.251)	NR	NR	NR	NR	NR	NR		
	Placebo	10	0.48 (5.065)								
Parent Reported Change from Baseline to Week 24 in Physical Functioning Score of Pediatric Quality of Life Inventory (PedsQL) (SE)	Odevixibat (all doses)	22	7.81 (6.219)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.1)
	Placebo	10	-5.94 (7.953)								
	Odevixibat 40 µg/kg	13	5.05 (6.452)	NR	NR	NR	NR	NR	NR		
	Placebo	10	-5.94 (7.953)								
	Odevixibat 120 µg/kg	9	11.81 (12.432)	NR	NR	NR	NR	NR	NR		
	Placebo	10	-5.94 (7.953)								
Parent Reported Change from Baseline to Week 24 in Emotional Functioning Score of Pediatric Quality of Life Inventory (PedsQL) (SE)	Odevixibat (all doses)	22	14.09 (5.166)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.1)
	Placebo	10	13.50 (5.273)								
	Odevixibat 40 µg/kg	13	7.31 (6.593)	NR	NR	NR	NR	NR	NR		
	Placebo	10	13.50 (5.273)								
	Odevixibat 120 µg/kg	9	23.89 (7.536)	NR	NR	NR	NR	NR	NR		
	Placebo	10	13.50 (5.273)								
Parent Reported Change from	Odevixibat (all doses)	22	3.64 (4.893)	NR	NR	NR	NR	NR	NR	Differences not reported	

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
Baseline to Week 24 in Social Functioning Score of Pediatric Quality of Life Inventory (PedsQL) (SE)	Placebo	10	-1.00 (6.092)								PEDFIC1 CSR (Table 14.2.3.5.1)
	Odevixibat 40 µg/kg	13	2.69 (6.114)	NR	NR	NR	NR	NR	NR		
	Placebo	10	-1.00 (6.092)								
	Odevixibat 120 µg/kg	9	5.00 (8.498)	NR	NR	NR	NR	NR	NR		
	Placebo	10	-1.00 (6.092)								
Parent Reported Change from Baseline to Week 24 in Social School Score of Pediatric Quality of Life Inventory (PedsQL) (SE)	Odevixibat (all doses)	15	2.33 (7.147)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.1)
	Placebo	6	-5.28 (8.907)								
	Odevixibat 40 µg/kg	9	7.78 (7.582)	NR	NR	NR	NR	NR	NR		
	Placebo	6	-5.28 (8.907)								
	Odevixibat 120 µg/kg	8	-5.83 (14.049)	NR	NR	NR	NR	NR	NR		
	Placebo	6	-5.28 (8.907)								
Change from Baseline to Week 24 in Total Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Odevixibat (all doses)	32	14.54 (4.335)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	5.64 (4.623)								
	Odevixibat 40 µg/kg	19	10.78 (6.185)	NR	NR	NR	NR	NR	NR		
	Placebo	17	5.64 (4.623)								
	Odevixibat 120 µg/kg	13	20.03 (5.604)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
	Placebo	17	5.64 (4.623)								
Change from Baseline to Week 24 in Physical Functioning Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Odevixibat (all doses)	32	18.88 (5.506)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	8.09 (5.541)								
	Odevixibat 40 µg/kg	19	15.13 (8.169)	NR	NR	NR	NR	NR	NR		
	Placebo	17	8.09 (5.541)								
	Odevixibat 120 µg/kg	13	24.36 (6.500)	NR	NR	NR	NR	NR	NR		
	Placebo	17	8.09 (5.541)								
Change from Baseline to Week 24 in Emotional Functioning Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Odevixibat (all doses)	32	13.44 (5.176)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	7.94 (6.766)								
	Odevixibat 40 µg/kg	19	8.42 (7.667)	NR	NR	NR	NR	NR	NR		
	Placebo	17	7.94 (6.766)								
	Odevixibat 120 µg/kg	13	20.77 (5.825)	NR	NR	NR	NR	NR	NR		
	Placebo	17	7.94 (6.766)								
Change from Baseline to Week 24 in Social Functioning Score of Pediatric Quality of Life Inventory	Odevixibat (all doses)	32	13.48 (5.927)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	8.46 (6.606)								
	Odevixibat 40 µg/kg	19	10.86 (9.092)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
(PedsQL) Family Impact Module (SE)	Placebo	17	8.46 (6.606)								
	Odevixibat 120 µg/kg	13	17.31 (6.336)	NR	NR	NR	NR	NR	NR		
	Placebo	17	8.46 (6.606)								
Change from Baseline to Week 24 in Cognitive Functioning Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Odevixibat (all doses)	32	16.41 (4.848)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	3.24 (4.792)								
	Odevixibat 40 µg/kg	19	13.16 (6.959)	NR	NR	NR	NR	NR	NR		
	Placebo	17	3.24 (4.792)								
	Odevixibat 120 µg/kg	13	21.15 (6.334)	NR	NR	NR	NR	NR	NR		
	Placebo	17	3.24 (4.792)								
Change from Baseline to Week 24 in Communications Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Odevixibat (all doses)	32	8.33 (6.328)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	-4.41 (5.494)								
	Odevixibat 40 µg/kg	19	1.32 (8.364)	NR	NR	NR	NR	NR	NR		
	Placebo	17	-4.41 (5.494)								
	Odevixibat 120 µg/kg	13	18.59 (9.300)	NR	NR	NR	NR	NR	NR		
	Placebo	17	-4.41 (5.494)								
Change from Baseline to Week	Odevixibat (all doses)	32	12.81 (4.944)	NR	NR	NR	NR	NR	NR	Differences not reported	

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
24 in Worry Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Placebo	17	7.94 (5.056)								PEDFIC1 CSR (Table 14.2.3.5.2)
	Odevixibat 40 µg/kg	19	10.26 (7.556)	NR	NR	NR	NR	NR	NR		
	Placebo	17	7.94 (5.056)								
	Odevixibat 120 µg/kg	13	16.54 (5.322)	NR	NR	NR	NR	NR	NR		
	Placebo	17	7.94 (5.056)								
Change from Baseline to Week 24 in Daily Activities Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Odevixibat (all doses)	32	21.09 (5.674)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	9.31 (6.584)								
	Odevixibat 40 µg/kg	19	20.61 (7.021)	NR	NR	NR	NR	NR	NR		
	Placebo	17	9.31 (6.584)								
	Odevixibat 120 µg/kg	13	21.79 (9.830)	NR	NR	NR	NR	NR	NR		
	Placebo	17	9.31 (6.584)								
Change from Baseline to Week 24 in Family Relationships Score of Pediatric Quality of Life Inventory (PedsQL) Family Impact Module (SE)	Odevixibat (all doses)	32	10.94 (4.765)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.5.2)
	Placebo	17	2.06 (5.252)								
	Odevixibat 40 µg/kg	19	5.79 (6.435)	NR	NR	NR	NR	NR	NR		
	Placebo	17	2.06 (5.252)								
	Odevixibat 120 µg/kg	13	18.46 (6.755)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
	Placebo	17	2.06 (5.252)								
Caregiver Indicated Global Impression of Symptoms and Change - Improvement by week 24 - Itch/Scratching (%)	Odevixibat (all doses)	29	23 (79.2%)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.1.1)
	Placebo	13	6 (46.2%)								
	Odevixibat 40 µg/kg	16	14 (87.5%)	NR	NR	NR	NR	NR	NR		
	Placebo	13	6 (46.2%)								
	Odevixibat 120 µg/kg	13	9 (69.3%)	NR	NR	NR	NR	NR	NR		
	Placebo	13	6 (46.2%)								
Caregiver Indicated Global Impression of Symptoms and Change - Improvement by week 24 - Sleep (%)	Odevixibat (all doses)	29	22 (75.9%)	NR	NR	NR	NR	NR	NR	Differences not reported	PEDFIC1 CSR (Table 14.2.3.1.2)
	Placebo	13	5 (38.5%)								
	Odevixibat 40 µg/kg	16	14 (87.5%)	NR	NR	NR	NR	NR	NR		
	Placebo	13	5 (38.5%)								
	Odevixibat 120 µg/kg	13	8 (61.6%)	NR	NR	NR	NR	NR	NR		
	Placebo	13	5 (38.5%)								

The PEDFIC2 study is ongoing, without final results to report at this time.

Table 86. Detailed results of PEDFIC2 (NCT03659916) (ongoing)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Summary of Change from Baseline in Fasting Serum Bile Acid Concentration (umol/L) by Visit Average of Weeks 22 – 24 (SE)	Cohort 1 40 µg/kg	12	-13.25 (17.614)	NR	NR	NR	NR	NR	NR	Cohort 1: Baseline is calculated as the average of the last 2 values before the first dose of study drug in Study A4250-008. In general, these 2 values are the values of the last 2 assessments of Study A4250-005. If pre-dose assessments are collected in Study 008 for a patient, then the values of pre-dose assessments in Study A4250-008 are considered first and used to calculate the baseline. These 2 values need to be taken within 2 consecutive scheduled visits or unscheduled visits. If there is only one value is available within 2	PEDFIC2 CSR (Table 22, Table 14.2.1.1.2)
	Cohort 1 120 µg/kg	9	-24.39 (15.726)	NR	NR	NR	NR	NR	NR		
	Cohort 1 (all doses)	21	-18.02 (11.892)	NR	NR	NR	NR	NR	NR		
	Cohort 1 Placebo	11	-143.73 (48.601)	NR	NR	NR	NR	NR	NR		
	Cohort 2	5	-104.10 (38.770)	NR	NR	NR	NR	NR	NR		
	Cohort 2 + placebo	16	-131.34 (35.076)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										consecutive scheduled visits or unscheduled visits, then the value is used as baseline. Cohort 2: Baseline is calculated as the average of last 2 values before the first dose of study drug in Study A4250-008. Weeks 22 - 24, Weeks 46 - 48 and Weeks 70 - 72 are the average of all non-missing values collected in each period. At or after Week 88, the summary is based on the assessments during the optional extension period.	
Summary of the Proportion of Positive Pruritus Assessments at Patient Level over Time - Albireo ObsRO Instrument	Cohort 1 40 µg/kg	15	37.03 (9.384)	NR	NR	NR	NR	NR	NR	A positive pruritus assessment is defined as a scratching score of <=1 or at least a one-point drop from baseline on the Albireo ObsRO instrument based on rounded	PEDFIC2 CSR (Table 25, Table 14.2.1.2.2)
	Cohort 1 120 µg/kg	11	26.60 (8.721)	NR	NR	NR	NR	NR	NR		
	Cohort 1 (all doses)	26	32.62 (6.510)	NR	NR	NR	NR	NR	NR		
	Cohort 1 Placebo	11	56.26 (10.869)	NR	NR	NR	NR	NR	NR		
	Cohort 2	5	61.63 (19.866)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Cohort 2 + placebo	16	57.94 (9.352)							baseline. All assessments after intercurrent events (premature treatment discontinuation, death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) are excluded from analysis. The reported AM and PM assessments are included in the denominator.	

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from Baseline in Scratching Severity Weekly Score - Albireo ObsRO Instrument (AM and PM Scores) Week 24 (SE)	Cohort 1 40 µg/kg	12	-0.60 (0.222)	NR	NR	NR	NR	NR	NR	Baseline is the average of AM scores from the period of 14 days before or on the first dose day of study drug and PM scores from the period of 14 days before the first dose day of study drug. For each post-baseline week, the weekly scores are summarized. The change from baseline is calculated as the average of values of change from baseline in AM scores and PM scores. Data after intercurrent events (premature treatment discontinuation, death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) are	PEDFIC2 CSR (Table 14.2.3.8.1)
	Cohort 1 120 µg/kg	11	-0.44 (0.225)	NR	NR	NR	NR	NR	NR		
	Cohort 1 (all doses)	23	-0.52 (0.155)	NR	NR	NR	NR	NR	NR		
	Cohort 1 Placebo	9	-0.95 (0.300)	NR	NR	NR	NR	NR	NR		
	Cohort 2	5	-0.96 (0.320)	NR	NR	NR	NR	NR	NR		
	Cohort 2 + placebo	14	-0.95 (0.216)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										excluded from analysis. Scratching severity score: 0 = No scratching; 1 = A little scratching; 2 = Medium scratching; 3 = A lot of scratching; 4 = Worst possible scratching	
Change from Baseline in Scratching Severity Score after 24 Weeks of Treatment - Albireo ObsRO Instrument (AM and PM Scores) Cohort 1 Patients Treated with Odevixibat in Study A4250-005	Cohort 1 40 µg/kg	15	-1.44 (0.319) p-value: 0.0005	NR	NR	NR	NR	NR	NR	Monthly score of Weeks 21 - 24 is summarized. The change from baseline is calculated as the average of values of change from baseline in AM scores and PM scores. p-value is from 1-sample t-test.	PEDFIC2 CSR (Table 14.2.3.9.4)
	Cohort 1 120 µg/kg	11	-1.70 (0.375) p-value: 0.0011	NR	NR	NR	NR	NR	NR		
	Cohort 1 (all doses)	26	-1.55 (0.240) p-value: <.0001	NR	NR	NR	NR	NR	NR		
Summary of Change from Baseline to Weeks 24 Mean height z-score (SE)	Cohort 1 40 µg/kg	11	0.194 (0.1150)	NR	NR	NR	NR	NR	NR	Note: The assessments after intercurrent events (death, or initiation of rescue treatments such as biliary diversion surgery or liver	PEDFIC2 CSR (Table 26, Table 14.2.2.3)
	Cohort 1 120 µg/kg	7	0.563 (0.2039)	NR	NR	NR	NR	NR	NR		
	Cohort 1 (all doses)	18	0.337 (0.1112)	NR	NR	NR	NR	NR	NR		
	Cohort 1 Placebo	9	0.403 (0.1784)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Cohort 2	1	-0.316 (NA)	NR	NR	NR	NR	NR	NR	transplantation) are excluded from analysis. The summary is based on linear growth deficit (height, weight and BMI for age) compared to a standard growth curve (Z-score, SD from P50 standard growth curve), calculated by using the software or methods from the Centers for Disease Control (CDC) website for patients with age >= 2 years old and from the WHO website for patients with age < 2 years old. For patients whose accurate age is not available, Z-score is not calculated. Baseline is the last available assessment before the first dose of study drug in Study A4250-008 for all	
	Cohort 2 + placebo	10	0.331 (0.1750)	NR	NR	NR	NR	NR	NR		
Summary of Change from Baseline to Weeks 24 Mean weight z-score (SE)	Cohort 1 40 µg/kg	12	0.311 (0.1272)	NR	NR	NR	NR	NR	NR		PEDFIC2 CSR (Table 26, Table 14.2.2.3)
	Cohort 1 120 µg/kg	7	0.077 (0.1841)	NR	NR	NR	NR	NR	NR		
	Cohort 1 (all doses)	19	0.225 (0.1054)	NR	NR	NR	NR	NR	NR		
	Cohort 1 Placebo	9	0.466 (0.1933)	NR	NR	NR	NR	NR	NR		
	Cohort 2	1	0.689 (NA)	NR	NR	NR	NR	NR	NR		
	Cohort 2 + placebo	10	0.489 (0.1743)	NR	NR	NR	NR	NR	NR		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										patients. For Cohort 1 patients, the pre-dose assessment of Study A4250-008 can be from the last assessment in Study A4250-005.	

18. Appendix E – Safety data for intervention and comparator(s)

The studies presenting rates of adverse events with odevixibat have been identified as described PEDFIC1 and PEDFIC2. Safety data are also presented for the Phase 2 exploratory study A4250-003.

Study A4250-003 (phase 2)

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; neither led to discontinuation of study treatment. Both events were assessed as not related to study treatment. There were no 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 Gastrointestinal Disorders where seven patients reported an AE (29.2%). This was followed by SOC Respiratory, Thoracic, and Mediastinal Disorders where five patients reported an AE (20.8%).

Table 87. Overall summary of adverse events (safety set)

			Number of patients (%)			
	0.01 mg/kg	0.02 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]					
Possibly related TEAE						
Severe (Grade 3) TEAE						
AEs leading to discontinuation of study treatment						
Any SAE						

Abbreviations: AE, adverse event; SAE, serious adverse event, TEAE, treatment-emergent adverse event
Source: Phase 2 CSR [89]

In total, 36 AEs occurred during the study, with most events in the 0.2 mg/kg dose group (12 events) while the 0.03 mg/kg and 0.1 mg/kg groups had the lowest number of events (four 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, 14 patients (58.3%) had causality assessed as "not related." Three patients (12.5%) 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 not increased with odevixibat, nor were any changes seen in global symptom relief, international normalised ratio (INR), serum albumin or insulin like growth factor-binding protein 3 (IGFBP3).

Average increases in p-C4 and autotaxin levels were observed in all dose groups and a tendency to decrease was seen in FGF19. There was no obvious dose-dependency seen for p-C4, FGF19, or autotaxin.

Table 88. Summary of patients with any AE (safety set) (A4250-003)

	Number of patients (%)					
	0.01 mg/kg	0.02 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	[redacted]					
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 [89]

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 89. Summary of treatment-emergent adverse events (PEDFIC1)

	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 [9]; Thompson et al, 2020 [10]

TEAEs were reported in ≥5% of patients who received odevixibat vs placebo: diarrhoea (31% vs 5%), pyrexia (29% vs 25%), upper respiratory tract infection (19% vs 15%), vomiting (17% vs 0%), ALT increased (14% vs 5%), and blood bilirubin increased (12% vs 10%) (Table 90).

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

Table 90. Common treatment-emergent adverse events (PEDFIC1)

MedDRA SOC preferred term	Placebo N=20 n (%)	Odevixibat 40 µg/kg N=23 n (%)	Odevixibat 120 µg/kg N=19 n (%)
Gastrointestinal disorders	[redacted]		
Diarrhoea			
Vomiting			
Abdominal pain			
Infections and infestations			
Upper respiratory tract infection			
Nasopharyngitis			
Investigations			
Alanine aminotransferase increased			
Blood bilirubin increased			
Aspartate aminotransferase increased			
Blood alkaline phosphatase increased			
General disorders and administration site conditions			
Pyrexia			
Skin and subcutaneous tissue disorders			
Pruritus			

Abbreviations: MedDRA, Medical Dictionary for regulation Authorities; SOC, system organ class
Source: PEDFIC1 CSR [9]

Among patients who received odevixibat, the most commonly reported drug-related TEAEs were AST/ALT/bilirubin increases, and diarrhoea. All other drug-related TEAEs were reported in only one patient who received odevixibat (Table 91).

In the placebo group, drug-related TEAEs included one report each (5%) of ALT increased, AST increased, blood bilirubin increased, constipation and frequent bowel movements.

Table 91. Drug-related treatment-emergent adverse events (PEDFIC1)

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

Abbreviations: MedDRA, Medical Dictionary for regulation Authorities; SOC, system organ class
Source: PEDFIC1 CSR [9]

The majority of adverse events were mild to moderate in severity. [redacted]. All SAEs were assessed as unrelated to study treatment.

PEDFIC2

Of the 69 patients who received odevixibat, 50 (73%) experienced at least one TEAE (Table 92). 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 92. Summary of treatment-emergent adverse events (PEDFIC2)

	Odevixibat 120 µg/kg			
	Cohort 1			Cohort 2 N=16
	40 µg/kg N=19 n	120 µg/kg N=15 n	Placebo N=19	
TEAE	[redacted]			
Drug-related TEAE[c]				
Severe TEAE[d]				
Serious TEAE				
Drug-related serious TEAE				
TEAE leading to death				
TEAE leading to treatment discontinuation				

Source: PEDFIC2 CSR [11]

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 (Table 93). In general, the incidence of these commonly reported events was similar across the treatment groups in Cohort 1.

Table 93. Common treatment-emergent adverse events (PEDFIC2)

System organ class preferred term	Odevixibat 120 µg/kg			
	Cohort 1			Cohort 2 N=16 n (%)
	Placebo N=19 n (%)	40 µg/kg N=19 n (%)	120 µg/kg N=15 n (%)	
Infections and infestations	[redacted]			
Upper respiratory tract infection				
Otitis media				
Investigations				
Blood bilirubin increased				
Alanine aminotransferase increased				
Gastrointestinal disorders				
Diarrhoea				
Constipation				
Vomiting				
Respiratory, thoracic and mediastinal disorders				
Cough				
General disorders and administration site conditions				
Pyrexia				
Skin and subcutaneous tissue disorders				
Pruritus				
Blood and lymphatic system disorders				
Splenomegaly				

Source: PEDFIC2 CSR [11]

The most commonly reported drug-related TEAEs across the 62 patients were [redacted] (Table 94). [redacted].

Table 94. Drug-related treatment-emergent adverse events (PEDFIC2)

	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 n (%)**	**Cohort 1 (placebo) N=19 n (%)**	**Cohort 2 N=16 n (%)**
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 [11] [12]

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 (data cut-off December 2020) has recently been completed as part of the EMA assessment. The safety and tolerability profile of odevixibat in patients with PFIC remains acceptable and is consistent with that previously reported with no new safety signals observed during the update period [90].

A brief overview of the safety of the technology

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 87 patients with PFIC who received odevixibat in Phase 2 and 3 studies; 56 patients who received treatment for >= 6 months and 29 patients who received odevixibat for >0 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 most commonly used conventional therapies for PFIC. Most 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.

There was no indication of dose-dependent effects 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 comparable between the Pooled Phase 3 group (patients in Studies A4250005 and A4250-008) and that in Study A4250-005, indicating no cumulative toxicity.

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 seven (9%) of the 77 patients in the Pooled Phase 3 group; these were primarily reports of viral infections or infections. The only SAEs reported in more than one patient overall across the Phase 2 and 3 studies were urinary tract infection and influenza/H1N1 influenza. 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.

No clinically meaningful changes 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. No safety signals were observed based on review of vital signs or physical examination data.

In longer- term analysis of PEDFIC2 (data cut-off December 2020) the safety and tolerability profile of odevixibat in patients with PFIC remains acceptable and is consistent with that previously reported with no new safety signals observed during the update period [90].

19. Appendix F – Comparative analysis of efficacy and safety

N/A. There are no studies to compare PEDFIC estimates of the efficacy of odevixibat vs. placebo for treatment of PFIC with.

20. Appendix G – Extrapolation

There was no relevant survival evidence for odevixibat vs. placebo which could be used to extrapolate clinical effects of odevixibat.

Acute and long-term liver transplantation-related mortality was incorporated in the model based on evidence identified in the systematic literature review.

The studies identified to inform mortality from LTx are summarised in Table 95 and Table 96. These were identified as part of a systematic literature review. Given the variability in the estimates reported in the literature, meta-analysed and pooled rates are used in the model base case. NHS transplant data was not included in the base case meta-analysed/pooled estimates given these data are not specifically in PFIC patients. The NHS data are used as single inputs in scenario analysis.

Table 95. Summary of studies identified for acute LTx mortality

Study	Number of patients	Country	Date	Value reported
Outcomes of LTx for paediatric recipients with progressive familial intrahepatic cholestasis, Valamparampil et al	34 PFIC 1, 2, 3 & 4	India	2008	PFIC1: 15.4% 8-year rate PFIC2: 37% 8-year rate
Fifteen years single centre experience in the management of progressive familial intrahepatic cholestasis of infancy, Wanty et al	49	Belgium	2004	All PFIC; 5-year mortality: 8%
LTx for progressive familial intrahepatic cholestasis: Clinical and histopathological findings, outcome and impact on growth, Aydogdu et al	12 PFIC patients	Turkey	2007	1-year patient survival: 25%
NHS transplant	236 patients (not PFIC specific)	UK	2020	Paediatric mortality: 4.3%

Abbreviations: NHS, National Health Service; PFIC, progressive familial intrahepatic cholestasis; LTx, liver transplant.

Table 96. Summary of studies identified for long-term post-LTx mortality

Study	Number of patients	Country	Date	Value reported
Fifteen years single centre experience in the management of progressive familial intrahepatic cholestasis of infancy, Wanty et al	49	Belgium	2004	All PFIC; 5-year mortality: 8%
Progressive familial intrahepatic cholestasis: a single-centre experience of living-donor liver transplantation	14 PFIC (11 PFIC1, 3 PFIC2)	Japan	2010	PFIC1 at 5/10/15 years: 90.9%/72.7%/54.5%

Study	Number of patients	Country	Date	Value reported
during two decades in Japan, Hori et al				PFIC2: 100% at 5 years
NHS transplant	210 patients (not PFIC specific)	UK	2020	Paediatric mortality: 0.70%

Abbreviations: NHS, National Health Service; PFIC, progressive familial intrahepatic cholestasis.

Summary of meta-analysis method

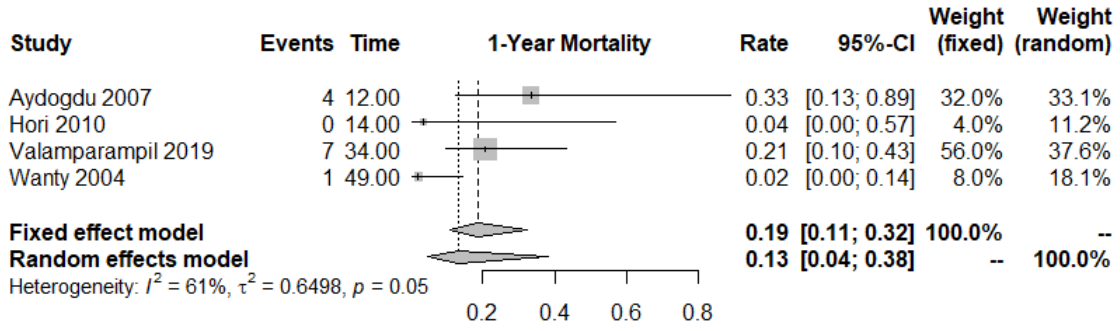
The meta-analysis was conducted for 1-year and 2–5-year post-LTx mortality. Overall incidence rates were synthesised from studies reporting events, with the assumptions that all the patients were followed up at the end of year 1 or year 5 to calculate the person-year, due to a lack of incident rates reporting in the studies. Inverse variance method was used for synthesis. The analysis was conducted in R with meta package.

Results from the meta-analysis for 1- and 5-year mortality are presented in Figure 34 and Figure 35.

For the 1-year survival estimate, the random effects model was considered most appropriate given the heterogeneity of the studies included. The resulting absolute mortality rate used in the model base case in the year of LTx is 0.13.

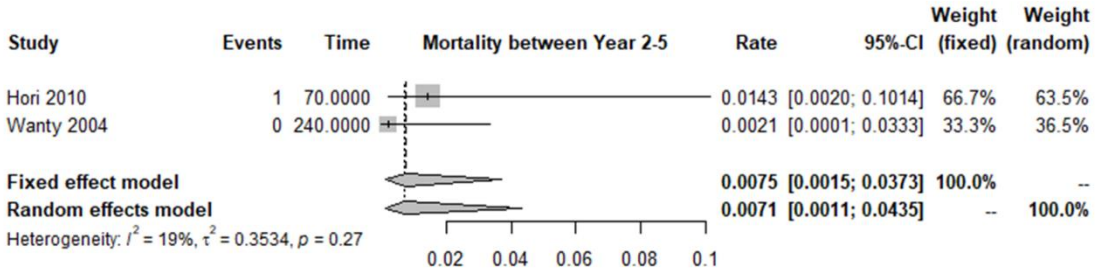
Only two studies were identified to estimate long-term post-LTx survival (Figure 35). The resulting absolute mortality rate for years 2–5 is 0.0071. However, only one death occurred in that time frame, and the majority of patients in the studies included were lost to follow-up – the meta-analysed rate was therefore not considered a representative estimate of long-term mortality, and a pooled approach was favoured.

Figure 34. Results from meta-analysis for 1-year post-liver transplant mortality



Abbreviations: CI, confidence interval

Figure 35. Results from meta-analysis for long-term post-liver transplant mortality

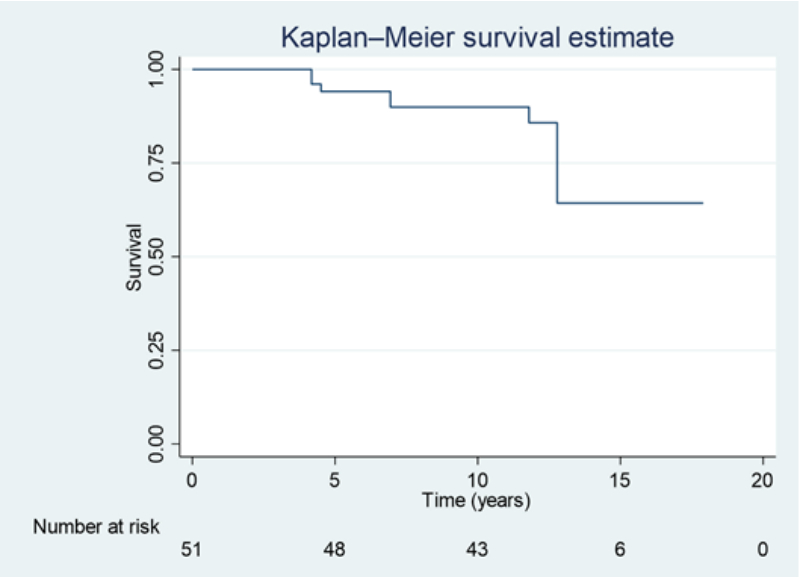


Abbreviations: CI, confidence interval

Summary of the pooled method

To obtain the pooled mortality rate from Hori [70] and Wanty [36], the Kaplan-Meier curves reported were digitised using Engauge Digitizer and pooled in Stata (Figure 36). An exponential model was fitted to the resulting curve (conditional on survival at 12 months) and the resulting annual probability of 1.45% was obtained. This approach accounts for all observed deaths and accounts for censoring, and the use of the exponential distribution was selected to limit model complexity. A summary of the exponential model statistics is provided in Table 97. Alternative distributions were considered, however these models could not be incorporated into a Markov model, thus for simplicity the exponential model was selected. AIC and BIC values for each model are presented in Table 98 and these show there is little difference in fit between models.

Figure 36. Pooled Kaplan-Meier from Hori [70] and Wanty [36], long-term post-liver transplant mortality



Note: 51 patients at baseline (38 from Wanty, 14 from Hori, excluding one patient from Wanty that died prior to 1 year post transplant)
Source: pooled from Hori [70] and Wanty [36]

Table 97. Exponential model results for pooled, long-term post-LTx mortality

	Constant term	Standard error	95% CI
Coefficient	0.0146	0.0049	0.0076-0.0281

Abbreviations: CI, confidence interval

Table 98. Model fits for alternative distributions

Model	AIC	BIC
Exponential	59.513	61.445
Weibull	58.541	62.405
Gompertz	59.578	63.442
Log-logistic	58.439	62.303
Log-normal	57.931	61.794
Generalised gamma	57.931	61.794

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

In addition to estimating parametric regression models, a standardised mortality ratio (SMR) comparing survival in patients post-liver transplant to general population survival was also estimated. The advantage of using an SMR is that it allows for the probability of death to vary with age. As digitized data has been used to generate the survival data, patient-level data on age is not available, thus it was necessary to assume an average age for the entire cohort. This was set to 6 years, the mean age of patients in Hori 2010. No data on age is available from Wanty 2004 [36]. As this average age was assumed, sensitivity analyses were also run assuming an average age of 9, 12 and 15 years. Analysis was performed using the "stptime" command in Stata 16. Results are presented in Table 99.

Table 99. SMRs for patients post-LTx

Average age	SMR	95% confidence interval
6 years	28.013	14.576; 53.839
9 years	24.412	12.702; 46.918
12 years	21.405	11.137; 41.138
15 years	18.784	9.774; 36.102

Abbreviations: SMR, standardised mortality ratio.

The estimated SMRs are large, as general population mortality for children is low and when extrapolated to the adult population these estimated probabilities of death can become implausibly large. In order to account for this, a cap on post-liver transplant mortality is applied when using the SMRs. In the base case this is set to the 1-year survival probability for patients receiving a liver transplant used in the model.

21. Appendix H – Literature search for HRQoL data

A systematic literature review (SLR) was carried out in order to identify HRQoL evidence for treatments for PFIC. In particular, in order to identify relevant estimates of health state utilities used in the economic model.

All of the utility and quality of life SLR database searches were conducted on 2nd March 2021.

- MEDLINE ALL (including MEDLINE daily, MEDLINE ePub ahead of print, MEDLINE (R) In-Process & Other Non-Indexed Citations) (via Ovid.com) 1946 to 26th February 2021
- Embase (via Ovid.com) 1974 to 26th February 2021
- The Cochrane Library databases (via the Wiley online platform):
    - Cochrane Database of Systematic Reviews (CDSR) Issue 3 of 12, March 2021
    - Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3 of 12, March 2021
- Centre for Reviews and Dissemination database (via york.ac.uk/crd):
    - Database of Abstracts of Reviews of Effects (DARE) Database inception to 2nd March 2021 (no date limits applied)
    - NHS Economic Evaluation Database (NHS EED) Database inception to 2nd March 2021 (no date limits applied)

Health Technology Assessment database (HTA database) Database inception to 2nd March 2021 (no date limits applied)

- EconLIT (via Ovid.com) 1886 to 18th February 2021
- ScHARRHUD database (https://www.scharrhud.org/index.php?home) Database inception to 2nd March 2021 (no date limits applied)

Eligibility criteria for the utility and HRQoL literature review are presented in Table 100.

Table 100. Eligibility criteria used in the utility and quality of life review

	Inclusion	Exclusion
Study design	Any primary publication in humans	Animal studies In-vitro studies Editorials Reviews Letters Comments Notes Erratum SLRs will be included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.
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:	Any other population

	Inclusion	Exclusion
	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	
Intervention	No restriction	No restriction
Comparators	No restriction	No restriction
Outcomes	Utilities e.g. directly elicited (TTO, SG) or generic preference-based utilities (e.g. EQ-5D, SF-6D, HUI, QWB) for relevant health states Mapping studies that allow another disease-specific measure to be mapped onto preference-based utilities Utilities and disutilities related to treatment and non-treatment related AEs Health-related quality of life (for patients and carers) Any PFIC-specific quality of life measures	Any other outcomes
Geographical location	No restriction	No restriction
Language	No restriction	No restriction
Publication date	No restriction; any study date	No restriction

Search strategies for each of the searched databases are presented in Table 101, Table 102, Table 103, Table 104, Table 105, and Table 106.

Search strategy

Table 101. Search terms for utility and quality of life SLR in MEDLINE (via Ovid)

Number	Search Term	Number of hits
1	exp intrahepatic cholestasis/ and (benign* or progress* or famil*).mp.	2380
2	(((famil* or progress* or benign* or recurrent or chronic) adj4 intrahepatic cholest*) or ((gamma-GT or gammaGT or greenland or (progress* adj4 famil*) or (benign adj4 recurrent)) adj4 cholest*) or PFIC* or Byler* disease* or byler* syndrome* or ((FIC1 or Familial intrahepatic cholestasis 1) adj4 deficien*) or BRIC or ((bile salt export pump or BSEP) adj4 deficien*) or ((MDR3 or multidrug resistance 3) adj4 deficien*) or ((TJP or tight junction protein) adj4 deficien*) or ((ATP8B1 or ABCB11 or ABCB4 or TJP2 or NR1H4 or MYO5B) adj10 cholest*)).mp.	1852
3	1 or 2	3605

Number	Search Term	Number of hits
4	exp quality of life/ or exp quality adjusted life years/ or exp health surveys/ or Value of Life/ or exp Disability Evaluation/ or exp models, economic/ or exp questionnaire/ or exp visual analog scale/	1258303
5	(quality of life or utilit* or quality adjusted or adjusted life or qaly* or qald* or qale* or qtime* or life year or life years or disability adjusted life or daly* or short form* or shortform* or sf* or hql or qol or HRQoL or hqol or h qol or hrqol or hr qol or hye or hyes or (health* adj2 year* adj2 equivalent*) or pqol or qls or quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb or nottingham health profile* or sickness impact profile or ((health or illness) adj3 stat*) or (preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)) or disutilit* or HSUV or HSUVs or rosser or willingness to pay or standard gamble* or sg or time trade off or time tradeoff or timetradeoff or tto or hui or hui1 or hui2 or hui3 or eq or euroqol* or euro qol* or EQ-5D or eq-5d or eq5-d or euroqual* or euro qual* or eq-sdq or eqsdq or duke health profile or functional status questionnaire or dartmouth coop functional health assessment* or multiattribute* or multi attribute* or 15D or 15-D or 15 dimension or medical outcome study or RAND36 or RAND12 or (health adj3 (status or index)) or PedsQL or Visual analog* scale or VAS).mp.	971047
6	4 or 5	1903608
7	3 and 6	257

Table 102. Search terms for utility and quality of life SLR in Embase (via Ovid)

Number	Search Term	Number of hits
1	intrahepatic cholestasis/ and (benign* or progress* or famil*).mp.	1967
2	(((famil* or progress* or benign* or recurrent or chronic) adj4 intrahepatic cholest*) or ((gamma-GT or gammaGT or greenland or (progress* adj4 famil*) or (benign adj4 recurrent)) adj4 cholest*) or PFIC* or Byler* disease* or byler* syndrome* or ((FIC1 or Familial intrahepatic cholestasis 1) adj4 deficien*) or BRIC or ((bile salt export pump or BSEP) adj4 deficien*) or ((MDR3 or multidrug resistance 3) adj4 deficien*) or ((TJP or tight junction protein) adj4 deficien*) or ((ATP8B1 or ABCB11 or ABCB4 or TJP2 or NR1H4 or MYO5B) adj10 cholest*)).mp.	2861
3	1 or 2	3546
4	socioeconomics/ or exp Quality of Life/ or exp Quality-Adjusted Life Year/ or nottingham health profile/ or sickness impact profile/ or exp health survey/ or exp Disability Evaluation/ or exp models, economic/ or exp questionnaire/ or exp visual analog scale/	1667662
5	(quality of life or utilit* or quality adjusted or adjusted life or qaly* or qald* or qale* or qtime* or life year or life years or disability adjusted life or daly* or short form* or shortform* or sf* or hql or qol or HRQoL or hqol or h qol or hrqol or hr qol or hye or hyes or (health* adj2 year* adj2 equivalent*) or pqol or qls or quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb or nottingham health profile* or sickness impact profile or ((health or illness) adj3 stat*) or (preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or	1442320

Number	Search Term	Number of hits
	disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)) or disutilit* or HSUV or HSUVs or rosser or willingness to pay or standard gamble* or sg or time trade off or time tradeoff or timetradeoff or tto or hui or hui1 or hui2 or hui3 or eq or euroqol* or euro qol* or EQ-5D or eq-5d or eq5-d or euroqual* or euro qual* or eq-sdq or eqsdq or duke health profile or functional status questionnaire or dartmouth coop functional health assessment* or multiattribute* or multi attribute* or 15D or 15-D or 15 dimension or medical outcome study or RAND36 or RAND12 or (health adj3 (status or index)) or PedsQL or Visual analog* scale or VAS).mp.	
6	4 or 5	2406357
7	3 and 6	187

Table 103. Search terms for utility and quality of life SLR in the Cochrane Library (via Wiley online)

Number	Search Term	Number of hits
1	[mh "intrahepatic cholestasis"] and (benign* or progress* or famil*):ti,ab,kw	68
2	(((famil* or progress* or benign* or recurrent or chronic) NEAR/4 intrahepatic cholest*) or ((gamma-GT or gammaGT or greenland or (progress* NEAR/4 famil*) or (benign NEAR/4 recurrent)) NEAR/4 cholest*) or PFIC* or Byler* disease* or byler* syndrome* or ((FIC1 or "Familial intrahepatic cholestasis 1") NEAR/4 deficien*) or BRIC or ((bile salt export pump or BSEP) NEAR/4 deficien*) or ((MDR3 or "multidrug resistance 3") NEAR/4 deficien*) or ((TJP or tight junction protein) NEAR/4 deficien*) or ((ATP8B1 or ABCB11 or ABCB4 or TJP2 or NR1H4 or MYO5B) NEAR/10 cholest*)):ti,ab,kw	384
3	#1 or #2	449
4	[mh "quality of life"] or [mh "quality adjusted life years"] or [mh "health survey"] or [mh ^"Value of Life"] or [mh "Disability Evaluation"] or [mh "models, economic"] or [mh "questionnaire"] or [mh "visual analog scale"]	75116
5	(quality of life or utilit* or quality adjusted or adjusted life or qaly* or qald* or qale* or qtime* or life year or life years or disability adjusted life or daly* or short form* or shortform* or sf* or hql or qol or HRQoL or hqol or h qol or hrqol or hr qol or hye or hyes or (health* NEAR/2 year* NEAR/2 equivalent*) or pqol or qls or quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb or nottingham health profile* or sickness impact profile or ((health or illness) NEAR/3 stat*) or (preference* NEAR/3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)) or disutilit* or HSUV or HSUVs or rosser or willingness to pay or standard gamble* or sg or time trade off or time tradeoff or timetradeoff or tto or hui or hui1 or hui2 or hui3 or eq or euroqol* or euro qol* or EQ-5D or eq-5d or eq5* or euroqual* or euro qual* or eqsdq or duke health profile or functional status questionnaire or dartmouth coop functional health assessment* or multiattribute* or multi attribute* or 15D or 15 D or 15 dimension or medical outcome study or RAND36 or RAND12 or (health NEAR/3 (status or index)) or PedsQL or Visual analog* scale or VAS):ti,ab,kw	304332
6	#4 or #5	341232

Number	Search Term	Number of hits
7	#3 and #6	98

Cochrane Database of Systematic Reviews Issue 3 of 12, March 2021 (n=7), Cochrane Central Register of Controlled Trials Issue 3 of 12, March 2021 (n=91)

Table 104. Search terms for utility and quality of life SLR in EconLit (via Ovid)

Number	Search Term	Number of hits
1	(((famil* or progress* or benign* or recurrent or chronic) adj4 intrahepatic cholest*) or ((gamma-GT or gammaGT or greenland or (progress* adj4 famil*) or (benign adj4 recurrent)) adj4 cholest*) or PFIC* or Byler* disease* or byler* syndrome* or ((FIC1 or Familial intrahepatic cholestasis 1) adj4 deficien*) or BRIC or ((bile salt export pump or BSEP) adj4 deficien*) or ((MDR3 or multidrug resistance 3) adj4 deficien*) or ((TJP or tight junction protein) adj4 deficien*) or ((ATP8B1 or ABCB11 or ABCB4 or TJP2 or NR1H4 or MYO5B) adj10 cholest*)).mp.	303

Table 105. Search terms for utility and quality of life SLR in the Database of Abstract Reviews of Effects, NHS Economic Evaluation Database, HTA Database (via York.ac.uk/crd interface)

Number	Search Term	Number of hits
1	cholestasis or cholestatic or PFIC or Byler disease or byler syndrome or Bylers disease or bylers syndrome or Byler's disease or byler's syndrome or FIC1 or BRIC or bile salt export pump deficiency or MDR3 or multidrug resistance 3 or TJP or tight junction protein	85

Table 106. Search terms for utility and quality of life SLR in ScHARRHUD (via https://www.scharrhud.org/)

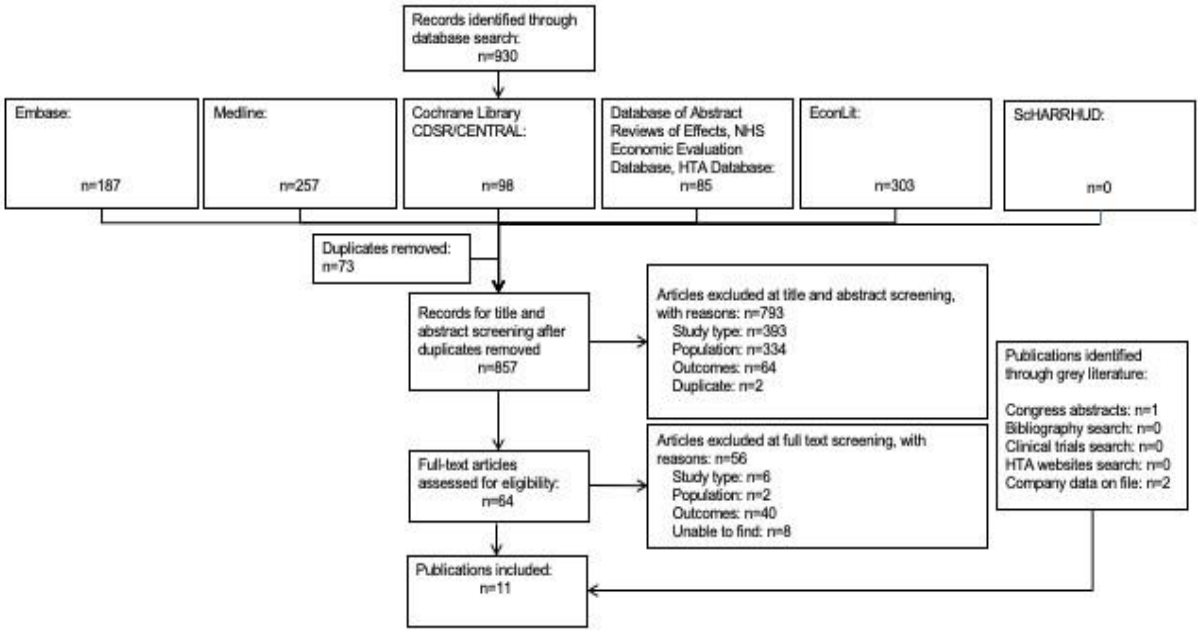
Number	Search Term	Number of hits
1	cholestasis or cholestatic or PFIC or Byler disease or byler syndrome or Bylers disease or bylers syndrome or Byler's disease or byler's syndrome or FIC1 or BRIC or bile salt export pump deficiency or MDR3 or multidrug resistance 3 or TJP or tight junction protein	0

Systematic selection of studies

The PRISMA flow diagram in Figure 37 of presents the flow of studies identified through the Utility and HRQoL SLR.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 37. Utility and health-related quality of life SLR PRISMA



Literature search results included in the model/analysis:

Table 107. List of included utility and health-related quality of life 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 postliver 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

Reference
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 PEDFIC1 Study. Value in Health. 2021;24(5):S1.
PEDFIC1 Clinical Study Report (company data on file)
PEDFIC2 Clinical Study Report (company data on file)

Excluded references

Table 108: Table of studies excluded at the full text review stage from the QoL SLR

Reference	Reason for exclusion
Robson SC, Kahn D, Gordon P, Jacobs P. A cost-to-benefit analysis of blood products used during the initiation of an orthotopic liver transplantation programme. South African journal of surgery. Suid-Afrikaanse tydskrif vir chirurgie. 1995 Dec 1;33(4):154-8.	Unable to find
Golovanova EV, Petrakov AV, Noskova KK. Intrahepatic cholestasis in chronic liver diseases. Eksperimental'naia i klinicheskaia gastroenterologiia= Experimental & clinical gastroenterology. 2011 Jan 1(2):58-67.	Unable to find
Holz R, Christidis G, Walther JK, Reichert M, Liebe R, Seiler-Mussler S, Zewinger S, Sester U, Schuster M, Bohle RM, Wasmuth HE. Plasma separation and anion adsorption results in rapid improvement of nasobiliary drainage (NBD)-refractory pruritus in BRIC type 2. Zeitschrift für Gastroenterologie. 2016 Aug;54(08):KV275.	Unable to find
Holz R, Schuster M, Bohle RM, Wasmuth HE, Lammert F, Krawczyk M. Extracorporeal blood purification improves nasobiliary drainage (NBD)-refractory pruritus in a BRIC type 2 patient. Zeitschrift für Gastroenterologie. 2016 Dec;54(12):A2-22.	Unable to find
JPRN. An exploratory study of efficacy and safety of sodium phenylbutyrate in progressive familial intrahepatic cholestasis type 1. 2017 http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000027666	Unable to find
Kaganov BS, Strokova TV, Machulan IV, Kamenets EA, Elu Z. A case report of Byler's syndrome. Eksperimental'naia i klinicheskaia gastroenterologiia= Experimental & clinical gastroenterology. 2012 Jan 1(1):43-9.	Unable to find
Kwak A, Dabrowska M, Jankowska I. Health related quality of life in children with progressive familial intrahepatic cholestasis after partial external biliray diversion. [Polish]. Pediatria Wspolczesna. 2005;7(3):201-204	Unable to find
Mentha G, Le Coultre C, Huber O, Meyer P, Belli D, Klopfenstein C, Kowalski M, Rohner A. Orthotopic liver transplantation--indications and results. Schweizerische Rundschau fur Medizin Praxis= Revue suisse de medecine Praxis. 1991 Dec 1;80(49):1380-7.	Unable to find
Baker A, Kerkar N, Kamath BM, Houwen RH. Sytematic review of the epidemiology and burden of disease of progressive familial intrahepatic cholestasis (PFIC): A genetic disease associated with liver failure in children. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S330-S331	Study design
Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RH. Systematic review of progressive familial intrahepatic cholestasis. Clinics and research in hepatology and gastroenterology. 2019 Feb 1;43(1):20-36.	Study design
Tandon P, Rowe BH, Vandermeer B, Bain VG. The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. American Journal of Gastroenterology. 2007 Jul 1;102(7):1528-36.	Study design

Reference	Reason for exclusion
Khurana S, Singh P. Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials. Liver International. 2006 Oct;26(8):943-8.	Study design
Davis AR, Rosenthal P, Newman TB. Nontransplant surgical interventions in progressive familial intrahepatic cholestasis. Journal of pediatric surgery. 2009 Apr 1;44(4):821-7.	Study design
NIHR Horizon Scanning Research&Intelligence Centre 2015. Lopixibat for progressive familial intrahepatic cholestasis in paediatric patients. http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32016000385	Study design
Kamath BM, Chen Z, Romero R, Fredericks EM, Alonso EM, Arnon R, Heubi J, Hertel PM, Karpen SJ, Loomes KM, Murray KF. Quality of life and its determinants in a multicenter cohort of children with Alagille syndrome. The Journal of pediatrics. 2015 Aug 1;167(2):390-6.	Population
Mazzetti M, de Vries E, Takkenberg B, Mostafavi N, Bikker H, Marzioni M, de Veer R, Van der Meer A, Doukas M, Verheij J, Beuers U. Heterozygous carriers of ABCB4 mutations show a mild clinical course, but impaired quality of life and limited risk for cholangiocarcinoma–a cohort study. Journal of Hepatology. 2020 Aug 1;73:S86.	Population
[Cholic acid: assessment according to section 35a (paragraph 1, sentence 10) Social Code Book V (dossier assessment)]	Outcomes
Alqabandi W, Thomas E, Buhamrah E. Pediatric liver transplantation for metabolic liver disease in Kuwait. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S129.	Outcomes
Appleby VJ, Hutchinson JM, Davies MH. Safety and efficacy of long-term nasobiliary drainage to treat intractable pruritus in cholestatic liver disease. Frontline gastroenterology. 2015 Oct 1;6(4):252-4.	Outcomes
Cheema HA, Prakash A, Cheema R. Partial internal biliary diversion improves clinical, biochemical and histological parameters in progressive, familial intrahepatic cholestasis: A study of 21 patients. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(S2):S336	Outcomes
Collyer EM, Hupertz V, Radhakrishnan K. Improved Neurologic Function after Refractory Vitamin E Deficiency Secondary To Progressive Familial Intrahepatic Cholestasis Type 2 in a Pediatric Patient Following Liver Transplant. Transplantation. 2015 Jul 1;99(7):304.	Outcomes
Czubkowski P, Jankowska I, Pawlowska J. Successful pregnancy after ileal exclusion in progressive familial intrahepatic cholestasis type 2. Annals of hepatology. 2015 Jul 15;14(4):550-2.	Outcomes
de Vries E, Mazzetti M, Takkenberg B, Mostafavi N, Bikker H, Marzioni M, de Veer R, van Der Meer A, Doukas M, Verheij J, Beuers U. Carriers of ABCB4 gene variants show a mild clinical course, but impaired quality of life and limited risk for cholangiocarcinoma. Liver International. 2020 Dec;40(12):3042-50.	Outcomes
Degtyareva A, Puchkova A, Pykov M, Filippova E, Ivanec T. Outcome of the children after liver transplantation: Abstract# P57. Pediatric Transplantation. 2015 May;19:118	Outcomes
Dinler GÖ, Koçak NU, Özen HA, Yüce AY, Gürakan FI. Ursodeoxycholic acid treatment in children with Byler disease. Pediatrics International. 1999 Dec;41(6):662-5.	Outcomes
Emond JC, Whitington PF. Selective surgical management of progressive familial intrahepatic cholestasis (Byler's disease). Journal of pediatric surgery. 1995 Dec 1;30(12):1635-41.	Outcomes
Fredericks EM, Dore-Stites D, Calderon SY, Well A, Eder SJ, Magee JC, Lopez MJ. Relationship between sleep problems and health-related quality of life among pediatric liver transplant recipients. Liver Transplantation. 2012 Jun;18(6):707-15.	Outcomes
Ghaffar TY, El Naghi S, Youssef A, El Adawy M, Moafy M, Sattar MA, Gamal M, Allam A, Hegazy N, Maksoud HA, Mokhtar A. Living Related Liver Transplantation (LRLT) for Progressive Familial Intrahepatic Cholestasis Type III (PFIC III) Children: A Single Center Experience. Hepatology. 2017 Oct 1;66(S1):892A	Outcomes
Grammatikopoulos T, Knisely AS, Dhawan A, Hadzic N, Thompson RJ. Anti-CD20 monoclonal antibody therapy in functional bile salt export pump deficiency after liver transplantation. Journal of pediatric gastroenterology and nutrition. 2015 Jun 1;60(6):e50-3.	Outcomes
Hasegawa Y, Hayashi H, Naoi S, Kondou H, Bessho K, Igarashi K, Hanada K, Nakao K, Kimura T, Konishi A, Nagasaka H. Intractable itch relieved by 4-phenylbutyrate therapy in patients with	Outcomes

Reference	Reason for exclusion
progressive familial intrahepatic cholestasis type 1. Orphanet journal of rare diseases. 2014 Dec;9(1):1-9.	
Hasegawa Y, Kondou H, Naoi S, Bessho K, Ukitsu M, Sasaki M, Tsunoda T, Inui A, Nagasaka H, Miyoshi Y, Hayashi H. O137 4-Phenylbutylate ameliorates liver fibrosis in patients with progressive familial intrahepatic cholestasis (PFIC) type 2 and pruritus in patients with pfic type 1. Journal of Hepatology. 2014;60(1):S58.	Outcomes
Kamath BM, Abetz-Webb L, Kennedy C, Hepburn B, Gauthier M, Johnson N, Medendorp S, Dorenbaum A, Todorova L, Shneider BL. Development of a novel tool to assess the impact of itching in pediatric cholestasis. The Patient-Patient-Centered Outcomes Research. 2018 Feb;11(1):69-82.	Outcomes
Kuiper EM, de Man RA, van Buuren HR. 671 Efficacy of nasobiliary drainage for refractory cholestatic pruritus. Journal of Hepatology. 2009(50):S246.	Outcomes
Kumagi T, Heathcote EJ. Successfully treated intractable pruritus with rifampin in a case of benign recurrent intrahepatic cholestasis. Clinical journal of gastroenterology. 2008 Dec;1(4):160-3.	Outcomes
Lind RC, Hoekstra-Weebers JE, Verkade HJ, Porte RJ, Hulscher JB. Quality of life in children after a partial external biliary diversion for progressive familial intrahepatic cholestasis or Alagille's disease. Journal Of Pediatric Gastroenterology And Nutrition. 2010 Jun 1;50:E155-E155.	Outcomes
Malatack JJ, Doyle D. A drug regimen for progressive familial cholestasis type 2. Pediatrics. 2018 Jan 1;141(1).	Outcomes
Ng VL, Ryckman FC, Porta G, Miura IK, de Carvalho E, Servidoni MF, Bezerra JA, Balistreri WF. Long-term outcome after partial external biliary diversion for intractable pruritus in patients with intrahepatic cholestasis. Journal of pediatric gastroenterology and nutrition. 2000 Feb 1;30(2):152-6.	Outcomes
Palaniappan K, Shrivastav M, Shanmugam N, Rajalingam R, Perumalla R, Narashiman G, Rela M. Monogenic Liver Diseases-Liver Transplantation As Gene Therapy. Liver Transplantation. 2014;20:S208.	Outcomes
Panasiti I, Briuglia S, Costa S, Caminiti L. Comorbidity between progressive familial intrahepatic cholestasis and atopic dermatitis in a 19-month-old child. BMJ Case Reports CP. 2019 Oct 1;12(10):e230152.	Outcomes
Panteleeva E, Zhelev C, Janeva P, Baicheva M. Post-transplantation follow-up of patients with progressive familial intrahepatic cholestasis. Abstract# 34. Pediatric Transplantation. 2011 Aug;15:49.	Outcomes
Podlaska, M.; Ismail, H.; Kalicinski, P.; Pawlowska, J.; Jankowska, I. Ileal exclusion in adolescent girl with progressive familial intrahepatic cholestasis (PFIC) - Due to a poor quality of life connected with biliary stoma Clinical and Experimental Hepatology.2015;1(2):81.	Outcomes
Posfay-Barbe KM, Barbe RP, Wetterwald R, Belli DC, McLin VA. Parental functioning improves the developmental quotient of pediatric liver transplant recipients. Pediatric transplantation. 2013 Jun;17(4):355-61.	Outcomes
Rakowska, M.; Naornakowska, M.; Pawloska, J.; Czubkowski, P.; Kalicinski, P.; Jankowska, I. 2017 [49] 14-year-old girl with PFIC-2-case report. Clinical and Experimental Hepatology 2017;3 (2):112.	Outcomes
Ruiz-Casas L, O'Hara S, Mighiu C, Finnegan A, Taylor A, Ventura E, Dhawan A, Murray KF, Schattenberg J, Willemse J, Karakaidos M. Burden of illness of progressive familial intrahepatic cholestasis in the US, UK, France, and Germany: study rationale and protocol of the PICTURE study. Expert Review of Pharmacoeconomics & Outcomes Research. 2021 Mar 4;21(2):247-53.	Outcomes
Serrano D, Gauthier M, Harrington M, Acevedo L. Psychometric validation of the Itch-Reported Outcome (ItchRO (TM)) assessment in pediatric patients with Alagille syndrome or progressive familial intrahepatic cholestasis. Hepatology 2016 Oct 1;64(1):284A-285A	Outcomes
Shimizu H, Migita O, Kosaki R, Kasahara M, Fukuda A, Sakamoto S, Shigeta T, Uemoto S, Nakazawa A, Kakiuchi T, Arai K. Living-Related Liver Transplantation for Siblings with Progressive Familial Intrahepatic Cholestasis 2, with Novel Genetic Findings. American Journal of Transplantation. 2011 Feb;11(2):394-8.	Outcomes

Reference	Reason for exclusion
Soubrane OL, Gauthier F, DeVictor D, Bernard OL, Valayer J, Houssin DI, Chapuis Y. Orthotopic liver transplantation for Byler disease. Transplantation. 1990 Nov 1;50(5):804-6.	Outcomes
Torfgard K, Gwaltney C, Paty J, Mattsson J, Soni P. Symptoms and daily impacts associated with progressive familial intrahepatic cholestasis and other pediatric cholestatic liver diseases: A qualitative study with patients and caregivers. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(S1):S208-S209.	Outcomes
Torfgard K, Gwaltney C, Paty J, Mattsson JP, Soni PN. Symptoms and daily impacts associated with progressive familial intrahepatic cholestasis and other pediatric cholestatic liver diseases: A qualitative study with patients and caregivers. Journal of Pediatric Gastroenterology and Nutrition. 2018;66(S2):813-814.	Outcomes
Van Vaisberg V, Tannuri AC, Lima FR, Tannuri U. Ileal exclusion for pruritus treatment in children with progressive familial intrahepatic cholestasis and other cholestatic diseases. Journal of pediatric surgery. 2020 Jul 1;55(7):1385-91.	Outcomes
Vij M, Shanmugam NP, Reddy MS, Sankaranarayanan S, Rela M. Paediatric hepatocellular carcinoma in tight junction protein 2 (TJP2) deficiency. Virchows Archiv. 2017 Nov;471(5):679-83.	Outcomes
Vimalesvaran S, Nevus L, Deheragoda M, Samyn M, Melendez H, Heaton N, Dhawan A. Allograft histology and biopsychosocial health 10 years after liver transplantation in children. Transplantation 2019 Aug 1;103(8S1):92.	Outcomes
Wang KS, Tiao G, Bass LM, Hertel PM, Mogul D, Kerkar N, Clifton M, Azen C, Bull L, Rosenthal P, Stewart D. Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. Hepatology. 2017 May;65(5):1645-54.	Outcomes
Whitington PF, Whitington GL. Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. Gastroenterology. 1988 Jul 1;95(1):130-6.	Outcomes
Yang H, Porte RJ, Verkade HJ, De Langen ZJ, Hulscher JB. Partial external biliary diversion in children with progressive familial intrahepatic cholestasis and Alagille disease. Journal of pediatric gastroenterology and nutrition. 2009 Aug 1;49(2):216-21.	Outcomes
Yee K, Moshkovich O, Llewellyn S, Benjamin K, Desai NK. A web-based survey of itch severity after surgical treatment of progressive familial intrahepatic cholestasis in children and adolescents. Hepatology 2018 Oct 1;68:1047A-1047A.	Outcomes

Quality assessment and generalizability of estimates

PFIC is an orphan disease with very little data to support specific quality of life estimates. While non-Danish data is used to inform health state-utilities in the economic model, given the rarity of PFIC, there is no reason to expect that the quality of life data that is available is ungeneralizable to the Danish context. Refer to the quality assessment in Appendix A – Literature search for efficacy and safety of intervention and comparator(s).

Unpublished data

22. Appendix I – Mapping of HRQoL data

PFIC is an orphan disease with an estimated number of patients in Denmark around 10, and the possibility to map the available utility data to Danish EQ-5D-5L utility data does not exist. The only utility measures directly related to treatment of patients with PFIC are based on the PedsQL quality of life measures, which was used in the PEDFIC1 study. A published mapping algorithm from the PedsQL to the EQ-5D was used [74].

Scores mapped from PEDIFC1 PedsQL data

Table 109 and Table 110 present the mapped EQ-5D scores from PEDFIC1 among pruritus responders and non-responders and sBA responders and non-responders respectively. These results are weight across patient-reported scores and parent-proxy scores. While the differences in utility scores between responders and non-responders at 24 weeks is marginal, this may be driven in large part by differences in baseline characteristics, as baseline scores are worse in the non-responder groups for both analyses, with larger changes from baseline observed in the response groups.

Table 109. Mapped EQ-5D scores among pruritus responders and non-responders at baseline and week 24

Time point	Responders	Non-responders
Baseline	[redacted]	
Week 24		
CFB		

Abbreviations: CFB, change from bas

Table 110. Mapped EQ-5D scores among sBA responders and non-responders at baseline and week 24

Time point	Responders	Non-responders
Baseline	[redacted]	
Week 24		
CFB		

Abbreviations: CFB, change from base

The patient numbers available for this analysis were small, especially in the patient-report group, with only a single observation for the sBA response group at baseline. 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.

Mapping algorithm – PedsQL to EQ-5D

The mapping algorithm used to obtain EQ-5D utilities from the PedsQL scores is from Khan et al [74].

A summary of the coefficients used is presented in Table 111. The resulting scores from the regression are presented in Table 112.

Table 111. Coefficients used in the mapping algorithm from PedsQL to EQ-5D, Kahn et al.

Regression term	Coefficient	Standard error
Physical Health	0.009127	0.002568
Emotional Health	0.006611	0.002530
Social Functioning	0.005705	0.002829
School Functioning	0.006011	0.002367
Physical Health squared	0.000020	0.000025
Emotional Health squared	-0.000048	0.000018
Social Functioning squared	0.000011	0.000016
School Functioning squared	-0.000017	0.000015
Physical x Emotional Health	-0.000004	0.000027
Physical x Social Functioning	-0.000055	0.000029
Physical x School Functioning	-0.000066	0.000030
Emotional x Social Health	-0.000009	0.000023
Emotional x School Functioning	0.000059	0.000021
Social x School Functioning	-0.000027	0.000022
Constant	-0.428496	0.094210

Table 112. Mapped EQ-5D scores obtained from the PedsQL scores reported in PEDFIC1

Mapped EQ-5D score	sBA response†	No sBA response	Pruritus response‡	No pruritus response
Self-reported	0.737	0.787	0.762	0.795
Parent-reported	0.791	0.679	0.750	0.679
Weighted score	0.783	0.711	0.754	0.710

†sBA response is defined as either a 70% reduction in sBA or reduction below the 70 µmol/L threshold; ‡Pruritus response is defined as a positive assessment using the ObsRO instrument at 24-weeks.
Abbreviations: CHU-9D, Child Health Utility 9D; sBA, serum bile acid.

Short stature disutility multiplier

A multiplier for short stature was obtained using PedsQL scores reported by Al-Uzri in children with chronic kidney disease [73], and mapped to the EQ-5D as described in the 'Mapping algorithm' section. 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 [19]. 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 [74]. This is equivalent to a multiplier of 0.977.

Table 113. Patient-reported PedsQL

Dimension	Short stature (SD), n=69	Normal height (SD), n=399
Physical Health	78.33 (18.63)	80.2 (15.5)
Emotional Health	73.78 (19.54)	73.46 (17.69)
Social Functioning	78.69 (22.63)	80.79 (18.69)
School Functioning	62.18 (20.49)	64.42 (18.13)
Mapped EQ-5D score	0.863	0.872

Abbreviations: PedsQL, paediatric quality of life; SD, standard deviation.

Table 114. Parent-reported PedsQL

Dimension	Short stature (SD), n=69	Normal height (SD), n=399
Physical Health	72.7 (24.09)	79.01 (20.92)
Emotional Health	73.49 (16.62)	74.52 (18.21)
Social Functioning	73.99 (23.02)	78.99 (21.2)
School Functioning	63.65 (22.14)	65.37 (21.47)
Mapped EQ-5D score	0.841	0.870

Abbreviations: PedsQL, paediatric quality of life; SD, standard deviation.

23. Appendix J – Probabilistic sensitivity analyses

Distributional assumptions of model parameters are found on the 'Control' sheet.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Age at baseline	4.25	Normal	0.493141	62			PEDFIC 1 CSR. Trial results.
% female	0.5	Beta	0.038266	31	15.5	15.5	PEDFIC 1 CSR. Trial results.
% PFIC 1	0.274	Beta	0.02097	17	4.658	12.342	PEDFIC 1 CSR. Trial results.
Response to odevixibat - sBA & pruritus response - 40 µg/kg	0.435	Beta	0.107961	23	10.005	12.995	PEDFIC 1 CSR. Trial results.
Response to odevixibat - sBA & pruritus response - 120 µg/kg	0.211	Beta	0.100818	19	4.009	14.991	PEDFIC 1 CSR. Trial results.
Response to odevixibat - sBA & pruritus response - combined doses	0.333	Beta	0.076481	42	13.986	28.014	PEDFIC 1 CSR. Trial results.
Response to odevixibat - sBA & pruritus response - uptitrators	0.25	Beta	0.178369	4	1	3	Data on file: Enhanced response 40 to 120
Response to odevixibat - pruritus response - 40 µg/kg	0.739	Beta	0.0974	23	16.997	6.003	PEDFIC 1 CSR. Table 20. Trial results.
Response to odevixibat - pruritus response - 120 µg/kg	0.474	Beta	0.119109	19	9.006	9.994	PEDFIC 1 CSR. Table 20. Trial results.
Response to odevixibat - pruritus response - combined doses	0.619	Beta	0.078547	42	25.998	16.002	PEDFIC 1 CSR. Table 20. Trial results.
Response to odevixibat - pruritus response - uptitrators	0.375	Beta	0.155766	8	3	5	Data on file: Enhanced response 40 to 120
Annual loss of response (odevixibat)	0.035314	Beta	0.002703	4662.977	164.667	4498.31	Based on proportion of patients discontinuing in PEDFIC 1. Data on file, Albireo 2021.
Response to SoC, any therapy	0	Not varied					Based on clinical opinion.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Annual loss of response (SoC)	0.035314	Not varied					Assumed as same as annual loss of response for odevixibat Based on proportion of patients discontinuing in PEDFIC 1. Data on file, Albireo 2021.
PEBD hazard, PFIC 2	0.05	Normal	0.005157				NAPPED data analysis, December 2019.
PEBD hazard, age <3, PFIC 1	-1.42	Normal	0.141421				NAPPED data analysis, December 2019.
PEBD hazard, age >=3, PFIC 1	-1.61	Normal	0.311325				NAPPED data analysis, December 2019.
Response to PEBD - PFIC 1	0.521739	Beta	0.098947	24	12.52174	11.47826	Response to PEBD in NAPPED (23 responders out of 41).
Response to PEBD - PFIC 2	0.631579	Beta	0.076739	38	24	14	Response to PEBD in NAPPED (23 responders out of 41).
Annual loss of response to PEBD	0.05	Beta	0.003827	3242.899	162.1449	3080.754	Assumption.
% LT, without PEBD, PFIC 2	0.078224	Normal	0.006941				NAPPED data analysis, December 2019.
Pruritus responders risk ratio - PFIC 1	0.321429	Beta	0.0246	138	44.35714	93.64286	NAPPED data analysis, December 2019.
Pruritus responders risk ratio - PFIC 2	0.43956	Beta	0.03364	138	60.65934	77.34066	NAPPED data analysis, December 2019.
% LT, without PEBD, PFIC 1	0.051985	Normal	0.010397				NAPPED data analysis, December 2019.
% LT, with PEBD, no response, PFIC 2	0.119279	Normal	0.03976				NAPPED data analysis, December 2019.
% LT, with PEBD, no response, PFIC 1	0.065472	Normal	0.032736				NAPPED data analysis, December 2019.
LTx mortality, in year of transplant - NHS pediatric transplant	0.043	Beta	0.003291	222	9.546	212.454	NHS pediatric transplant report, 2020.
LTx mortality, post-LTx - NHS pediatric transplant	0.007	Beta	0.000536	210	1.47	208.53	NHS pediatric transplant report, 2020.
LTx mortality, post-LTx - pooled rate	0.019111	Beta	0.005086	723.8234	13.83301	709.9904	Result from pooled Kaplan-Meier curves; Hori & Wanty
LTx mortality, in year of transplant - Valamparampil, BSEP-deficiency	0.37	Beta	0.028317	34	12.58	21.42	Valamparampil et al. Liver transplantation in progressive familial intrahepatic cholestasis: Outcome analysis from a single centre. 2018.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
LTx mortality, in year of transplant - Valamparampil, FIC 1-deficiency	0.154	Beta	0.011786	34	5.236	28.764	Valamparampil et al. Liver transplantation in progressive familial intrahepatic cholestasis: Outcome analysis from a single centre. 2018.
LTx mortality, in year of transplant - meta-analysis	0.11308	Beta	0.031074	102.8633	11.63174	91.23156	Result from meta-analysis; Valamparampil, Aydogdu & Wanty
LTx mortality, post-LTx -Wanty	0.0102	Beta	0.0007806	16,567	169	16398	Wanty et al. Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy. 2004
LTx mortality, SMR	28.013	Normal	10.01638				Result from pooled Kaplan-Meier curves; Hori & Wanty
Re-transplant rate - PFIC 1	0.04	Beta	0.003061	4	0.16	3.84	Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Re-transplant rate - PFIC 2	0.12	Beta	0.009184	19	2.28	16.72	Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Pre-transplant mortality - PFIC 1	0.00352	Beta	0.000269	46	0.161925	45.83808	Van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, et al. Factors associated with the natural course of disease in patients with FIC1-deficiency: The NAPPED-consortium. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(Supplement 1):688-9.
Pre-transplant mortality - PFIC 2	0.002354	Beta	0.00018	184	0.433168	183.5668	Van Wessel D, Thompson R, Grammatikopoulos T, Kadaristiana A, Jankowska I, Lipinski P, et al. The natural course of FIC1 deficiency and BSEP deficiency: Initial results from the NAPPEDconsortium (NAtural course andprognosis of PFIC and effect of biliary diversion). Journal of Pediatric Gastroenterology and Nutrition. 2018;66(Supplement 2):650-2.
Diarrhoea - incidence, SoC	0.05	Not varied					PEDFIC 1 CSR. Trial results.
Vomiting - incidence, SoC	0	Not varied					PEDFIC 1 CSR. Trial results.
Abdominal pain - incidence, SoC	0	Not varied					PEDFIC 1 CSR. Trial results.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Upper respiratory infection - incidence, SoC	0.15	Not varied					PEDFIC 1 CSR. Trial results.
Nasopharyngitis - incidence, SoC	0.05	Not varied					PEDFIC 1 CSR. Trial results.
Alanine aminotransferase ↑ - incidence, SoC	0.05	Not varied					PEDFIC 1 CSR. Trial results.
Blood bilirubin ↑ - incidence, SoC	0.1	Not varied					PEDFIC 1 CSR. Trial results.
Aspartate aminotransferase ↑ - incidence, SoC	0.05	Not varied					PEDFIC 1 CSR. Trial results.
Blood alkaline phosphatase ↑ - incidence, SoC	0.05	Not varied					PEDFIC 1 CSR. Trial results.
Pyrexia - incidence, SoC	0.25	Not varied					PEDFIC 1 CSR. Trial results.
Pruritus - incidence, SoC	0.05	Not varied					PEDFIC 1 CSR. Trial results.
Diarrhoea - incidence, Odevixibat	0.31	Not varied					PEDFIC 1 CSR. Trial results.
Vomiting - incidence, Odevixibat	0.167	Not varied					PEDFIC 1 CSR. Trial results.
Abdominal pain - incidence, Odevixibat	0.071	Not varied					PEDFIC 1 CSR. Trial results.
Upper respiratory infection - incidence, Odevixibat	0.19	Not varied					PEDFIC 1 CSR. Trial results.
Nasopharyngitis - incidence, Odevixibat	0.071	Not varied					PEDFIC 1 CSR. Trial results.
Alanine aminotransferase ↑ - incidence, Odevixibat	0.143	Not varied					PEDFIC 1 CSR. Trial results.
Blood bilirubin ↑ - incidence, Odevixibat	0.119	Not varied					PEDFIC 1 CSR. Trial results.
Aspartate aminotransferase ↑ - incidence, Odevixibat	0.071	Not varied					PEDFIC 1 CSR. Trial results.
Blood alkaline phosphatase ↑ - incidence, Odevixibat	0.071	Not varied					PEDFIC 1 CSR. Trial results.
Pyrexia - incidence, Odevixibat	0.285	Not varied					PEDFIC 1 CSR. Trial results.
Pruritus - incidence, Odevixibat	0.071	Not varied					PEDFIC 1 CSR. Trial results.

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Parameter	Value	Parameter distribution	se	n	α	β	Reference
Diarrhoea - Post-LTx complications PFIC 1	0.81	Beta	0.079466	17	13.77	3.23	Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Liver steatosis - Post-LTx complications PFIC 1	0.9	Beta	0.05995	19	17.1	1.9	Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Stunted growth - Post-LTx complications PFIC 1	0.67	Beta	0.051276	4	2.68	1.32	ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC). Davit-Spraul, 2010.
Deafness - Post-LTx complications PFIC 1	0.33	Beta	0.025256	2	0.66	1.34	ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC). Davit-Spraul, 2010.
Pancreatitis - Post-LTx complications PFIC 1	0.4	Beta	0.030613	8	3.2	4.8	Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Diarrhoea - Post-LTx complications PFIC 2	0.07	Beta	0.005357	2	0.14	1.86	Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Liver steatosis - Post-LTx complications PFIC 2	0.06	Beta	0.004592	2	0.12	1.88	Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Stunted growth - Post-LTx complications PFIC 2	0	Not varied					ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC). Davit-Spraul, 2010.
Deafness - Post-LTx complications PFIC 2	0	Not varied					ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC). Davit-Spraul, 2010.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Pancreatitis - Post-LTx complications PFIC 2	0	Not varied					Bull et al, Outcomes of Surgical Management of Familial Intrahepatic Cholestasis 1 and Bile Salt Export Protein Deficiencies, 2018.
Utility value - LTx	0.71	Beta	0.41	73	51.83	21.17	Kini et al., The Impact of Pruritus on Quality of Life, Arch Dermatol., 2011.
Disutility of LTx - PFIC 1 only	0	Not varied					Assumption.
Disutility of LTx - all patients	0	Not varied					Assumption.
Disutility of stoma bag - colorectal cancer	0.945205	Beta	0.050148	640	604.9315	35.06849	Hornbrook, M.C., et al., Complications among colorectal cancer survivors: SF-6D preference-weighted quality of life scores. Medical care, 2011. 49(3): p. 321.
Disutility of stoma bag - ulcerative colitis	0.721519	Beta	0.098652	48	34.63291	13.36709	Arseneau et al. Do Patient Preferences Influence Decisions on Treatment for Patients With Steroid-Refractory Ulcerative Colitis? 2006.
Age-based multiplier - constant	0.950857	Not varied					Ara and Brazier, 2010. Populating an economic model with health state utility values: moving toward better practice.
Age-based multiplier - male	0.021213	Not varied					Ara and Brazier, 2010. Populating an economic model with health state utility values: moving toward better practice.
Age-based multiplier - age	-0.00026	Not varied					Ara and Brazier, 2010. Populating an economic model with health state utility values: moving toward better practice.
Age-based multiplier - age^2	-3.3E-05	Not varied					Ara and Brazier, 2010. Populating an economic model with health state utility values: moving toward better practice.
PedsQL to EQ-5D mapping - Physical Health	0.009127	Normal	0.002568				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
PedsQL to EQ-5D mapping - Emotional Health	0.006611	Normal	0.00253				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Social Functioning	0.005705	Normal	0.002829				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - School Functioning	0.006011	Normal	0.002367				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Physical Health squared	0.00002	Normal	0.000025				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Emotional Health squared	-4.8E-05	Normal	0.000018				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Social Functioning squared	0.000011	Normal	0.000016				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - School Functioning squared	-1.7E-05	Normal	0.000015				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014

Parameter	Value	Parameter distribution	se	n	α	β	Reference
							Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Physical x Emotional Health	-4E-06	Normal	0.000027				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Physical x Social Functioning	-5.5E-05	Normal	0.000029				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Physical x School Functioning	-6.6E-05	Normal	0.00003				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Emotional x Social Health	-9E-06	Normal	0.000023				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Emotional x School Functioning	0.000059	Normal	0.000021				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
PedsQL to EQ-5D mapping - Social x School Functioning	-2.7E-05	Normal	0.000022				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
PedsQL to EQ-5D mapping - Constant	-0.4285	Normal	0.09421				Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706. doi: 10.1007/s40273-014-0153-y. PMID: 24715604.
Post-LTx PedsQL - total score	77.29048	Not varied					Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Post-LTx PedsQL - physical score	68.46241	Not varied					Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Post-LTx PedsQL - emotional score	74.96887	Not varied					Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Post-LTx PedsQL - social score	81.11387	Not varied					Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Post-LTx PedsQL - school score	71.47313	Not varied					Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Healthy PedsQL - total score (Kamath 2015)	83.91	Normal	12.47	5079			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi:

Parameter	Value	Parameter distribution	se	n	α	β	Reference
							10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Healthy PedsQL - physical score (Kamath 2015)	87.77	Normal	13.12	5070			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Healthy PedsQL - emotional score (Kamath 2015)	79.21	Normal	18.02	5068			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Healthy PedsQL - social score (Kamath 2015)	84.97	Normal	16.71	5056			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Healthy PedsQL - school score (Kamath 2015)	81.31	Normal	16.09	5026			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
sBA≥118 PedsQL - total score (Kamath 2015)	73.04	Normal	15.8	49			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
sBA≥118 PedsQL - physical score (Kamath 2015)	78.91	Normal	16.06	49			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
sBA≥118 PedsQL - emotional score (Kamath 2015)	67.35	Normal	21.56	49			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
sBA≥118 PedsQL - social score (Kamath 2015)	76.26	Normal	20.81	49			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
sBA≥118 PedsQL - school score (Kamath 2015)	65.94	Normal	19.75	48			Kamath et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3. doi: 10.1016/j.jpeds.2015.04.077. Epub 2015 Jun 6. PMID: 26059338; PMCID: PMC4516587.
Vignette study (EQ-5D) - Without PEBD, Response	0.661	Beta	0.011183	95	62.795	32.205	Vignette study, May 2021. Albireo data on file.
Vignette study (EQ-5D) - Without PEBD, Loss of response	0.409	Beta	0.020417	95	38.855	56.145	Vignette study, May 2021. Albireo data on file.
Vignette study (EQ-5D) - With PEBD, Response	0.6	Beta	0.011594	95	57	38	Vignette study, May 2021. Albireo data on file.
Vignette study (EQ-5D) - With PEBD, Loss of response	0.36	Beta	0.019596	95	34.2	60.8	Vignette study, May 2021. Albireo data on file.
Vignette study (EQ-5D) - LTx	0.47	Beta	0.021033	95	44.65	50.35	Vignette study, May 2021. Albireo data on file.
Vignette study (EQ-5D) - Post-LTx	0.679	Beta	0.01539	95	64.505	30.495	Vignette study, May 2021. Albireo data on file.
Vignette study (TTO) - Without PEBD, Response	0.884	Beta	0.012825	95	83.98	11.02	Vignette study, May 2021. Albireo data on file.
Vignette study (TTO) - Without PEBD, Loss of response	0.692	Beta	0.031395	95	65.74	29.26	Vignette study, May 2021. Albireo data on file.
Vignette study (TTO) - With PEBD, Response	0.84	Beta	0.015492	95	79.8	15.2	Vignette study, May 2021. Albireo data on file.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Vignette study (TTO) - With PEBD, Loss of response	0.604	Beta	0.03909	95	57.38	37.62	Vignette study, May 2021. Albireo data on file.
Vignette study (TTO) - LTx	0.732	Beta	0.030677	95	69.54	25.46	Vignette study, May 2021. Albireo data on file.
Vignette study (TTO) - Post-LTx	0.879	Beta	0.014877	95	83.505	11.495	Vignette study, May 2021. Albireo data on file.
PEBD vignette study - Doctor, Age 7 with PEBD	0.553	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Doctor, Age 14 with PEBD	0.333	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Doctor, Age 7 without PEBD	0.333	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Doctor, Age 14 without PEBD	0.127	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent A, Age 7 with PEBD	0.243	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent A, Age 14 with PEBD	0.323	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent A, Age 7 without PEBD	0.427	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent A, Age 14 without PEBD	0.433	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent B, Age 7 with PEBD	-0.196	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent B, Age 7 without PEBD	0.725	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent C, Age 7 with PEBD	0.156	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent C, Age 14 with PEBD	0.063	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent C, Age 7 without PEBD	0.156	Not varied					PEBD vignette study, June 2021. Albireo data on file.
PEBD vignette study - Parent C, Age 14 without PEBD	0.404	Not varied					PEBD vignette study, June 2021. Albireo data on file.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Caregiver utility - mean	0.7975	Beta	0.082176	22.91459	18.27439	4.640205	Bastida et al., Social/economic costs and health-related quality of life in patients with rare diseases in Europe, 2015.
Caregiver disutility - adjacent decrement	0.05	Gamma	0.003827		170.7315	0.000293	Bastida et al., Social/economic costs and health-related quality of life in patients with rare diseases in Europe, 2015.
Short stature multiplier	0.977187	Gamma	0.043213		511.3615	0.001911	Al-Uzri et al, 2013. The Impact of Short Stature on HRQoL in Children with Chronic Kidney Disease.
UDCA - % patients treated	0.95	Beta	0.049108	18.69647	17.76164	0.934823	Burden of illness study, April 2021. HCD Data on file.
Cholestyramine - % patients treated	0.375	Beta	0.173791	6.75987	2.534951	4.224919	Burden of illness study, April 2021. HCD Data on file.
Rifampicin - % patients treated	0.66	Beta	0.050511	86.95259	57.38871	29.56388	Burden of illness study, April 2021. HCD Data on file.
Naltrexone - % patients treated	0.1	Beta	0.007653	1535.584	153.5584	1382.025	Burden of illness study, April 2021. HCD Data on file.
UDCA - Days/cycle	365.25	Gamma	27.95332		170.7315	2.139324	BNF, accessed October 2019.
Cholestyramine (pediatric) - Days/cycle	365.25	Gamma	27.95332		170.7315	2.139324	BNF, accessed October 2019.
Rifampicin (pediatric) - Days/cycle	365.25	Gamma	27.95332		170.7315	2.139324	Use of rifampicin for severe pruritus in children with chronic cholestasis, Yerushalmi et al., 1999
Naltrexone - Days/cycle	365.25	Gamma	27.95332		170.7315	2.139324	Use of oral naltrexone for severe pruritus due to cholestatic liver disease in children, Zellos et al, 1998.
Cholestyramine (pediatric) - Dose/day (mg)	4000	Gamma	306.1281		170.7315	23.4286	BNF, accessed October 2019.
Cholestyramine (adult) - Dose/day (mg)	6000	Gamma	459.1921		170.7315	35.1429	BNF, accessed May 2021.
Rifampicin (pediatric) - Dose/day (mg)	10	Gamma	0.76532		170.7315	0.058571	Use of rifampicin for severe pruritus in children with chronic cholestasis, Yerushalmi et al., 1999
Rifampicin (adult) - Dose/day (mg)	450	Gamma	34.43941		170.7315	2.635717	Khurana S, Singh P. Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials, 2007.
UDCA - Mg/kg	12	Not varied					BNF, accessed October 2019.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Naltrexone - Mg/kg	2	Not varied					Use of oral naltrexone for severe pruritus due to cholestatic liver disease in children, Zellos et al, 1998.
UDCA - Mg/unit	250	Not varied					MEDICINPRISER.DK, 2 September 2021 (Ursodeoxycholsyre "Paranova")
Cholestyramine (pediatric) - Mg/unit	4000	Not varied					MEDICINPRISER.DK, 2 September 2021 (Colestyramin (uestran))
Rifampicin (pediatric) - Mg/unit	300	Not varied					MEDICINPRISER.DK, 2 September 2021 (rifampicin (Rimactan))
Naltrexone - Mg/unit	50	Not varied					MEDICINPRISER.DK, 2 September 2021 (Naltrexone "POA Pharma")
UDCA - AIP Cost/pack	137.9	Not varied					MEDICINPRISER.DK, 2 September 2021 (Ursodeoxycholsyre "Paranova")
Cholestyramine (pediatric) - AIP Cost/pack	194.35	Not varied					MEDICINPRISER.DK, 2 September 2021 (Colestyramin (uestran))
Rifampicin (pediatric) - AIP Cost/pack	372	Not varied					MEDICINPRISER.DK, 2 September 2021 (rifampicin (Rimactan))
Naltrexone - AIP Cost/pack	222.6	Not varied					MEDICINPRISER.DK, 2 September 2021 (Naltrexone "POA Pharma")
UDCA - Units/pack	100	Not varied					MEDICINPRISER.DK, 2 September 2021 (Ursodeoxycholsyre "Paranova")
Cholestyramine (pediatric) - Units/pack	50	Not varied					MEDICINPRISER.DK, 2 September 2021 (Colestyramin (uestran))
Rifampicin (pediatric) - Units/pack	100	Not varied					MEDICINPRISER.DK, 2 September 2021 (rifampicin (Rimactan))
Naltrexone - Units/pack	28	Not varied					MEDICINPRISER.DK, 2 September 2021 (Naltrexone "POA Pharma")
Odevixibat, number of days	365.25	Not varied					Trial protocol, PEDFIC 1.
Odevixibat, capsules per pack	30	Not varied					Data on file, Albireo.
Odevixibat, cost of low dose bottle	27541	Not varied					Data on file, Albireo.
Proportion of patients - Pediatrician - Pre-surgery	0.615	Beta	0.047067	43	26.445	16.555	Burden of illness study, April 2021. HCD Data on file.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Proportion of patients - Hepatologist - Pre-surgery	0.077	Beta	0.005893	43	3.311	39.689	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Gastroenterologist - Pre-surgery	0.308	Beta	0.023572	43	13.244	29.756	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Dietitian - Pre-surgery	0.077	Beta	0.005893	43	3.311	39.689	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Emergency medicine - Pre-surgery	0.154	Beta	0.011786	43	6.622	36.378	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Orthopedist - Pre-surgery	0.077	Beta	0.005893	43	3.311	39.689	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Physiotherapist - Pre-surgery	0.077	Beta	0.005893	43	3.311	39.689	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Psychologist - Pre-surgery	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Speech and language therapist - Pre-surgery	0.077	Beta	0.005893	43	3.311	39.689	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Endocrinologist - Pre-surgery	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - GP visit - Pre-surgery	0.077	Beta	0.005893	43	3.311	39.689	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Nurse visit - Pre-surgery	0.791	Beta	0.060537	43	34.013	8.987	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Stoma care - Pre-surgery	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Pediatrician - Post-PEBD	0.5	Beta	0.038266	26	13	13	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Hepatologist - Post-PEBD	0.1	Beta	0.007653	26	2.6	23.4	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Gastroenterologist - Post-PEBD	0.2	Beta	0.015306	26	5.2	20.8	Burden of illness study, April 2021. HCD Data on file.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Proportion of patients - Dietitian - Post-PEBD	0.4	Beta	0.030613	26	10.4	15.6	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Emergency medicine - Post-PEBD	0.2	Beta	0.015306	26	5.2	20.8	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Orthopedist - Post-PEBD	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Physiotherapist - Post-PEBD	0.1	Beta	0.007653	26	2.6	23.4	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Psychologist - Post-PEBD	0.1	Beta	0.007653	26	2.6	23.4	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Speech and language therapist - Post-PEBD	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Endocrinologist - Post-PEBD	0.1	Beta	0.007653	26	2.6	23.4	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - GP visit - Post-PEBD	0.2	Beta	0.015306	26	5.2	20.8	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Nurse visit - Post-PEBD	0.962	Beta	0.073624	26	25.012	0.988	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Stoma care - Post-PEBD	1	Beta	0.038266	26	1	25	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Pediatrician - Post-LTx	0.5	Beta	0.038266	10	5	5	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Hepatologist - Post-LTx	0.25	Beta	0.019133	10	2.5	7.5	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Gastroenterologist - Post-LTx	0.25	Beta	0.019133	10	2.5	7.5	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Dietitian - Post-LTx	0.625	Beta	0.047833	10	6.25	3.75	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Emergency medicine - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Orthopedist - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Proportion of patients - Physiotherapist - Post-LTx	0.125	Beta	0.009567	10	1.25	8.75	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Psychologist - Post-LTx	0.375	Beta	0.0287	10	3.75	6.25	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Speech and language therapist - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Endocrinologist - Post-LTx	0.125	Beta	0.009567	10	1.25	8.75	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - GP visit - Post-LTx	0.375	Beta	0.0287	10	3.75	6.25	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Nurse visit - Post-LTx	1	Beta	0.038266	10	1	9	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Stoma care - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Pediatrician - Pre-surgery	2.9	Gamma	0.121999	43	565.0469	0.005132	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Hepatologist - Pre-surgery	8	Gamma	0.612256	43	170.7315	0.046857	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Gastroenterologist - Pre-surgery	4.5	Gamma	0.442246	43	103.5375	0.043463	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Dietitian - Pre-surgery	3	Gamma	0.229596	43	170.7315	0.017571	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Emergency medicine - Pre-surgery	2	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Orthopedist - Pre-surgery	3	Gamma	0.229596	43	170.7315	0.017571	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Physiotherapist - Pre-surgery	8	Gamma	0.612256	43	170.7315	0.046857	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Psychologist - Pre-surgery	0	Not varied					Burden of illness study, April 2021. HCD Data on file.

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Parameter	Value	Parameter distribution	se	n	α	β	Reference
Mean number of visits - Speech and language therapist - Pre-surgery	8	Gamma	0.612256	43	170.7315	0.046857	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Endocrinologist - Pre-surgery	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - GP visit - Pre-surgery	1	Gamma	0.076532	43	170.7315	0.005857	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Nurse visit - Pre-surgery	3.5	Gamma	0.267862	43	170.7315	0.0205	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Stoma care - Pre-surgery	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Pediatrician - Post-PEBD	3.4	Gamma	0.260209	26	170.7315	0.019914	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Hepatologist - Post-PEBD	1	Gamma	0.076532	26	170.7315	0.005857	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Gastroenterologist - Post-PEBD	3	Gamma	0.549125	26	29.84694	0.100513	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Dietitian - Post-PEBD	3.8	Gamma	0.372621	26	104	0.036538	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Emergency medicine - Post-PEBD	2	Gamma	0.274563	26	53.06122	0.037692	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Orthopedist - Post-PEBD	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Physiotherapist - Post-PEBD	6	Gamma	0.459192	26	170.7315	0.035143	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Psychologist - Post-PEBD	10	Gamma	0.76532	26	170.7315	0.058571	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Speech and language therapist - Post-PEBD	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Endocrinologist - Post-PEBD	1	Gamma	0.076532	26	170.7315	0.005857	Burden of illness study, April 2021. HCD Data on file.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Mean number of visits - GP visit - Post-PEBD	5	Gamma	0.274563	26	331.6327	0.015077	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Nurse visit - Post-PEBD	4.2	Gamma	0.321434	26	170.7315	0.0246	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Stoma care - Post-PEBD	1	Gamma	0.076532	26	170.7315	0.005857	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Pediatrician - Post-LTx	3.8	Gamma	0.290822	10	170.7315	0.022257	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Hepatologist - Post-LTx	4.5	Gamma	0.664078	10	45.91837	0.098	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Gastroenterologist - Post-LTx	6	Gamma	1.802498	10	11.08033	0.5415	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Dietitian - Post-LTx	3.4	Gamma	0.56921	10	35.67901	0.095294	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Emergency medicine - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Orthopedist - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Physiotherapist - Post-LTx	6	Gamma	0.459192	10	170.7315	0.035143	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Psychologist - Post-LTx	5.3	Gamma	0.980306	10	29.22997	0.181321	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Speech and language therapist - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Endocrinologist - Post-LTx	1	Gamma	0.076532	10	170.7315	0.005857	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - GP visit - Post-LTx	4.7	Gamma	0.189737	10	613.6111	0.00766	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Nurse visit - Post-LTx	3.5	Gamma	0.267862	10	170.7315	0.0205	Burden of illness study, April 2021. HCD Data on file.
Mean number of visits - Stoma care - Post-LTx	0	Not varied					Burden of illness study, April 2021. HCD Data on file.

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Parameter	Value	Parameter distribution	se	n	α	β	Reference
Unit cost - Pediatrician	730.56	Gamma	55.91123		170.7315	4.278999	www.laeger.dk/sites/default/files/paediatri_takstkort_pr_040121_0.pdf: consultation 0120
Unit cost - Hepatologist	662.2	Gamma	50.6795		170.7315	3.878605	www.laeger.dk/sites/default/files/internmedicin_takstkort_pr_040121.pdf: consultation 0110 internal Medicin taskort
Unit cost - Gastroenterologist	662.2	Gamma	50.6795		170.7315	3.878605	www.laeger.dk/sites/default/files/internmedicin_takstkort_pr_040121.pdf: consultation 0110 internal Medicin taskort
Unit cost - Dietitian	534.2236	Gamma	40.88521		170.7315	3.129028	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Kliniske diætister average total pay 2020 (samlet løn) 454624.289500363 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Unit cost - Emergency medicine	1718.91	Gamma	131.5517		170.7315	10.06791	Converted from UK 2020 NICE PSSRU estimate £181 using OECD 2020 PPP exchange rate 6.597435 DKK/0.699569 GBP, inflated to 2021 based on 2020 inflation rate 1.007
Unit cost - Orthopedist	667.59	Gamma	51.09201		170.7315	3.910175	www.laeger.dk/sites/default/files/ortopaediskkirurgi_takstkort_pr_040121_1.pdf: consultation 0110 ortopaediskkiurgi taskort
Unit cost - Physiotherapist	532.5929	Gamma	40.76041		170.7315	3.119476	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Fysioterapeuter average total pay 2020 (samlet løn) 453236.549179268 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Unit cost - Psychologist	1548.8	Gamma	118.5328		170.7315	9.071554	www.laeger.dk/sites/default/files/boernepsykatri_takstkort_pr_040121.pdf: 0150 Behandlingsforløb med primært psykoterapeutisk behandlingssigte
Unit cost - Speech and language therapist	532.5929	Gamma	40.76041		170.7315	3.119476	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Fysioterapeuter average total pay 2020 (samlet løn)

Parameter	Value	Parameter distribution	se	n	α	β	Reference
							453236.549179268 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Unit cost - Endocrinologist	662.2	Gamma	50.6795		170.7315	3.878605	www.laeger.dk/sites/default/files/internmedicin_takstkort_pr_040121.pdf: consultation 0110 internal Medicin taskort
Unit cost - GP visit	146.79	Gamma	11.23414		170.7315	0.859771	https://www.laeger.dk/sites/default/files/honorartabel_01.04.2021.pdf
Unit cost - Nurse visit	591.0911	Gamma	45.2374		170.7315	3.462109	DMC Document Værdisætning af enhedsomkostninger Version 1.3 process: assumed as Nurse average total pay 2020 (samlet løn) 503018.52641154 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads)
Unit cost - Stoma care	14738.25	Gamma	1127.948		170.7315	86.32413	Reference: Buchanan et al. Managing the long term care of inflammatory bowel disease patients: The cost to European health care providers . Average of the cost of stoma care for ulcerative colitis and Crohn's disease, converted by PPP and inflated to 2021 DKK. (1002+1555 euros)/2 (2008 prices) converted by PPP to 2008 DKK (x7.944128 / 0.806152) and then inflated to 2021 DKK (x105.4 / 90.1)
Proportion of patients - Serum bilirubin	0.698	Beta	0.053419	43	30.014	12.986	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Serum bile acid	0.302	Beta	0.023113	43	12.986	30.014	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Complete blood count	0.674	Beta	0.051583	43	28.982	14.018	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - ALT	0.721	Beta	0.05518	43	31.003	11.997	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - AFP	0.256	Beta	0.019592	43	11.008	31.992	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - GGT	0.465	Beta	0.035587	43	19.995	23.005	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - AST	0.698	Beta	0.053419	43	30.014	12.986	Burden of illness study, April 2021. HCD Data on file.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Proportion of patients - PT	0.395	Beta	0.03023	43	16.985	26.015	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Glucose	0.372	Beta	0.02847	43	15.996	27.004	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Albumin	0.372	Beta	0.02847	43	15.996	27.004	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Vitamin A, E, D, K status	0.326	Beta	0.024949	43	14.018	28.982	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - TSH	0.163	Beta	0.012475	43	7.009	35.991	Burden of illness study, April 2021. HCD Data on file.
Proportion of patients - Ultrasound (abdominal)	0.372	Beta	0.02847	43	15.996	27.004	Burden of illness study, April 2021. HCD Data on file.
Unit cost - Serum bilirubin	24	Gamma	1.836768		170.7315	0.140572	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2294
Unit cost - Serum bile acid	24	Gamma	1.836768		170.7315	0.140572	assume as equal to glucose: No unit cost provided https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3682
Unit cost - Complete blood count	61	Gamma	4.668453		170.7315	0.357286	assume as (B-Haemoglobin https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2403, B - THROM; https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5438)
Unit cost - ALT	24	Gamma	1.836768		170.7315	0.140572	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3982
Unit cost - AFP	79	Gamma	6.046029		170.7315	0.462715	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5195
Unit cost - GGT	24	Gamma	1.836768		170.7315	0.140572	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3939
Unit cost - AST	24	Gamma	1.836768		170.7315	0.140572	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3994
Unit cost - PT	919	Gamma	70.33293		170.7315	5.382721	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5618
Unit cost - Glucose	24	Gamma	1.836768		170.7315	0.140572	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2380
Unit cost - Albumin	24	Gamma	1.836768		170.7315	0.140572	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3886

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Unit cost - Vitamin A, E, D, K status	596	Gamma	45.61308		170.7315	3.490861	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2944
Unit cost - TSH	79	Gamma	6.046029		170.7315	0.462715	https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=6769
Unit cost - Ultrasound (abdominal)	860.43	Gamma	65.85044		170.7315	5.039667	internmedicin_takstkort_pr_040121 specialist service service 2309 (gastroenterology)
Immunosuppression - azathioprine, daily dose month 0-3	1	Gamma	0.038266		682.926	0.001464	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - azathioprine, daily dose month 3-6	1	Gamma	0.038266		682.926	0.001464	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - azathioprine, daily dose month 6-9	1	Gamma	0.038266		682.926	0.001464	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - azathioprine, daily dose month 9-12	1	Gamma	0.038266		682.926	0.001464	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - azathioprine, daily dose month 12	1	Gamma	0.038266		682.926	0.001464	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Azathioprine, cost per pack	46	Gamma	3.520473		170.7315	0.269429	MEDICINPRISER.DK, 2 September 2021 (Azathioprin "Ratiopharm")
Azathioprine, pack size	100	Not varied					MEDICINPRISER.DK, 2 September 2021 (Azathioprin "Ratiopharm")
Azathioprine, mg per pack	50	Not varied					MEDICINPRISER.DK, 2 September 2021 (Azathioprin "Ratiopharm")
Immunosuppression - tacrolimus, daily dose month 0-3	0.12	Gamma	0.009184		170.7315	0.000703	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - tacrolimus, daily dose month 3-6	0.09	Gamma	0.006888		170.7315	0.000527	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.

Parameter	Value	Parameter distribution	se	n	α	β	Reference
Immunosuppression - tacrolimus, daily dose month 6-9	0.08	Gamma	0.006123		170.7315	0.000469	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - tacrolimus, daily dose month 9-12	0.07	Gamma	0.005357		170.7315	0.00041	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - tacrolimus, daily dose month 12	0.07	Gamma	0.005357		170.7315	0.00041	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Tacrolimus, cost per pack	856.04	Gamma	65.51447		170.7315	5.013955	MEDICINPRISER.DK, 2 September 2021 (Tacrimolus (Dailiport))
Tacrolimus, pack size	50	Not varied					MEDICINPRISER.DK, 2 September 2021 (Tacrimolus (Dailiport))
Tacrolimus, mg per pack	2	Not varied					MEDICINPRISER.DK, 2 September 2021 (Tacrimolus (Dailiport))
Immunosuppression - prednisolone, daily dose month 0-3	15	Gamma	1.14798		170.7315	0.087857	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - prednisolone, daily dose month 3-6	7.5	Gamma	0.57399		170.7315	0.043929	Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - prednisolone, daily dose month 6-9	0	Not varied					Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - prednisolone, daily dose month 9-12	0	Not varied					Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
Immunosuppression - prednisolone, daily dose month 12	0	Not varied					Assumed equivalent to TA348, Everolimus (Certican®) for preventing organ rejection in liver transplantation. 2014.
prednisolone, cost per pack	38.42	Gamma	2.94036		170.7315	0.225032	MEDICINPRISER.DK, 2 September 2021 (Prednisolon "DAK")

Parameter	Value	Parameter distribution	se	n	α	β	Reference
prednisolone, pack size	100	Not varied					MEDICINPRISER.DK, 2 September 2021 (Prednisolon "DAK")
prednisolone, mg per pack	5	Not varied					MEDICINPRISER.DK, 2 September 2021 (Prednisolon "DAK")
PEBD - cost of procedure	94133	Gamma	7204.19		171	551	DRG 2021, 06MP10: Større operationer på tyndtarm og tyktarm u. kompl. bidiag. 94133DKK
PEBD - cost of reoperation	94133	Gamma	7204.19		171	551	DRG 2021, 06MP10: Større operationer på tyndtarm og tyktarm u. kompl. bidiag. 94133DKK
PEBD - cost of treating infections	27594	Gamma	2111.825		170.7315	161.6222	Danish 2021 DRG tariffs Mand , 32 År (DT814I)Postoperativ intraabdominal infektion UNS, 18MA03 - Postoperative og posttraumatiske infektioner, u. kompl. Faktorer 2kontact days task 27594kr https://interaktivdrg.sundhedsdata.dk/
PEBD - cost of treating bowel prolapse	22789	Gamma	1744.088		170.7315	133.4786	Danish 2021 DRG tariffs Mand , 32 År (DK638E)Prolapsus coli06MA14 - Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år 2 kontact days 22.789 https://interaktivdrg.sundhedsdata.dk/
PEBD - % patients - procedure	1	Not varied					Assumption.
PEBD - % patients - reoperation	0.67	Beta	0.051276	22	14.74	7.26	Bjornland et al. Partial Biliary Diversion May Promote Long- Term Relief of Pruritus and Native Liver Survival in Children with Cholestatic Liver Diseases. 2020.
PEBD - % patients - infections	0.428571	Beta	0.032799	6	2.571429	3.428571	Bjornland et al. Partial Biliary Diversion May Promote Long- Term Relief of Pruritus and Native Liver Survival in Children with Cholestatic Liver Diseases. 2020.
PEBD - % patients - bowel prolapse	0.071429	Beta	0.005467	1	0.071429	0.928571	Bjornland et al. Partial Biliary Diversion May Promote Long- Term Relief of Pruritus and Native Liver Survival in Children with Cholestatic Liver Diseases. 2020.
Liver transplant - transplant phase cost	910271	Gamma	69664.88		170.7315	5331.594	Danish 2021 DRG tariffs, 26MP06 Levertransplantation
Liver transplant - 2-years post-transplant cost	93038.2	Gamma	7120.401		170.7315	544.9387	2016 Folkhalsomyndigheten (Swedish) report: Hepatit B-vaccination som ett särskilt vaccinationsprogram. 70000 1st year + 40000

Parameter	Value	Parameter distribution	se	n	α	β	Reference
							2nd year. Cost estimates converted from SEK to DKK and inflated to 2021 https://www.folkhalsomyndigheten.se/contentassets/9e8ec828b7d64d4c858a2aa590ebf7ba/hepatit-b-sarskilt-vaccinationsprogram-15112.pdf
LTx complications - cost of diarrhoea	5130	Gamma	392.6093		170.7315	30.04718	Danish 2021 DRG tariffs, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
LTx complications - cost of liver steatosis	30893	Not varied					Mand , 32 År (DK760A)Ikke-alkoholisk fedtdegeneration i leveren 07MA05 - Kronisk leversygdom uden komplikationer 2 kontact days task 30.893 https://interaktivdrg.sundhedsdata.dk/
LTx complications - cost of stunted growth	0	Not varied					Assumption.
LTx complications - cost of deafness	0	Not varied					Assumption.
LTx complications - cost of pancreatitis	2610	Gamma	9.623136		73561.02	0.035481	Danish 2021 DRG tariffs, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DK859: Akut pankreatitis UNS
Adverse event - cost of Diarrhoea	125.74	Gamma	9.623136		170.7315	0.736478	assumed as AIP package price of loperamid from https://medicinpriser.dk/Default.aspx?id=15&vnr=154521 60x2mg Orifarm Generics
Adverse event - cost of Vomiting	63.33	Gamma	4.846773		170.7315	0.370933	assumed as AIP package price of ondansetron https://medicinpriser.dk/Default.aspx?id=15&vnr=591441 10x4mg from 2care4
Adverse event - cost of Abdominal pain	0	Not varied					Assumption.
Adverse event - cost of Upper respiratory infection	16	Gamma	1.224512		170.7315	0.093714	assumed as AIP package price of amoxicilin from medicinpricer.dk

Parameter	Value	Parameter distribution	se	n	α	β	Reference
							https://medicinpriser.dk/Default.aspx?id=15&vnr=598949 30x500mg from Sandoz
Adverse event - cost of Nasopharyngitis	16	Gamma	1.224512		170.7315	0.093714	assumed as AIP package price of amoxicilin from medicinpricer.dk https://medicinpriser.dk/Default.aspx?id=15&vnr=598949 30x500mg from Sandoz
Adverse event - cost of Pyrexia	8.52	Gamma	0.652053		170.7315	0.049903	assumed as AIP package price of paracetemol from medicinpricer.dk https://medicinpriser.dk/Default.aspx?id=15&vnr=580984 20x500mg from Vitabalans
Hours of travel time and healthcare visit	2	Gamma	0.153064		170.7315	0.011714	Assumption.

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24. Appendix K – European Public Assessment Report (EPAR)

bylvay-epar-public-assessment-report_e

25. Appendix L – Main characteristics of phase 2 safety and efficacy study A4250-003

Table 115. Main characteristics of A4250-003

Trial name: A4250-003: An Exploratory Phase II Study to Demonstrate the Safety and Efficacy of A4250 in Children with Cholestatic Pruritus	**NCT number: NCT02630875**
Objective	Primary: The primary aims of this Phase II exploratory study in patients treated with A4250 due to cholestasis induced pruritus are to: • Assess the safety and tolerability of A4250, orally administered first as a single dose and then during a four week treatment period, as determined by the occurrence of treatment-emergent SAEs • Explore changes in serum total bile acids after a four week treatment period Secondary: Secondary safety objectives of this study included assessment of the safety and tolerability of A4250 first as a single administration and then during a 4-week treatment period, as determined by the occurrence of treatment-emergent adverse events (TEAEs) and changes in safety parameters including laboratory tests and vital signs. Secondary efficacy objectives of this study were to: • Demonstrate the efficacy of A4250, orally administered during a 4-week treatment period, on liver biochemistry variables and on pruritus parameters

	• Evaluate the pharmacokinetic (PK) properties of A4250 orally administered first as a single dose and then after a 4-week treatment period • Evaluate changes in visual analogue scale (VAS)-itch score after a 4-week treatment period
Publications – title, author, journal, year	Baumann U, Sturm E, Lacaille F, Gonzalès E, Arnell H, Fischler B, Jørgensen MH, Thompson RJ, Mattsson JP, Ekelund M, Lindström E, Gillberg PG, Torfgård K, Soni PN. Effects of odevixibat on pruritus and bile acids in children with cholestatic liver disease: Phase 2 study. Clin Res Hepatol Gastroenterol. 2021 Sep;45(5):101751. doi: 10.1016/j.clinre.2021.101751. Epub 2021 Jun 26. PMID: 34182185. Slavetinsky C, Sturm E. Odevixibat and partial external biliary diversion showed equal improvement of cholestasis in a patient with progressive familial intrahepatic cholestasis. BMJ Case Rep. 2020 Jun 29;13(6):e234185. doi: 10.1136/bcr-2019-234185. PMID: 32601135; PMCID: PMC7326258.
Study type and design	This was a Phase II single and multiple dosing open-label study of A4250 to evaluate the safety and efficacy of A4250 when administered for 4 weeks in up to 24 pediatric patients diagnosed with cholestatic pruritus. Eligible patients made 6 site visits, beginning with screening (Visit 1) and baseline recording of symptoms in a diary. During Visit 2, a single dose was administered, and patients remained in hospital for at least 8 hours. During Visit 2, samples for PK analyses were obtained before first dose and 1, 2, 4, and 8 hours after dose administration. A follow-up visit (Visit 3) was made to evaluate any change in symptoms and suitability for participation in a 4-week treatment period. Visit 4 was the start of 4-week daily dosing, with the same dose as during the single dosing. Visit 5 was the End of Treatment visit with efficacy and safety evaluation. During Visit 5, one PK sample was obtained prior to the administration of the last dose of study drug. The follow-up visit (Visit 6) was performed within 14 days after last dose of study medication, whether the patient completed the study or discontinued prematurely. The study was conducted at 6 active sites and included 5 dose cohorts, with 4 or 6 patients in each cohort. Patients were permitted to re-enroll into a later cohort after completion and a washout period following treatment in their first cohort. The study was originally designed to evaluate doses up to 0.3 mg/kg/day; however, dose escalation over 0.2 mg/kg/day was not performed based on the recommendation of the Data and Safety Monitoring Board (DSMB).
Sample size (n)	n=24
Main inclusion and exclusion criteria	The study population was children with cholestatic pruritus. The patients were between 1-17 years of age. The inclusion criteria for study participation eligibility were as follows: • Diagnosis of pruritus due to chronic cholestasis based on history and Investigator judgment

	• This included but was not restricted to patients with progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome (ALGS), biliary atresia and sclerosing cholangitis • Laboratory markers of cholestasis identified within 3 months before Visit 1 • Total serum bile acids at least 2 times above upper limit of normal (ULN) • A VAS-itch of at least 3 (average of 7 days) on a 0-10 grade VAS at Visit 2 • The caretaker(s)/patient reported having understood and signed the informed consent form (ICF) and was willing to comply with all study visits and assessments • The patient was a male or non-pregnant female ≥12 months of age and <18 years of age with a body weight exceeding 7 kg The exclusion criteria for study participation eligibility were as follows: • Any condition that in the opinion of the Investigator constituted a risk for the patient or a contraindication for participation and completion of the study, or could interfere with study objectives, conduct, or evaluations • Clinical or biochemical signs of decompensated liver disease (such as ascites) • Liver transplantation • Structural abnormality of the gastrointestinal (GI) tract (biliary diversion procedures accepted) • Known, active, clinically significant acute or chronic infection, or 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 • A history of cancer with last date of proven disease activity/presence of malignancy within 5 years, except for adequately treated basal cell carcinoma of the skin, cervical dysplasia, or carcinoma in situ of the skin or the cervix • Other reason for pruritus than chronic cholestasis such as treatment refractory atopic dermatitis, other primary skin diseases, etc. • Treatment with bile acid sequestrants (cholestyramine, colesevelam, colestipol, or similar) during the screening period • Chronic kidney disease with an impaired renal function and a glomerular filtration rate (GFR) <70 mL/min/1.73 m2 • Active substance abuse in the year before screening • A history of a psychiatric disorder requiring hospitalization or suicide attempt in the 2 years prior to screening • Participation in any investigational clinical study, with the exception of the low doses of this study, within 30 days prior to screening, or plans to participate in another clinical study during this study

	• Ongoing pregnancy, breast-feeding, or lactation
Intervention	The following A4250 dose levels in mg/kg/day were evaluated in 5 dose cohorts, each including 4 or 6 patients: Cohort 1: 0.01, n=4 Cohort 2: 0.03, n=6 Cohort 3: 0.06, n=4 Cohort 4: 0.1, n=6 Cohort 5: 0.2, n=4 Each patient received: 1. One single dose, followed by at least a 14-day washout 2. Daily dosing for 4 weeks
Comparator(s)	none
Follow-up time	4 week treatment period
Is the study used in the health economic model?	No.
Primary, secondary and exploratory endpoints	Efficacy: Study baseline was defined as the last assessment prior to administration of the single dose at Visit 2. Study baseline for diary endpoints was defined as diary recordings corresponding to the last 7 days prior to the administration of the single dose at Visit 2. Secondary efficacy assessments of pruritus and sleep-related endpoints were based upon patients' reports through the paper diary of the following questionnaires: VAS-itch, patient-oriented scoring atopic dermatitis (PO-SCORAD)-itching, and Whitington and PO-SCORAD-sleep disturbance scales. Additional secondary efficacy assessments included liver biochemistry evaluation (alanine aminotransferase [ALT]), asparagine aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma glutamyl transferase [GGT]).

	PK samples were obtained at single-dose administration and at the end of treatment period (Visit 5). During Visit 2 (single-dose administration), samples for PK analyses were obtained before first dose and 1, 2, 4, and 8 hours after dose administration. During Visit 5, one PK sample was obtained prior to the administration of the last dose of study drug. Safety: Safety assessments included adverse events (AEs) assessments, clinical laboratory tests, vital signs assessments, physical examinations, concomitant medications assessments, and patient diary assessments about diarrhea, including the Bristol Stool Frequency Scale (BSFS), and symptom assessment.
Method of analysis	In general, descriptive statistics were presented for all efficacy variables and endpoints, PK parameters and safety variables, as appropriate. Continuous variables including change from baseline were summarized by descriptive statistics (sample size [n], mean, standard deviation [StDev], minimum, first quartile, median, third quartile, and maximum value). Percent change from baseline was presented in addition to absolute change from baseline for some variables, as appropriate. Categorical data were summarized in frequency tables showing number of subjects and frequency and percentage of occurrence. Individual data (raw data and derived variables) were presented in subject listings.
Subgroup analyses	None
Other relevant information	None

26. Appendix M – Patient- and observer-reported outcome measures for pruritus

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©; Figure 38) instruments for the paediatric cholestatic liver disease population to assess itching, scratching, and sleep disturbance [91] [92]. 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 [93] [94] [95]. 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 small sample size (n=9). However, the results may be unstable due to the small sample and should be interpreted with caution.

Figure 38. Validated PRUCISION (ObsRO) instrument - summary

- Patients' scratching was recorded by an observer twice daily using an eDiary o The PRUCISION scale ranges from 0 to 4
- Higher scores indicate worse symptoms
- The PRUCISION instrument was validated via blinded psychometric analyses conducted by an independent group o Test-retest reliability, construct validity, and sensitivity to change were assessed o Based on comparison to patient-, caregiver-, and clinician-reported Global Impression of Change and Global Impression of Symptom ratings, a ≥1-point decrease in ObsRO score was determined to be clinically meaningful

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 39). Items on the ObsRO consisted of 9-item questionnaire with a mix of response formats including binary (i.e. no, yes), rating scales (e.g. 0 = no scratching 1 = a little scratching, 2 = medium scratching, 3 = a lot of scratching, 4 = worst possible scratching), and numeric (i.e. 0-99). 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 40). Items on the PRO consisted of 7item questionnaires with a mix of response formats including binary (i.e. no, yes) and rating scales (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.

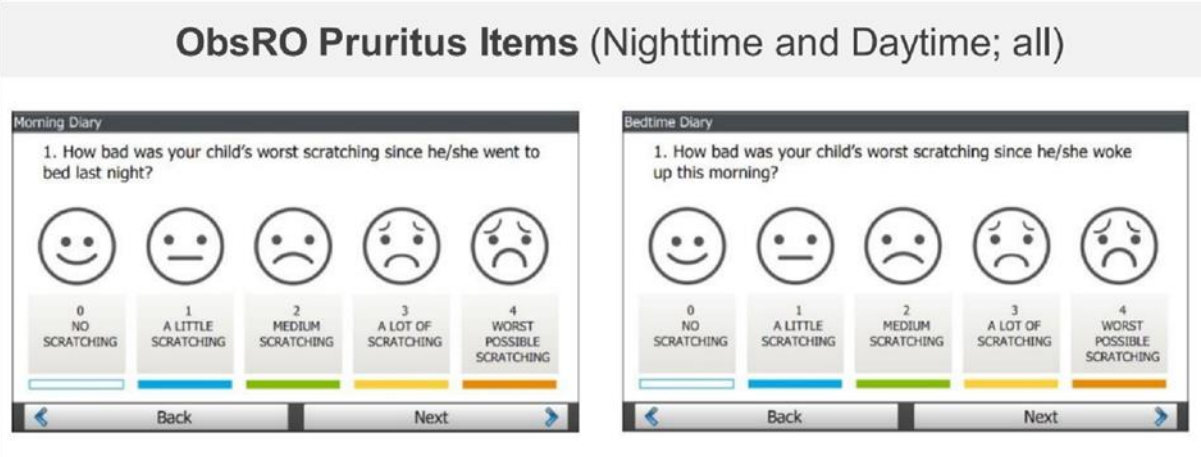
The measurement characteristics of the ObsRO pruritus measure have been established. The measure is reliable, valid, and sensitive to change. Thresholds for meaningful change from Baseline to Week 24 have been established:

- 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 regardless of baseline pruritus score (i.e. across the scale). This is based on the fact that it was established during development of the instruments that patients and caregivers interpreted the response scales as intended – this included confirmation that the response options were distinguishable. For example, it was demonstrated that patients could sort the response scale faces into the appropriate order, which indicated that they perceived the differences between the options and understood how each reflected a different level of severity [96].

Therefore, the developed ObsRO instrument is fit for purpose in evaluating pruritus among paediatric patients with PFIC in the PEDFIC1 study. Despite the small sample size, supportive evidence was also obtained for the PRO pruritus measure. The measures may also be used in other cholestatic liver disease areas, such as Alagille syndrome, because patients from these other, related paediatric populations were included in the initial development of the PRO and ObsRO items.

Figure 39. Albireo ObsRo instrument (PRUCISION©)



ObsRO Morning Diary:

How bad was your child's worst scratching since he/she went to bed last night?

Since your child went to bed last night, did you see blood due to scratching?

Did your child need a caregiver to help him/her fall asleep last night due to his/her itching?

Did your child need a caregiver to soothe him/her at some time during the night last night due to his/her itching?

Did your child need a caregiver to sleep with him/her at some time during the night last night due to his/her itching?

How many times did you notice that your child woke up last night?

Did your child take any prescribed or over-the-counter medicines before going to bed last night that may have made him/her sleepy?

ObsRO Evening Diary:

How bad was your child's worst scratching since he/she woke up this morning?

How tired did your child seem to be today?

Figure 40. 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?	

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