20 May 2021
EMA/319560/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bylvay

International non-proprietary name: odevixibat

Procedure No. EMEA/H/C/004691/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARUP	Associated Regional and University Pathologists, Inc.
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
BMI	Body mass index
BRIC	Benign recurrent intrahepatic cholestasis
BSEP	Bile salt export pump
C4	7ά-hydroxy-4-cholesten-3-one
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum plasma concentration
CMH	Cochran Mantel Haenszel
COA	Clinical Outcomes Assessments (instrument)
CPP	Critical process parameter
CQA	Critical quality attribute
CSR	Clinical Study Report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DoE	Design of experiments
DSC	Differential scanning calorimetry
DSMB	Data Safety Monitoring Board
DVS	Dynamic vapour sorption
EAIR	Exposure-adjusted incidence rates
EC	European Commission

Abbreviation	Definition
ECG	Electrocardiograms
ED50/90/95	Effective dose with 50% / 90% / 95% inhibition
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENPP - 2	ectonucleotide pyrophosphatase/phosphodiesterase 2
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF19	Fibroblast growth factor 19
FIC1	Familial intrahepatic cholestasis-1
FT-IR	Fourrier transform infrared spectroscopy
GC	Gas chromatography
GC-HS	Gas chromatography headspace
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIC	Global Impression of Change (instrument)
GIS	Global Impression of Symptoms (instrument)
GMP	Good manufacturing practice
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
IBAT	Ileal bile acid transporter
ICH	International Council for Harmonisation
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma - mass spectrometry
INR	International normalized ratio
IPC	In-process control
IR	Infrared
ISE	Integrated Summary of Efficacy
KF	Karl Fischer titration
LALLS	Low angle laser light scattering

Abbreviation	Definition
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LDPE	Low density polyethylene
LFT	Liver function test
LoQ	Limit of Quantitation
LS	Least square
MAA	Marketing Authorisation Application
MAD	Multiple ascending dose (study)
MAH	Marketing authorisation holder
MATE	Multidrug and toxin extrusion
MCC	Microcrystalline cellulose
MDR3	Multidrug resistance 3 protein
MedDRA	Medical Dictionary for Regulatory Activities
NAPPED	NAtural course and Prognosis of PFIC and Effect of biliary Diversion
NDA	New Drug Application
NDMA	N-Nitrosodimethylamine
NMBA	N-Nitroso-N-methyl-4-aminobutanoic acid
NMR	Nuclear magnetic resonance
NOS	Not otherwise specified
OAT	Organic anion transporter
ObsRO	Observer Reported Outcome (instrument)
OOS	Out of specification
PD	Pharmacodynamics
PDE	Permitted daily exposure
PEBD	Partial external biliary diversion
PELD	Paediatric End-Stage Liver Disease
PFIC	Progressive familial intrahepatic cholestasis
PFIC1, PFIC2, and PFIC3	Progressive familial intrahepatic cholestasis subtypes
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PP	Process parameter

Abbreviation	Definition
PRO	Patient Reported Outcomes
PT	Preferred term
QbD	Quality by design
QC	Quality control
QD	Once daily
QoL	Quality of life
QTPP	Quality target product profile
RH	Relative humidity
RoW	Rest of the world
SAD	Single ascending dose (study)
SAE	Serious adverse event
SAP	Statistical analysis plan
SBAs	Serum bile acids
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
SMQs	Standardise MedDRA Queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
TGA	Thermogravimetric analysis
UDCA	Ursodeoxycholic acid
UK	United Kingdom
ULN	Upper limit of normal
UPLC	ultra-high performance liquid chromatography
US	United States
UV	Ultraviolet
V/F	Volume of distribution
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Albireo submitted on 6 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Bylvay, through the centralised procedure under Article 3 (1) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2016.

Bylvay, was designated as an orphan medicinal product EU/3/12/1028 on 2012-07-17 in the following condition: Treatment of progressive familial intrahepatic cholestasis.

Bylvay was granted eligibility to PRIME on 13 October 2016 in the following indication: Treatment of Progressive Familial Intrahepatic Cholestasis.

Eligibility to PRIME was granted at the time in view of the following:

- Progressive Familial Intrahepatic Cholestasis (PFIC) has a dramatic disease course with only 1 in 2 patients surviving their 10 year and a maximum life expectancy of around 20 years without surgical relief or liver transplant.
- The currently available treatment options are insufficient. The unmet medical need can be agreed.
- The applicant has produced some non-clinical data supporting the mode of action and providing some indication of activity of the product for the use in humans. Clinical data, so far, suggests an acceptable safety profile. The clinical data, however, cannot be considered overwhelmingly convincing to support the notion of a highly efficacious product for the treatment of PFIC. Despite the ability of the product to reduce serum bile acid levels, there appears to be no information at the time of PRIME designation on positive influence on growth, decrease of the need for surgery or time to surgery, time to cirrhosis and other clinically relevant outcome parameters.
- In principle, with no long-term clinical data available yet, results from non-clinical investigations could be taken into account to allow inclusion into the PRIME scheme by early entry. To better support this there should be a reasonable expectation that this early data will be complemented by clinical proof of concept results. In this specific case, the non-clinical data presented comes from 2 models of which one could be considered to more closely resemble the clinical setting. Some evidence is being presented that would indicate benefit with regard to liver histology, liver biochemistry and serum bile acid levels. The product's activity is supported by this non-clinical data. In addition, the applicant does already present early clinical data supportive of the mode of action of the product. Taken together, this non-clinical and early clinical data could support inclusion of the product into the PRIME at the proof of principle stage.

Furthermore, progress to proof of concept and confirmation of eligibility to the PRIME scheme were agreed on 13 October 2017 in view of the following:

- The high unmet medical need for effective treatments for Progressive Familial Intrahepatic Cholestasis has been adequately supported and is agreed.
- A4250 is a selective inhibitor of ileal sodium-dependent bile acid transporter (IBAT). It acts locally in the gut blocking reabsorption of bile acids and consecutively reducing systemic bile acid levels. The product could represent a valuable option for the treatment of PFIC.
- Data from the completed open-label paediatric study 003 support short-term activity in terms of reduction of serum bile acid levels and pruritus control; data from the study and the presented

systematic literature review of PFIC patients treated with biliary diversion surgery suggest a correlation between serum bile acid levels and short and long-term outcomes and can be regarded as valid proof of concept.

- Clinical data to date suggest an acceptable safety profile; data from higher dose groups showed few cases of increased liver enzymes and/or bilirubin; this potential safety signal will have to be investigated thoroughly and will have to be put into perspective with a view to the differing pathophysiology between PFIC subtypes/mutations.

The applicant applied for the following indication: Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Bylvay as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Bylvay

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0377/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product in a condition related to the proposed indication.

Applicant's requests for consideration

Marketing authorisation under exceptional circumstances and Accelerated assessment

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

The CHMP agreed on 12 November 2020 to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on promising results shown by the submitted clinical data. The efficacy results for PFIC1 and PFIC2 patients seem to be in line with results obtained after surgical intervention (NAPPED study), showing resolution of pruritis and reduction of the circulating bile acid pool. Although only a limited number of patients are included in the clinical studies – which is not uncommon in orphan diseases – the data seem sufficient to make a benefit/risk assessment. The ultimate goal in treating PFIC patients with odevixibat is a long-term transplant-free or surgical biliary diversion free period.

New active substance status

The applicant requested the active substance odevixibat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

PRIME support

Upon granting of eligibility to PRIME, Johann Lodewijk Hillege was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 23 April 2018. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

Use of ObsRO/PRO in study A4250-005 and the related analysis plan including long-term liver assessment, handling of missing data using mixed model repeated measurement (MMRM), follow-up of patients after exiting the extension study and maintenance of ODD.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference
19 December 2013	EMEA/H/SA/2645/2/2013/PA/PED/SME/III
18 May 2017	EMEA/H/SA/2645/3/2017/PA/PED/SME/PR/III
14 September 2017	EMEA/H/SA/2645/4/2017/PA/SME/PR/I
15 November 2018	EMEA/H/SA/2645/5/2018/PA/PED/SME/PR/II

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Starting materials for the drug substance.

- Adequacy of the nonclinical programme support further clinical development and a MAA.
- Design of an exploratory dose selection Phase II study, including population, doses and endpoints.

  Design of a placebo-controlled Phase III study to evaluate the efficacy and safety of 2 dose levels of A4250 after 12 weeks (A4250-005) followed by an open-label extension study to evaluate long-term outcomes (A4250-008), including population, duration and endpoints. Specific issues discussed included reduction of serum bile acids as primary endpoint and its correlation with clinical endpoints, e.g. need for surgery, acceleration of growth, liver histology, and time to cirrhosis or liver transplantation and death; secondary endpoints including pruritus, sleep performance and QoL; concomitant medications; assessment of liver fibrosis. Development and validation of a PRO/ObsRO for pruritus. Acceptability of a single pivotal study and the statistical analyses in support of MAA. The possibility to base an initial MAA on study A4250-005, and that study A4250-008 is submitted as a post-marketing obligation.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	6 November 2020
Accelerated Assessment procedure was agreed-upon by CHMP on	12 November 2020
The procedure started on	26 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	26 January 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	26 January 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	09 April 2021
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 April 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	20 April 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 April 2021

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 May 2021
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 May 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bylvay on	20 May 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication claimed for Odevixibat is for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

2.1.2. Epidemiology

PFIC is a rare disease estimated to affect between one in every 50,000 to 100,000 children born worldwide [Davit-Spraul 2009]. Based on a recent literature review of PFIC conducted by Baker and colleagues [Baker 2019], including publications that described European and worldwide populations, the prevalence of PFIC in Europe was estimated at 0.07/10,000 persons. Given a population of 520 million [Eurostat 2020], this would correspond to a total number of patients with PFIC of somewhere between 4000 and 5000 patients in the European Economic Association.

Both sexes seem to be equally affected. PFIC represents 10% to 15% of cases of cholestasis in children and 10% to 15% of liver transplantation indications in children.

2.1.3. Aetiology and pathogenesis

Entero-hepatic circulation

Bile acids are synthesized from cholesterol in the liver, excreted with bile into the duodenum, almost completely taken up again in the distal ileum and finally returned to the liver with portal blood in a process termed enterohepatic circulation.

Bile acid synthesis, excretion, and reuptake are tightly regulated. The apical sodium-dependent bile acid transporter [ASBT; also known as ileal bile acid transporter (IBAT) and SLC10A2] is pivotal for the almost complete reabsorption of conjugated bile acids (e.g. 95%) in the ileum. Pharmacological IBAT inhibition results in an increased bile acid load in the colon and subsequently, a lower bile acid pool associated with improved liver histology in animal models of cholestatic liver disease and non-alcoholic steatohepatitis (NASH).

The disease

PFIC is generally categorised into 3 main subtypes, PFIC1, PFIC2, and PFIC3, although at least 3 other subtypes have been described in the literature (PFIC4-6) [Gunaydin 2018; Jacquemin 2000; Mehl 2016; Srivastava 2014]. PFIC1 and PFIC2 together represent approximately two-thirds of cases of PFIC, and PFIC3, approximately one-third [Davit-Spraul 2009].

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).

BSEP3 (or truncated BSEP) are mutations that are predicted to have a non-functional protein are have the most severe disease form of PFIC2 (e.g. lowest native liver survival, hepatocellular carcinoma) [Wessel et al. 2020].

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.

Mutations in genes TJP2, NR1H4, or MYO5B have also been proposed as causes of PFIC [Henkel 2019]. In addition, some patients with PFIC do not have a mutation in any of these genes. In these cases, the cause of the condition is unknown [Goldberg 2020].

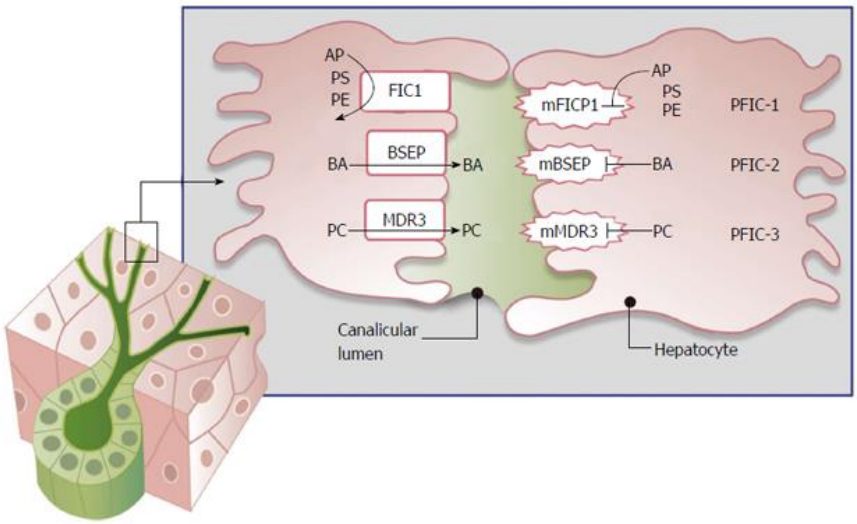


Figure 1: Disruption of bile flow and progressive familial intrahepatic cholestasis.

AP: Aminophospholipids; PS: Phosphatidylserine; PE: Phosphatidylethinolamine; BA: Bile acids; PC: Phosphatidylcholine; FIC1: Familial intrahepatic cholestasis protein 1; BSEP: Bile salt exporter pump; MDR3: Multidrug resistance protein 3; mFIC1: Mutant familial intrahepatic cholestasis protein 1; mBSEP: Mutant bile salt exporter pump; mMDR3: Mutant multidrug resistance protein; PFIC: Progressive familial intrahepatic cholestasis (adapted from Mehl et al., 2016).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

PFIC considers a heterogeneous group of autosomal recessive genetic diseases, all of which result in intra-hepatic cholestasis with impaired bile acid secretion and transport [Alissa 2008; Bull 2018b] resulting in an accumulation of the components of bile within the liver, including bilirubin and bile acids. As hepatic levels of these components increase, they are excreted into the systemic circulation leading to jaundice and severe pruritus [Gunaydin 2018]. Due to the hepatic damage, the condition ultimately leads to portal hypertension, liver failure, cirrhosis, and hepatocellular carcinoma [Hori 2010].

Severe pruritus is common in children diagnosed with PFIC. Significant pruritus can lead to severe cutaneous mutilation (often drawing blood), loss of sleep, irritability, poor attention, and impaired school performance [Mehl 2016].

The age of presentation varies by PFIC subtype, but typically the disease occurs in infancy and early childhood. Symptoms develop early with a median age at onset of approximately 3 months; 78% of patients develop jaundice before 12 months of age [Pawlikowska 2010].

The diagnosis of PFIC is confirmed and the subtype identified by genetic analysis [Bull 2018b]. Portal hypertension and decompensation may be evident in the first year of life in PFIC2 and in early childhood in PFIC1 [Davit-Spraul 2009; Srivastava 2014]. Other features include fat malabsorption resulting in weight and height below normal centiles, and fat-soluble vitamin (A, D, E, and K) deficiency.

Review of the literature indicates that histological findings in liver tissue obtained by biopsy in patients with PFIC vary depending upon the subtype, but for all subtypes, the findings progress from cholestasis to fibrosis to cirrhosis as was initially described by Alonso and colleagues [Alonso 1994]. The rate of progression varies by subtype and reflects the general rate of progression of clinical symptomatology. Patients with PFIC Type 2 cirrhosis have been identified as early as 6 months of age and most patients rapidly progress cirrhosis [Morotti 2011]. Patients with PFIC Type 1 typically demonstrate a slower progression; however, micronodular cirrhosis has been described in the second and third year of life. Progression to cirrhosis is typically even slower in patients with PFIC Type 3, where cirrhosis is usually first identified in the second decade of life [Morotti 2011].

The prognosis is poor; many PFIC patients progress to end-stage liver disease and require liver transplantation [Mehl 2016].

The main features of the major PFIC subtypes are summarized in Table 1 and an overview of common complications and manifestations of PFIC are summarised in Table 1.

Table 1: Main Features of PFIC1, PFIC2, and PFIC3.

FEATURE	PFIC1	PFIC2	PFIC3
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
Course of disease	Moderately severe	Very severe	Insidious
Pruritus	Severe	Very severe	Moderate
Extrahepatic features	Present	Absent	Absent
Risk of development of liver tumours	Not reported	High	Low
Serum ALT	Mild elevation	Moderate elevation	Mild elevation
Serum GGT	Normal	Normal	Elevated
Serum bile acids	Raised++	Raised +++	Raised +

Adapted from [Srivastava 2014]

Table 2: **Complications and Manifestations of Progressive Familial Intrahepatic Cholestasis.**

Complications	Manifestations
• Hepatocellular carcinoma • Significantly elevated serum bile acid levels • Jaundice with hepatomegaly and/or splenomegaly • Clinically significantly abnormal hepatic biochemical parameters • Liver decompensation • Liver cirrhosis and end-stage liver disease • Severe pruritus: severe cutaneous mutilation (often drawing blood), loss of sleep, irritability, poor attention, and impaired school performance	• Diarrhoea • Poor growth and failure to thrive • Coagulopathy • Prone to infections • Pancreatitis • Fat malabsorption with fat-soluble vitamin deficiencies and poor growth • Vitamin A: tiredness, weight loss, hair loss • Vitamin D: rickets • Vitamin E: neuropathy • Vitamin K: bleeding (e.g. cerebral, gastrointestinal, severe and recurrent epistaxis)

*Source: [*Davit-Spraul 2010*;* Henriksen 1981*;* Hori 2011*;* Nielsen 2004*;* Schukfeh 2012*;* Whitington 1994*].*

2.1.5. Management

There is currently no pharmaceutical treatment approved for use in PFIC1 and PFIC2. The therapeutic choices are restricted to supportive care such as nutritional support, prevention of vitamin deficiencies, and symptomatic treatment of extrahepatic features, including pruritus. Medical treatment options include off-label use of ursodeoxycholic acid (UDCA), rifampicin, hydroxyzine, antihistamines, and naltrexone, but none of these therapies have proven benefits for the long-term prognosis of patients with PFIC [European Association for the Study of the Liver 2009; Hori 2010]. A minority of patients respond nominally and transiently to these interventions [Hori 2010].

In France, UDCA is approved for the treatment of PFIC3, but not for PFIC1 and PFIC2. UDCA has been shown to improve symptoms and hepatic biochemical parameters in up to 50% of patients with PFIC3, yet limited effects of off-label use have been reported in patients with PFIC1 and PFIC2 [Baker 2019; European Association for the Study of the Liver 2009]. The ability of UDCA to mitigate liver damage has not been evaluated in controlled trials in patients with PFIC1, PFIC2, or PFIC3.

Rifampicin, an antibiotic, inhibits bile acid uptake into hepatocytes. The mechanism of its effect on pruritus is unknown [Galeazzi 1980; Ghent 1988] but may include alterations of intestinal flora leading to changes in the secondary bile acid pool [Kriegermeier 2020].

As symptomatic medical treatment is rarely effective, surgical options are considered, including biliary diversion (such as partial external biliary diversion [PEBD] or ileal exclusion) and liver transplantation. Treatment-resistant pruritus is the leading indication for surgical biliary diversion, particularly in patients with PFIC2 where it is listed as an indication for surgery in 89% of patients [van Wessel

2019b]. Surgical biliary diversion often results in rapid and dramatic reductions in serum bile acids and pruritus, as well as improvements in sleep disturbance and, in the long term, it is associated with less fibrosis and a catch-up in linear growth over 1 to 2 years [Arnell 2010; Melter 2000; Schukfeh 2012; Yang 2009]. The beneficial impact of surgical biliary diversion on long-term native liver survival has recently been shown to correlate with reducing serum bile acids observed following the surgery [van Wessel 2019a; van Wessel 2020]. For many patients, biliary diversion is not a permanent solution due to refractory pruritus or end-stage liver disease [Baker 2019; Bull 2018a]. Continued elevated serum bile acids and pruritus are also seen in some patients after biliary diversion surgery.

While biliary diversion surgery may postpone or eliminate the need for liver transplantation and improve pruritus associated with PFIC in some patients, it is an invasive procedure with unwanted consequences. Patients experience complications related to the external stoma requiring surgical revision and biliary diversion, leading to postoperative cholangitis [Gunaydin 2018]. High rates of clinically significant dehydration and hyponatremia have also been reported after biliary diversion surgery [Mehl 2016].

Liver transplantation will, however, rarely be avoided despite biliary diversion. Liver transplantation is considered when patients have end-stage liver disease, hepatocellular carcinoma, have failed off-label medical treatment and/or biliary diversion surgery and refractory pruritus results in poor QoL. Reported rates of liver transplantation range between 40 to 100% in patients with PFIC1 and PFIC2 [Baker 2019]. A recent large case series reported that 30% of a cohort of patients with PFIC2 underwent liver transplant a median of 2.4 years after surgical biliary diversion and by 18 years of age only 32% of patients with PFIC2 were alive with native liver [van Wessel 2020]. This underscores how common liver transplantation is in this disease.

Although liver transplantation may resolve cholestasis in patients with PFIC1 and PFIC2, the overall outcome remains unsatisfactory in many patients with PFIC1; this is mainly due to extrahepatic manifestations, organ rejection, and the complications and the risks associated with chronic immune-suppressant therapy [Baker 2019; Bull 2018a]. Specific to PFIC1, an undesired effect of liver transplant is worsening of the extrahepatic manifestations, such as diarrhoea and short stature. The increase in bile acid secretion in the stool post-transplant causes high-volume osmotic diarrhoea that has a significant impact on QoL [Mehl 2016]. High-volume osmotic diarrhoea is often associated with severe liver steatosis and/or steatohepatitis that may lead to cirrhosis and re-transplantation [Davit-Spraul 2009].

Survival in patients with PFIC not undergoing surgical biliary diversion or liver transplant is 50% at 10 years of age and <10% at 20 years of age, highlighting the rapid rate of progression of this life-threatening disease [Pawlikowska 2010].

In summary, PFIC is a life-threatening disease associated with significant morbidity. There is a high unmet need for these patients whose treatment options are limited and restricted to surgical intervention and off-label symptomatic medical therapies. A treatment option that reduces pruritus would not only provide much needed symptomatic relief, but if that reduction in pruritus reduces the need for biliary diversion surgery or liver transplantation, would also be disease-modifying.

About the product

Odevixibat (A4250) is a small molecule that acts as a potent, selective inhibitor of the IBAT, alternatively known as the ASBT. Odevixibat is being developed for the treatment of cholestatic liver diseases.

IBAT is a luminal epithelium glycoprotein expressed mainly in the distal ileum that co-transports sodium and bile acids, efficiently moving bile acids from the lumen of the small intestine across the apical brush border membrane. As part of enterohepatic circulation, bile acids are then shuttled to the basolateral membrane, ultimately returning to the liver via portal venous blood. While minimal passive reabsorption of bile acids occurs throughout the intestine, active transport via IBAT is the major mechanism for bile acid reabsorption. Over 95% of the circulating bile acid pool is returned to the liver on a daily basis [Hofmann 2009; Miethke 2016]. Therefore, IBAT is a key regulator of the bile acid pool and a key element in enterohepatic circulation [Dawson 2003].

Odevixibat is orally administered and acts locally in the gut where it binds reversibly to IBAT to decrease the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acids (Figure 2). Odevixibat has minimal systemic exposure at therapeutic dose ranges. 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.

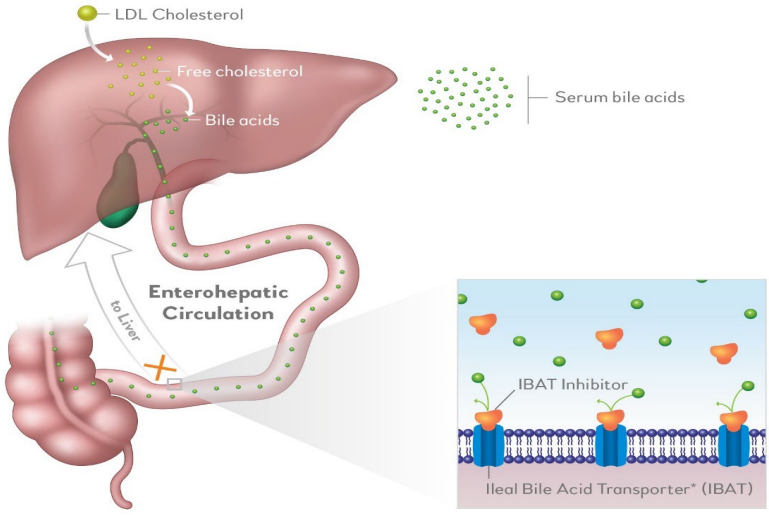


Figure 2: Role of IBAT in the Enterohepatic Circulation of Bile Acids.

IBAT: ileal bile acid transporter; LD: low-density lipoprotein.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on promising results shown by the submitted clinical data. The efficacy results for PFIC1 and PFIC2 patients seemed to be in line with results obtained after surgical intervention (NAPPED study), showing resolution of pruritis and reduction of the circulating bile acid pool. Although only a limited number of patients are included in the clinical studies – which is not uncommon in orphan diseases – the data were sufficient to allow for evaluation of the benefit/risk of odevixibat under an accelerated timetable.

The applicant requested consideration of its application for a Marketing Authorisation (MA) under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation based on applicant's claim that the applicant is not able to provide comprehensive data on the efficacy and safety under normal conditions of use.

Referring to Part II.6 of Annex I of Directive 2001/83/EC, the applicant submitted the following justification for this request:

- ***The indications for which the product is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or***

PFIC is a rare disease estimated to affect one in every 50,000 to 100,000 children born worldwide. The Applicant has conducted a randomized, placebo-controlled trial in this rare indication. The study met both regional (EU and FDA) primary efficacy endpoints. Based on review of the pooled data across the two Phase 3 studies (A4250-005 and A4250-008) the improvements in serum bile acids levels and pruritus severity were maintained for up to 96 weeks. Evidence from literature was provided to show that the demonstrated treatment effect can be translated into improved long-term (about 10 years) liver survival. The literature data discussing serum bile acids were provided since it appears impossible to provide clinical trial follow-up data over a time span of about 10 years, especially in an extremely rare disease. It is acknowledged that, although improvements in hepatic parameters and liver histopathology parameters were observed, a delay of surgical biliary diversion (SBD) or orthotopic liver transplant (OLT) has not been fully demonstrated. As such, an indisputable favourable effect on the underlying disease has not been comprehensively demonstrated. Therefore, it can be appreciated that the data are not comprehensive in the sense that the clinical benefit for a full treatment effect has been demonstrated.

Thus, it may be impossible to establish a comprehensive clinical database based on clinical trial data to determine the long-term effect on liver survival (delay of SBD/OLT). Given that PFIC is an orphan disease it is anticipated that robust confirmation of delay of relevant clinical outcome parameters like SBD/OLT is challenging, if not unfeasible. Taken together, it can be concluded that the applicant cannot reasonably be expected to provide comprehensive evidence for the long-term benefit despite literature data that support the observation that this long-term effect will be achieved.

- ***In the present state of scientific knowledge, comprehensive information cannot be provided***

It has not been firmly established whether serum bile acids are predictive as a surrogate parameter for liver survival. Based on review of the published literature, there were no conclusions regarding or negating the potential for serum bile acid levels to be or become a surrogate endpoint for predicting liver survival. Rather, the conclusions pointed at the observed treatment benefit following surgical intervention (SBD or liver transplantation) and intermediate and long-term benefits following alleviation of cholestasis, reduction or normalization of serum bile acid levels on clinical outcomes. Decades of published data from clinical cohort studies have consistently shown the clinical benefits of surgical biliary diversion and liver transplantation on cholestasis (reduction in serum bile acid and hepatic health), alleviation of cholestatic pruritus, catch up in growth and native liver survival/reversal of disease progression in PFIC patients. The applicant indicated that the relevance of bile acids as a key component of the hepatic pathology in PFIC has been demonstrated also by recent publications from the Natural course and Prognosis of PFIC and Effect of biliary Diversion (NAPPED) consortium (van Wessel 2019a; van Wessel 2020).

In addition, the applicant highlighted that NAPPED data show that approximately 50% of the liver transplants in patients with PFIC1 and PFIC2 are performed for the relief of intractable pruritus prior to the development of end-stage liver disease.

Therefore, in the absence of long-term clinical trial data in the very rare disease, the applicant considers that the results of the A4250-005 and A4250-008 studies have not unequivocally qualified serum bile acids as a surrogate parameter for long-term liver survival.

- ***It would be contrary to generally accepted principles of medical ethics to collect such information***

This is not considered applicable for this application.

The Directive contemplates that the specific obligations be directed toward studies that will further elucidate the benefit-risk profile *("the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile"*).

The applicant accepted the premise of the following post-authorisation measures:

- In order to investigate whether odevixibat treatment delays surgical biliary diversion (SBD) and/or liver transplantation (OLT), with matched comparison against untreated PFIC patients, the MAH should conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) according to an agreed protocol. Annual interim reports are to be submitted along with the annual reassessments.

Taken together, an application for a marketing authorization under exceptional circumstances, given the view that the requirements laid down in Part II.6 of Annex I of Directive 2001/83/EC apply.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing odevixibat sesquihydrate equivalent to 200, 400, 600 or 1200 micrograms odevixibat.

Other ingredients are:

Capsule contents: microcrystalline cellulose and hypromellose.

Capsule shells: hypromellose, titanium dioxide (E171) and yellow iron oxide (E172). In addition, the 400 and 1200 microgram capsules contain iron oxide red.

Printing ink: shellac, propylene glycol (E1520) and black iron oxide (E172)

The product is available in HDPE bottles with tamper evident, child resistant polypropylene closures as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of odevixibat sesquihydrate is (2*S*)-2-{[(2*R*)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1λ^6,2,5-benzothiadiazepin-8-yl]oxy}acetamido)-2-(4-hydroxyphenyl)acetly]amino}butanoic acid sesquihydrate corresponding to the molecular formula $C_{37}H_{48}N_4O_8S_2.$•1.5 H_2O. It has a relative molecular mass of 768.0 g/mol and the following structure:

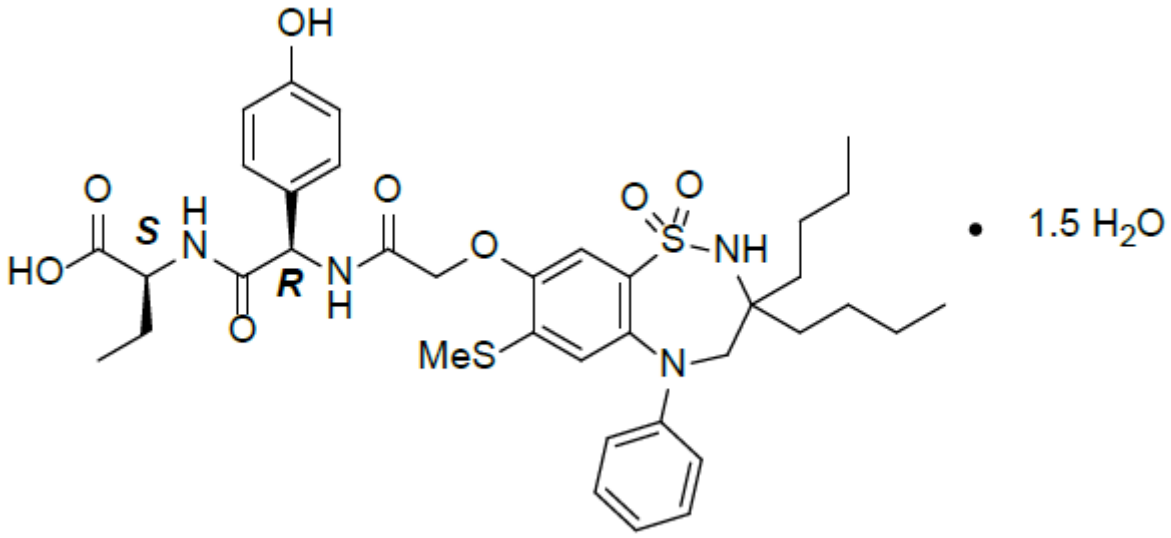


Figure 3: active substance structure

The chemical structure of odevixibat sesquihydrate was elucidated by a combination of elemental analysis, infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, single crystal x-ray diffraction and specific optical rotation. The solid-state properties of the active substance were measured by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapour sorption (DVS), x-ray powder diffraction (XRPD) and variable humidity XRPD. Crystals were further analysed by scanning electron microscopy, light microscopy, specific surface area measurements and particle size distribution.

The active substance is a white to off-white hygroscopic crystalline solid with some amorphous content. It exhibits pH-dependent solubility, being insoluble from pH 1-4 with a maximum solubility at neutral pH. Polymorphic form and particle size are controlled in the active substance specification.

Odevixibat exhibits stereoisomerism due to the presence of 2 chiral centres. Chiral purity is controlled in 2 starting materials and is controlled routinely by chiral HPLC in the active substance.

Polymorphism has been observed. Two forms were identified but only one was found to be stable and is routinely produced by the proposed commercial manufacturing process, along with some amorphous material.

Manufacture, characterisation and process controls

Odevixibat sesquihydrate is synthesized convergently by a single manufacturer in 6 main steps followed by crystallisation using 3 well-defined starting materials with acceptable specifications. The starting materials are defined in line with CHMP scientific advice. The final crystallisation conditions ensure formation of the sesquihydrate salt in the desired polymorphic form.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The specification for one raw material was not considered acceptable due to the lack of an assay test. It was not possible to revise the specification during the procedure due to the hygroscopic nature of the material and requires installation of specialized equipment to test. Given that the charge of this material is variable and determined by an in-process control (IPC), it is agreed that additional development can be done post-authorisation. The applicant should provide an updated specification, including a limit for assay, as soon as practically available, but within three months of authorisation.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. In the initial submission, the risk assessment for genotoxic impurities was lacking detail resulting in a major objection from CHMP. In response, the company provided a thorough risk assessment for potential and actual genotoxic impurities, using the hazard assessment tools from ICH M7, as well as providing experimental and calculated purge data. The response was deemed adequate and the control strategy for genotoxic impurities is acceptable. Other potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The bond forming reactions have been consistent, but reaction conditions, reagents, solvents, and isolation steps have changed over time. Changes introduced have been presented in sufficient detail and have been justified.

The process was developed using elements of Quality by Design (QbD) including extensive use of risk assessments. For low risk parameters, acceptable ranges have been defined. For medium and high-risk parameters, multivariate design of experiments (DoE) studies were conducted to optimise reaction conditions and define critical process parameters (CPPs). No design spaces are claimed. The overall control strategy is considered acceptable.

The active substance is packaged in double, semi-transparent low-density polyethylene (LDPE) bags secured with plastic ties. Silica gel desiccant is placed between the inner and outer LDPE bags. The double LDPE bags are placed in an aluminium can. The LDPE bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual), identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC), chiral impurities (chiral HPLC), residual solvents (GC-HS), particle size distribution (LALLS), polymorphic form (XRPD), water content (KF), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.) and microbial enumeration (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and most non-compendial methods appropriately validated in accordance with the ICH guidelines. However, the method for particle size distribution is not considered fully validated yet. The applicant should complete validation of the analytical method for particle size distribution post-authorisation including accuracy and robustness. The applicant should provide the requested additional data as soon as practically available, but within one month of authorisation. In addition, the applicant should provide data which demonstrates the stability indicating nature of the chiral HPLC method as soon as practically available, but within three months of authorisation. It is acceptable to provide this data post-approval since no critical impact on the quality of the active substance is expected. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from the 4 process performance qualification batches of the active substance are provided. The results are within the specifications and consistent from batch to batch. Batch analysis data from development and stability batches made with earlier processes met with the specifications in place at the time.

Stability

Stability data from 6 production scale batches of active substance from the proposed manufacturer but using an earlier process stored in the intended commercial package for up to 18 months under long term conditions (25°C / 60% RH), for up to 12 months under intermediate conditions (30°C / 65% RH), and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Three of the batches contained a different amount of crystalline to amorphous material than in the intended commercial material. The following parameters were tested: description, assay, impurities, chiral impurities, water content, solid-state form, and microbiological attributes. The analytical methods used were the same as for release and are stability indicating. An IPC for particle size distribution is included in the finished product process so this attribute was not measured during stability studies.

One impurity was out of specification (OOS) in 4 batches at every time-point including at release. No increase was seen over time and it is not considered a degradant. The process was subsequently amended to reduce the amount of this impurity to below 0.1% in the active substance. Water content does increase in a non-linear fashion over time. Extrapolation data indicate that water content will not increase above the specification limit within the assigned re-test period. No trends were observed for any of the other measured parameters.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. No changes were observed to measured parameters including impurities, other than some discolouration. The active substance is stored protected from light as a precaution.

Results under stressed conditions were also provided. The active substance is relatively stable in the solid state to thermal and photolytic conditions. Degradation occurs in aqueous solution under acidic, basic and oxidative conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months, with the storage condition "Store below 25°C in the proposed container in order to protect from light."

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as hard capsules in 4 strengths containing spherical microcrystalline cellulose (MCC) pellets coated with hypromellose and odevixibat sesquihydrate equivalent to 200, 400, 600, or 1200 µg of odevixibat (anhydrous form).

The coated pellets are prepared in 2 concentrations: 5 and 15 mg/g of active substance.

- The 200 and 400 µg capsules are manufactured from the 5 mg/g pellets by adjusting the fill weights (40 and 80 mg, respectively).
- The 600 and 1200 µg capsules are manufactured from the 15 mg/g pellets by adjusting the fill weights (40 and 80 mg, respectively).

The 400 and 1200 µg strength capsules are intended for direct oral administration to patients with body weight >19.5 kg.

The 200 and 600 µg strength capsules are intended for oral administration after opening the capsule shell and sprinkling the contents onto a food vehicle. These capsules will be used for patients with body

weight <19.5 kg. However, all strengths may be swallowed or sprinkled onto food. The capsules are distinguishable by size, colour and printing as shown in the following tables:

Table 3: Composition of oral capsules

	Strength	
	400 µg	1200 µg
Fill weight (mg)	80	80
Odevixibat pellet assay	5 mg/g	15 mg/g
Capsule size	Size 3	Size 3
Capsule type	Vcaps® Plus capsules	Vcaps® Plus capsules
Capsule colour	Cap: medium orange opaque Body: white opaque	Cap: medium orange opaque Body: medium orange opaque
Capsule markings	'A400'	'A1200'
Capsule image		

Table 4: Composition of oral capsules

	Strength	
	200 µg	600 µg
Fill weight (mg)	40	40
Odevixibat pellet assay	5 mg/g	15 mg/g
Capsule size	Size 0	Size 0
Capsule type	Vcaps® Plus Coni-Snap® Sprinkle capsules	Vcaps® Plus Coni-Snap® Sprinkle capsules
Capsule colour	Cap: ivory opaque Body: white opaque	Cap: ivory opaque Body: ivory opaque
Capsule markings	'A200'	'A600'
Capsule Image		

The compositions of the finished product components are provided in the following tables:

Table 5: Composition of oral capsules

Ingredient	Reference	Function
Coating component		
Odevixibat (equivalent to odevixibat sesquihydrate)	In-House	Active
Hypromellose 3mPa.s	Ph.Eur.	Film coating agent

Ingredient	Reference	Function
Purified water [a]	Ph.Eur.	Processing solvent
Core component		
MCC spheres 700	Ph.Eur.	Inert carrier
Total content of capsules		
Capsule component		
Hypromellose capsule [b]		Encapsulation
Opacode monogramming ink black		Markings

[a] Purified water is removed during the drying step after the coating.
[b] A single Size 3 capsule is used as listed in M3.2.P.4.1.

Table 6: Composition of sprinkle capsules

Ingredient	Reference	Function
Coating component		
Odevixibat (equivalent to odevixibat sesquihydrate)	In-House	Active
Hypromellose 3mPa.s	Ph.Eur.	Film coating agent
Purified water [a]	Ph.Eur.	Processing solvent
Core component		
MCC spheres 700	Ph.Eur.	Inert carrier
Total content of capsules		
Capsule component		
Hypromellose capsule [b]		Encapsulation
Opacode monogramming ink black		Markings

[a] Purified water is removed during the drying step after the coating.
[b] A single Size 3 capsule is used as listed in M3.2.P.4.1.

Table 7: Composition of hypromellose capsule shell

Component	**Reference**	**Function**
Cap		
Hypromellose	Ph.Eur.	Structure
Titanium dioxide	Ph.Eur.	Opacifier
FDA/E172 yellow iron oxide	NF/ EU 231/2012	Colorant
FDA/E172 red iron oxide	NF/ EU 231/2012	Colorant

Total cap		
Shell body		
Hypromellose	Ph.Eur.	Structure
Titanium dioxide	Ph.Eur.	Opacifier
FDA/E172 yellow iron oxide	NF/ EU 231/2012	Colorant
FDA/E172 red iron oxide	NF/ EU 231/2012	Colorant
Total body		
Total		

Table 8: Composition Opacode monogramming ink Black

Component	**Reference**
Shellac Glaze in Ethanol	Ph.Eur.
Propylene Glycol	Ph.Eur.
Ammonia Hydroxide 28%	Ph.Eur.
Isopropyl Alcohol	Ph.Eur.
N-butyl Alcohol	NF
Ferrosoferric Oxide / Black Iron Oxide	NF, *JECFA*

The finished product was developed for immediate release using common pharmaceutical excipients and conventional manufacturing procedures. The formulation used in Phase 3 clinical studies and the intended commercial formulation was designed to be appropriate for the paediatric patient population and to allow for weight-based dosing using these fixed strengths. The formulation was designed to support the administration in paediatric patients with potential swallowing difficulties, providing the possibility to either swallow the capsules whole or to open the capsules and add the contents to suitable soft foods for administration. The formulation was designed for acceptable palatability considering capsule size, pellet diameter, and the number of pellets.

Based on the clinical and pharmacokinetic (PK) characteristics, as well as commercial requirements, a QTPP was defined for the development of odevixibat oral capsules and sprinkle capsules. The QTPP included the route of administration, palatability, dosage strength, size, appearance, container closure system, pharmacokinetic/ pharmacodynamic characteristics, excipients and stability. The critical quality attributes identified are description, identification, assay, uniformity of dosage units, dissolution, degradation products, water content and microbiological quality.

During the formulation development, the size of capsules used to facilitate ease of dosing was considered, the size of the pellets was considered. The overall excipient content was reduced following phase 2 clinical studies in order to minimize the amount ingested by the target paediatric patients. Various coating agents were investigated and hypromellose was found to be compatible with the active substance. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The active substance is poorly soluble in aqueous media and is isolated as a partially amorphous crystalline solid. In order to coat the MCC pellets, the active substance is prepared as a coating suspension with hypromellose. Studies have shown that the crystalline fraction retains the same polymorphic form during manufacture and storage. A biorelevant dissolution study was undertaken to investigate the performance *in vivo*, considering the site of action in the terminal ileum. Odevixibat has very low solubility in Fed state simulated gastric fluid, irrespective of the degree of crystallinity. In Fasted state simulated intestinal fluid, only modest differences in odevixibat solubility for the low and high crystalline material were observed over a 5-hour period. Under conditions representative of the fed small intestine, the solubility threshold for the maximum daily dose of odevixibat (7.2 mg) is 29 µg/mL and, under these conditions, all crystalline forms exceeded the solubility threshold by at least 10-fold in the Fed state simulated intestinal fluid media. This is particularly important because patients are instructed to take the drug in the fed state. As a consequence, irrespective of the crystalline form of the active substance in the finished product, full dissolution of the active substance will readily occur in the fed state following immediate-release dosing given the 3-5-hour transit of material to the terminal ileum, the site of action.

CHMP originally raised 2 major objections in relation to the dissolution method. In the first, the applicant was asked to redevelop the method as it was not considered sufficiently discriminatory and the use of a surfactant was not justified. In the second, the proposed dissolution specification was deemed to be too wide. In response, the applicant extensively described efforts to develop a discriminatory dissolution method for quality control (QC) purposes. The method had to take into account both the dissolution of capsules and the active substance. The applicant investigated different apparatus, media of different pH and ionic strength, the need for a surfactant and other parameters such as impeller speed and justified the proposed method.

Discriminatory power was investigated in relation to active substance properties including crystalline content (30-70%) and active substance particle size (milled vs unmilled) as well as MCC pellet size and thickness of the hypromellose coating. In addition, the applicant tightened the dissolution specification to Q=80% in 15 mins (pellets) and 20 mins (capsules). Considering the site of action, the biorelevant solubility study data, the efforts made to develop a more discriminatory method, the inherent properties of the active substance and other elements of the control strategy which ensure the quality of the finished product, the current method is considered sufficiently discriminatory as a QC method. Given that all capsules strengths may be swallowed or sprinkled on food, the applicant is recommended to perform additional experimental work in order to develop a single dissolution specification for all capsule strengths.

The dissolution profiles of batches used in clinical trials and the process validation batches were shown to be similar. Similarly, dissolution profiles of the different capsule strengths were shown to be equivalent.

The development and optimisation of the manufacturing process used to produce the finished product are described by the following:

- Conduct of risk assessment examining material attributes and finished product process steps
- Discussion of each process step and associated development experiments
- Discussion of DoE studies to challenge the process robustness, determine parameter ranges, and assess the impact on critical quality attributes (CQAs) for commercial production.

From these activities, a control strategy was developed for each process step.

A risk assessment was performed to identify the potential impact of materials (active substance attributes and finished product excipients), and each process step on the CQAs of the finished product.

Based on this risk assessment for each process step, the process parameters potentially affecting the identified CQAs were identified. Particle size was defined for the MCC pellets to ensure a consistency with the grade used throughout development and viscosity requirements are defined for the hypromellose coating agent to ensure consistent coating. Each process parameter was determined to be either a critical process parameter (CPP) or a non-critical process parameter (PP). The evaluation of the process parameters, together with the risk assessment, formed the basis for the control strategy for the finished product manufacturing process.

The compatibility of the odevixibat pellets and the specified soft foods was evaluated by sprinkling approximately 40 mg of 5 mg/g or 15 mg/g odevixibat pellet sample equivalent to that contained in one 200 or 600 µg capsule, onto approximately 15 g (1 tablespoon) of soft food. Comparison of the recovery results of odevixibat from each FAV with that from the control pellet samples demonstrate that patients will receive the intended dose once the pellets sprinkled onto soft food are entirely ingested within 2 hours.

The primary packaging is HDPE bottles with tamper evident, child resistant polypropylene closures. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process along with the in-process controls consists of 3 main steps: preparation of the coating mixture, coating of the MCC pellets and encapsulation. The process is considered to be a non-standard manufacturing process due to the low active substance content.

Given the non-standard manufacturing process, full validation would normally be required at the time of submission of the application. This data was not provided resulting in a major objection. In response, the applicant justified the approach on several grounds:

- The product is indicated for an unmet medical need and early access to patients would be life-saving;
- Despite the low active substance content, the dispersion and milling of the active substance in the coating suspension ensures homogeneous distribution as evidenced by blend and content uniformity data. In addition, uniformity of dosage units is routinely tested at release;
- The validation campaign is almost complete and will be finalized by the time a marketing authorisation is granted. In addition, data from IPCs during the completed batches was presented, providing further evidence of content uniformity;
- A concurrent validation approach is proposed as allowed by GMP and explained in the "draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications" (EMA/CHMP/BWP/QWP/IWG/694114/2019). A validation protocol has been provided to support this approach.

Given the PRIME status, the unmet medical need, the data provided so far and following consultation with the inspectorate with oversight over the manufacturing site, this approach is deemed acceptable.

So far, all evidence indicates that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including description (visual), identification (UPLC, UV), assay (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC), water content (Ph. Eur.) and microbiological attributes (Ph. Eur.).

Limits for specified impurities are set in line with ICH Q3B.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on a batch of each strength using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that no elemental impurity controls are required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Both *N*,*N*-dimethylformamide and *N*-methylpyrrolidone are used as solvents in the active substance process which could potentially lead to formation of NDMA and NMBA should a nitrosating agent be present. Although no nitrosating agents are deliberately added, the applicant nonetheless chose to test 7 batches of active substance for both NDMA and NMBA using a validated and sufficiently sensitive method (LoQ < 10% acceptable intake). No nitrosamines were detected. No risks were identified associated with the finished product. Based on the information provided no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 production scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Primary stability studies were conducted using a matrixed design, covering 8 production scale batches in total across the different strength (3 batches each of the 200 and 1200 µg capsules, 1 batch each of the 400 and 600 µg capsules). Samples were stored for up to 12 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, dissolution, water content and microbiological attributes. The analytical procedures used are stability indicating.

The stability data show that the finished product is stable when packaged in the intended container closure system under all storage conditions. There is little or no variability with respect to the

attributes of assay, total degradation products, dissolution, water content, and microbiological attributes. For individual degradation products, there were changes observed during the stability studies – some increased over time while others decreased. The results justify wider shelf-life limits for specified impurities.

An in-use study was conducted to simulate patient handling. One batch of each dosage strength packaged in the commercial packaging configuration was evaluated. The stability results obtained after 4 weeks at 25°C/60% RH show no significant changes that would adversely impact product quality for the attributes tested. All the results are within the proposed commercial specifications. No special directions or labelling requirements are considered necessary for the finished product.

A photostability study was conducted to evaluate intrinsic stability characteristics of the finished product on exposure to ultraviolet (UV) and visible light. Open-dish samples showed a very slight increase in degradation products but remained compliant with the proposed commercial specification.

A bulk holding time of 12 months for the capsules packaged in double polyethylene bags and placed in HDPE drums is justified given the provided stability data.

Based on the provided stability data, the shelf life of 24 months without special storage conditions when stored in HDPE bottle with a tamper evident, child-resistant polypropylene closure as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The major objections relating to potential genotoxic impurities have been adequately resolved. The applicant provided adequate justification that the QC dissolution method is suitable for its intended purpose and tightened the specification limit but is recommended to derive a single limit for all capsules. The applicant also provided a justification for not submitting full process validation data and the proposed concurrent validation approach is acceptable.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points included as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should provide an updated specification for sodium thiomethoxide, including a limit for assay, as soon as practically available, but within three months of authorisation;
- The applicant should complete validation of the analytical method for particle size distribution. A sample concentration range should be proposed and data on the accuracy and robustness of the method is awaited. The applicant should provide the requested additional data as soon as practically available, but within one month of authorisation;
- The applicant should provide data which demonstrates the stability indicating nature of the chiral HPLC method as soon as practically available, but within three months of authorisation;
- Given that all capsules strengths may be swallowed or sprinkled on food, the applicant is recommended to perform additional experimental work in order to develop a single dissolution specification for all capsule strengths.

2.3. Non-clinical aspects

2.3.1. Introduction

Odevixibat acts as a potent, selective inhibitor of the IBAT (also known as the ASBT). It is intended to prevent reabsorption of bile acids from the gastrointestinal tract (inhibit the enterohepatic circulation of bile acids). It is proposed to be indicated for the treatment of is PFIC. This is a group of familial cholestatic conditions caused by defects in biliary epithelial transporters. Four types can be distinguished:

- Type 1, mutations in ATP8B1, a gene coding for a P-type ATPase protein, FIC-1, that is responsible for phospholipid translocation across membranes, also called Byler disease
- Type 2, mutations in ABCB11, the gene that codes for the bile salt export pump, or BSEP, also called ABCB11 deficiency or BSEP deficiency
- Type 3 mutations in ABCB4, the gene encoding multidrug resistance protein 3 (MDR3),[5] which codes for a floppase responsible for phosphatidylcholine translocation, also called ABCB4 deficiency or MDR3 deficiency
- Type 4 (OMIM #615878), from mutation in TJP2.

The clinical presentation usually occurs first in childhood with progressive cholestasis. This usually leads to failure to thrive, cirrhosis, and the need for liver transplantation.

2.3.2. Pharmacology

Primary pharmacodynamic studies

OVERVIEW				TEST ARTICLE: ODEVIXIBAT		
TYPE OF STUDY	SPECIES/STRAIN	METHOD OF ADMIN.	DOSES	GENDER AND NO. PER GROUP	NOTEWORTHY FINDINGS	STUDY NO.
In vitro potency and selectivity	HEK 293 cells	In vitro		NA	Highly specific for the ileal (apical) bile acid transporters with IC_{50} =0.13, 0.12, and 1.4 nM for the human, mouse, and canine transporters, respectively, whereas the corresponding value for the human liver (basolateral) sodium/bile acid co-transporter was found to be 93 nM (~700-fold higher). Apparent K_m-value for the natural substrate, glycocholate, is around 10 µM for all the apical sodium/bile acid transporters while it is slightly higher for the human basolateral transporter (~20 µM). Apparent K_m-value for sodium stimulated AIB-uptake in the HEK 293 cells is ~280 µM.	25881
^{75}SeHCAT (Taura-23-selena-25-homocholic acid) intestinal absorption	ApoE knockout mice	Oral	7.409, 28.90, 115.58, 463.06 □g/kg	Female, 3/group	^{75}SeHCAT faecal excretion during the 24-hour period was 37%, 91%, 85%, 56%, and 42% in mice given vehicle or odevixibat at doses of 463.06, 115.58, 28.90, or 7.41 µ g/kg, respectively. Inhibition of odevixibat by the doses mentioned above on intestinal ^{75}SeHCAT absorption was 86%, 76%, 30%, and 8%, respectively.	24546

OVERVIEW				TEST ARTICLE: ODEVIXIBAT		
TYPE OF STUDY	SPECIES/STRAIN	METHOD OF ADMIN.	DOSES	GENDER AND NO. PER GROUP	NOTEWORTHY FINDINGS	STUDY NO.
					The ED_{50} of the inhibitory effect was estimated to be 54.09 □g/kg.	
Duration of inhibition of bile salt absorption	ApoE knockout mice	Oral	0, 463.06 □g/kg	Female, 3-4/group	Inhibition of absorption of intestinal bile salts was approximately 81% up to 3 hours and 28% at 10 hours after odevixibat administration.	24872
Effects on lipids	ApoE/LDL receptor knockout mice	Oral	0, 463.06 □g/kg	Female, 7/group	Plasma cholesterol reduced by 40% due to VLDL (45%-61% reduction) and LDL (7%-24% reduction) decreases while HDL cholesterol levels were unaffected. No changes in ALT; bile acid secretion increased in all treated groups (from 2.3 ± 0.8 up to a maximum of 4.1 ± 1.3 µ M).	24052-23
Impact of bile acid depletion on the liver in a mouse model of cholestasis	Mdr2 knockout mice	Feed	0, 0.03% (w/w) for 4 weeks	Male, 5/group	No mortality was seen. Moderate decreased liver/body weight ratios were seen when compared to vehicle or norUDCA positive controls. Decreased ALT and AST compared to controls; no effects on serum bile acids or bilirubin.	ARR4250000117
Faecal evaluation after cholestyramine administration	Beagle dog	Oral	30 mg/kg	Male, n=4	Trend toward normalisation of odevixibat induced increase instances/number of defecations and faecal consistency following rectal cholestyramine administration.	74519

OVERVIEW				TEST ARTICLE: ODEVIXIBAT		
TYPE OF STUDY	SPECIES/STRAIN	METHOD OF ADMIN.	DOSES	GENDER AND NO. PER GROUP	NOTEWORTHY FINDINGS	STUDY NO.
Effect on charcoal propulsion	Wistar rat	Oral	0, 0.741, 7.41, 74.09 mg/kg	Male, 10/group	No effects on intestinal tract length of charcoal transit time at any dose.	AA19205

In vitro

Potency and selectivity of the human, mouse, and canine ileal (apical) sodium/bile acid co-transporters (IBAT/ASBT) with AZD8294 (odevixibat) and its specificity versus the human liver (basolateral) sodium/bile acid co- transporter and amino acid (α-aminoisobutyric acid) uptake have been tested in transfected human embryonic kidney (HEK) 293 cells. Odevixibat was found to be highly specific for the ileal (apical) bile acid transporters with IC_{50} = 0.13, 0.12, and 1.4 nM for the human, mouse, and canine transporters, respectively, whereas the corresponding value for the human liver (basolateral) sodium/bile acid co-transporter was found to be 93 nM (approximately 700--fold higher). The apparent K_m-value for the natural substrate, glycocholate, is approximately 10 µM for all the apical sodium/bile acid transporters, while it is slightly higher for the human basolateral transporter (approximately 20 µM). Under the same conditions, 3.125, 12.5, and 50 µM odevixibat resulted in 21%, 73%, and 84% inhibition of the sodium-stimulated uptake of 0.5 mM ^{14}C-α-aminoisobutyric acid (AIB), respectively. The apparent K_m-value for sodium-stimulated AIB-uptake in the HEK293 cells is approximately 280 µM.

In vivo

The ED_{50} of AZD8294 on ^{75}SeHCAT (Taura-23-selena-25-Homocholic Acid) Intestinal Absorption in ApoE Knockout Mice In Vivo (Study 24546)

This study was conducted to assess the effect of AZD8294 (odevixibat) on intestinal bile acid absorption using ^{75}SeHCAT (Tauro-23-[^{75}-Se] Selena-25-homocholic acid) as a tracer in ApoE knockout mice. Groups of the mice were orally administered vehicle or odevixibat with the doses 0.01, 0.039, 0.156, or 0.625 µmol/kg (7.409, 28.90, 115.58, or 463.06 µg/kg), respectively. Approximately 30 minutes later, ^{75}SeHCAT (0.1 µCi per 0.1 mL per mouse) was orally given to each mouse. The radioactivity of ^{75}SeHCAT remaining in the body of the mouse and in the faeces excreted by the mouse during a 24-hour period after ^{75}SeHCAT administration were measured separately, and the inhibitory effect of odevixibat on intestinal ^{75}SeHCAT absorption was estimated.

The ^{75}SeHCAT faecal excretion during the 24-hour period after ^{75}SeHCAT administration was 37%, 91%, 85%, 56%, and 42% of the administered dosage in the mice given vehicle or odevixibat at doses of 0.625 µmol/kg, 0.156 µmol/kg, 0.039 µmol/kg, and 0.01 µmol/kg (463.06, 115.58, 28.90, or 7.409 µg/kg), respectively. Correspondingly, the inhibition of odevixibat by the doses mentioned above on intestinal ^{75}SeHCAT absorption was 86%, 76%, 30%, and 8%, respectively. The ED_{50} of the inhibitory effect was estimated to be 0.073 µmol/kg (54.09 µg/kg).

AR-H064974 (Odevixibat), AR-H073582, AR-H064965, and AR-H073559: Lipid-Lowering Effect in ApoE/LDL-Receptor Knockout Mice In Vivo (Study 24052-23)

The effect of 4 IBAT inhibitors on cholesterol lowering has been studied in ApoE/low-density lipoprotein (LDL)-receptor knockout mice at a concentration of 0.625 µmol/kg (463.08 µg/kg) or vehicle (polyethylene glycol [PEG]:ethanol:water 7:1:2) as a control via oral gavage. The most potent compound, odevixibat, reduced plasma cholesterol levels by 40% (p=0.001) and FPLC measurements showed that this reduction of cholesterol was due to reductions in very low-density lipoprotein (VLDL; 45% to 61% reduction) and LDL (7% to 24% reduction), whereas high-density lipoprotein (HDL) cholesterol levels were unaffected (odevixibat, AR-H073582) or slightly but not significantly increased (AR-H064965, AR-H073559). Odevixibat, AR-H073582, and AR-H073559 did not decrease triglycerides significantly. Plasma levels of alanine aminotransferase (ALT) were not affected by drug treatment, and bile-acid secretion was increased in all treated groups (from 2.3 ± 0.8 up to a maximum of 4.1 ± 1.3 µM).

AZD8294: Duration of the Inhibitory Effect on the Intestinal Bile Salt Absorption in ApoE Knockout Mice In Vivo (Study 24872)

Groups of mice were administered a single oral dose by gavage of vehicle (PEG:ethanol:water 70:10:20) or odevixibat (0.625 µmol/kg or 463.08 µg/kg). Odevixibat was given to the mice 0.5, 3, 6, and 10 hours in advance of administration of the bile acid marker ^{75}SeHCAT (0.25 µCi/mouse, PO) and faecal excretion of ^{75}SeHCAT was measured over 24 hours. The faecal excretion of ^{75}SeHCAT during a 24-hour period was significantly increased in the mice given odevixibat in comparison with that in the mice given vehicle. The inhibition of ^{75}SeHCAT absorption during a 24-hour period was 85%, 81%, 40%, and 28% when odevixibat was administered 0.5, 3, 6, or 10 hours, respectively, in advance of ^{75}SeHCAT.

IBAT/ASBT Inhibition with A4250 in the Mdr2 Knockout Model (Study ARR4250000117)

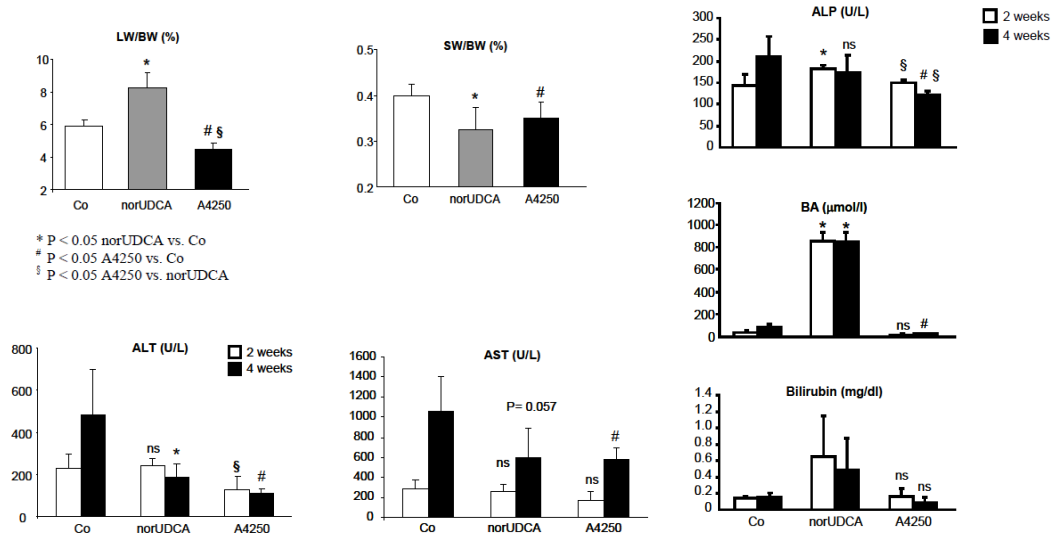
A pilot experiment was conducted in wild-type male mice of FVB/N background fed either control diet or food with the IBAT/ASBT inhibitor A4250 (odevixibat) included (0.001% and 0.03% w/w) for 1 week (n=5 in control group and n=6 in each treatment group). After one week, gain in body weight, macroscopic examination of organs, serum liver enzymes, liver weight, spleen weight, as well as hepatic and ileal mRNA analysis was performed to assess potential liver toxicity and effectiveness of IBAT inhibition by the 2 administered doses in wild-type mice.

In 1-week pilot experiment, body weight as well as survival rate were not affected by the compound at either dose. There were no test article-related changes in serum liver enzymes or hepatic expression of pro-inflammatory gene tumour necrosis factor-alpha (TNF-α), indicating that the test article was not hepatotoxic. However, odevixibat did repress expression of ileal FGF15 and induced hepatic CYP7A1 expression by 2.5- to 3-fold. There were no test article-related alterations in serum total bile acid concentration, which might result from increased passive bile acid reabsorption from the colon, and no changes in bile salt export pump (BSEP) expression.

In the experiment with male Mdr2-/- mice (n=5, 8 weeks old), animals received 0.03% (w/w) odevixibat in the diet for 4 weeks. Two control groups (n=5/group) were used: untreated Mdr2-/- mice and a positive control group of norursodeoxycholic acid (norUDCA)-fed Mdr2-/- mice dosed at 0.5% (w/w). Survival and serum hepatic enzyme levels were assessed after 2 weeks or 4 weeks of feeding. There was no mortality in any group. Liver weight/body weight ratio was increased in the norUDCA animals by about 33% but decreased by about 33% in the odevixibat-treated animals after 4 weeks ($p<0.05$ for both comparisons). Serum ALT levels were significantly decreased compared to untreated controls after 4 weeks of feeding ($p<0.05$) in both the norUDCA and odevixibat groups; aspartate aminotransferase (AST) levels were increased 5-fold between 2 and 4 weeks of feeding in the untreated control animals but only 2- to 3-fold in the norUDCA and odevixibat groups. Levels of alkaline phosphatase (ALP) were also decreased significantly in the odevixibat animals after 4 weeks of treatment. Serum bile acid concentrations were increased about 9-fold in the norUDCA animals

compared to untreated controls after 2 or 4 weeks of dosing and levels of bilirubin were also increased by approximately 3-fold in the norUDCA animals compared to untreated controls. In contrast, levels of bile acids and bilirubin were similar between untreated control and odevixibat animals at both 2 and 4 weeks of feeding. There was an increase in gallbladder size in norUDCA animals but not in untreated control or odevixibat animals after 4 weeks of dosing based on histopathological analysis.

Figure 3: Impact of bile acid depletion with odevixibat on the liver in a mouse model of cholestasis (Study ARR42500000117)



A4250, Substance B (Cholestryamine), Substance C (Placebo). Faecal Evaluation Study in Dogs (Study 74519)

Oral administration of odevixibat (30 mg/kg) was performed on Days 1 and 4 followed immediately by rectal catheterisation in order to apply either cholestyramine suspension (Substance B) or placebo (Substance C) into the proximal part of colon (at doses of either 12 or 22 mL per animal). After dosing, the animals were housed individually and observed continuously during a 6-hour observation period. Faeces were evaluated for numbers of defecation and amount of passed faeces for each defecation. Faeces consistency was evaluated using the Bristol Stool Form Scale (BSFS). Clinical signs, body weights, and food consumption were evaluated. Pre-treatment evaluation of normal defecation pattern and consistency was performed on Day -1.

Oral treatment with odevixibat caused several episodes (1-6 per animal) of very soft to watery faeces (Score 6-7 on BSFS) in animals receiving placebo treatment with rectal administration. Rectal administration of cholestyramine suspension resulted in faeces with consistency scores of 5 or less (normal consistency in dogs), except for 1 animal (animal No. 4 on Day 1, cholestyramine suspension 12 mL) which had 2 occasions of Score 7 (diarrhoea).

In conclusion, evaluation of faeces from 4 dogs after receiving an oral dose of odevixibat demonstrated a clear tendency toward normalisation of number of defecations and normalisation of faeces consistency after rectal (intracolonic) treatment with cholestyramine suspension when compared with placebo treatment. The effect of cholestyramine treatment seemed to be more pronounced at 22 mL per animal compared to 12 mL per animal.

AZD8294: Charcoal Propulsion Test in the Rat after Single Oral Administration (Study AA19205)

Groups A, B, C, and D animals received the vehicle or odevixibat by the oral route. Group E animals received the reference item (morphine) by the subcutaneous (SC) route. Approximately 70 minutes after the test item or vehicle administration and approximately 45 minutes after reference item

administration, animals received a charcoal meal (at 1 mL/100 g body weight) of 10% charcoal suspension in 5% arabic gum in sterile water. Blood sampling was performed approximately 90 minutes after odevixibat or reference item administration.

After blood sampling, animals were euthanised and subjected to necropsy examination. The intestinal tract from the pylorus sphincter to the ileocecal junction was sampled. The intestinal transit was expressed as the percentage of the total intestinal tract length travelled by the charcoal test meal 20 minutes after administration. No acute mortality was observed following administration of either vehicle or odevixibat. There were no significant effects on the total length of the intestinal tracts or intestinal transit of rats at any dose tested (1, 10, or 100 µmol/kg or 0.74, 7.41, or 74.09 mg/kg) compared to vehicle-treated animals. Morphine administered SC (20 mg/kg) significantly delayed intestinal transit of male Wistar rats 20 minutes after administration of a charcoal test meal, as compared to vehicle-treated animals.

Secondary pharmacodynamic studies

AZD8294 (odevixibat) is a potent inhibitor of the human ileal (apical) sodium/bile acid co-transporter (IC_{50}=0.1 nM). To investigate the bioselectivity of odevixibat, the compound was tested in a panel of 17 enzyme activity and binding assays along with 2 tissue models provided by MDS Pharma Services, Taiwan. This study was conducted by AstraZeneca in 2002.

Odevixibat (1 µM) showed 66% inhibition of protein serine/threonine kinase, ERK2 in the first round of testing in the biochemical assays. No significant effect (>50% change) was seen in any of the other 16 enzyme/receptor models assayed. When odevixibat was retested at 0.1 to 10 µM (74.09 to 7409 µg/L) in the ERK2 assay, no significant effect (>50%) was detected at any concentration. In addition, it was found that 1 µM odevixibat had no effect in the 2 tissue models (calcium channel of L-type and sodium channel site 2) tested.

Safety pharmacology programme

In vitro studies

hERG channel (Study 0062SZ)

hERG-expressing human embryonic kidney cells were recorded at approximately 20°C in the whole cell configuration of the patch clamp technique. Odevixibat and AR-H064965 were tested at unbound concentrations of 1 µM, and a positive control of 3 µM cisapride was also tested. For each cell recorded, data obtained in the presence of the test compound were expressed as a percentage of the inhibition produced by the positive control. Both odevixibat and AR-H064965 did not affect hERG channel activity at an unbound concentration of 1 µM (740.9 µg/L).

In vivo studies

Table 9: Summary of In Vivo Safety Pharmacology Studies

Study Number/GLP compliance	Test System	Species/No. of animals per group	Route/Dose groups	Major Findings
20040102PGR; GLP	CNS: spontaneous	Wistar Rats; 8/Group; males only	Oral;	At 30 hours post dosing significant decreases in number of rearings in central

	locomotor function		0, 0.741, 7.41 & 74.09 mg/kg	zone. Effect was not considered adverse. NOAEL was 74.09 mg/kg Toxicokinetics revealed dose dependent increase in plasma drug levels
20040103PGR; GLP	CNS: rota-rod test	Wistar Rats; 10/Group; males only	Oral; 0, 0.741, 7.41 & 74.09 mg/kg	No effects at any dose. Measured plasma concentrations were below the LoQ (4 nmol/L) for all dose levels as measured at 24 h after dosing
20040104PGR; GLP	CNS: Irwin test	Wistar Rats; 8/Group; males only	Oral; 0, 0.741, 7.41 & 74.09 mg/kg	No effects at any dose. Plasma concentrations at 24 h were below the LoQ (4 nmol/L) except in high dose group
20040105PGR; GLP	Cardiovascular: heart rate and blood pressure	Wistar Rats; 6/Group; males only	Oral; 0, 0.741, 7.41 & 74.09 mg/kg	No effects on heart rate or blood pressure. Toxicokinetics revealed dose dependent increase in plasma drug levels
20040106PGR; GLP	Respiration	Wistar Rats; 8/Group; males only	Oral; 0, 0.741, 7.41 & 74.09 mg/kg	No effects on respiratory parameters (respiratory rate; peak inspiratory and peak expiratory flows; inspiration and expiration times; airway resistance; tidal volume; and minute volume)
20040107PCC; GLP	Cardiovascular: Haemodynamic Effects	Beagle Dogs (Anaesthetised); 3 M/F per group	IV; 0; 0, 0.741, 7.41 & 74.09 μg/kg	No effect on cardiovascular function in anaesthetised dogs.
20040181PGR; GLP	Renal Function	Wistar Rats; 8/Group; males only	Oral; 0, 0.741, 7.41 & 74.09 mg/kg	No effect on urine output, urinary pH, electrolyte balance and glomerular filtration rate in the rat with a saline overload at any dose level tested

Odevixibat had no effects on the central nervous system (CNS) (Studies 20040102PGR, 20040103PGR, and 20040104PGR), respiratory system (Study 20040106PCR), renal function (Study 20040181PGR), or on cardiovascular parameters, including blood pressure and heart rate (Study 20040105PCR), at oral dosages (≤100 µmol/kg [≤74.09 mg/kg]) in rats. No haemodynamic effects on cardiovascular function and electrocardiogram morphology were seen in dogs following intravenous odevixibat administration (≤0.1 µmol/kg [≤74.09 µg/kg]).

Pharmacodynamic drug interactions

Non-clinical studies on pharmacodynamic (PD) drug interactions have not been conducted. Clinical studies on odevixibat and bile acid sequestrants are reported in the clinical study report (CSR) for A4250-001. The CHMP agrees with the applicant that in the presence of a clinical study investigating the co-administration of odevixibat and bile acid sequestrants, non-clinical studies to address a potential pharmacodynamic interaction can be waived.

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) and metabolism of odevixibat were studied in mouse, rat, dog, and human tissues in vitro and in mouse, rat, dog, marmoset, and human in vivo. Odevixibat toxicokinetics (TK) were determined in general toxicology studies conducted in mice (14-day and 13-week studies), rats (5- and 7-day, 1-month, and 26-week studies), dogs (7- and 14-day plus the 13- and 39-week studies), and marmosets (7-day study) and in rat and rabbit (embryo-foetal development studies at doses ranging from 10 to 300 mg/kg/day).

Methods of analysis

Non validated LC-MS/MS assays were used to analyse total plasma concentration of odevixibat in mouse and rat single-dose oral toxicity studies, 1-month oral toxicity studies in rats (calibration range 3 to 1800 ng/mL), and a single-dose administration intravenous and oral PK study and a 7-day repeated daily oral toxicity study in marmoset (LLOQ 0.741 and 1.48 ng/mL).

In the pivotal toxicity studies, validated LC-MS/MS assays were used to analyse total plasma concentration of odevixibat. LLOQ in these assays ranged from 0.1-0.76 ng/ml. Assay reproducibility was confirmed in incurred samples.

It is noted that in several studies, the test item was found in plasma from control animals. Measured concentrations in control samples were sometimes even higher than the concentrations in treated groups. This is explained by the high nonselective binding of odevixibat to various types of labware and the absence of precautions to prevent contaminations in some of the studies.

Distribution of radioactivity in rats was analysed by measuring radioactivity via liquid scintillation counting and quantitatively by whole-body autoradiography in rats.

Absorption

In vitro permeability and solubility studies indicate that odevixibat can be classified as a biopharmaceutical classification system (BCS) Class 4 (low permeability and low solubility) substance. This is not considered an issue, since the site of action is locally in the gut and not systemic.

Although a single-dose study in mouse was performed, no PK parameters were determined. The repeat-dose TK of odevixibat were evaluated in a 14 day (non-GLP) and a 13 week (GLP) oral toxicity study in CD-1 mice (dose levels 100-1500 mg/kg/day and 10-300 mg/kg/day, respectively). In general, Cmax was reached in 1-4 hours after administration. In both studies, exposure (Cmax as well

as AUC0-24) increased sub-proportional to dose. The elimination half-life was between 1.9 and 4.5 h. No accumulation was observed after repeated dosing. No gender differences were observed.

Also, in the single-dose PK study in rats, no PK parameters were determined. The repeat-dose TK of odevixibat were evaluated in a 7 day, 1 month (non-GLP) and a 26 week (GLP) oral toxicity study in Han Wistar rats (dose levels 10-1000 mg/kg/day, 10-1000 mg/kg twice daily and 10-300 mg/kg/day, respectively). The increase in exposure (based on AUC) to AZD8294 was less than proportional to the dose increase. The increase in Cmax was also less than proportional to increase in dose at most days/doses, except for 100 to 300 mg/kg on Days 1 and 177 in males and 10 to 100 mg/kg on Day 1 in females, where the increase was greater than dose-proportional. On day 89, abnormal unexplained high exposures (Cmax and AUC) were observed in both males and females at the low dose (12-50x exposure at day 1 and day 177). Also, Tmax was much higher than on day 1 and day 177. No explanation was provided. For the other dose groups and timepoints, accumulation was minimal to low (0.8-4.9). The elimination half-life was between 5 and 11 hours.

No single dose PK study was performed in dogs. The repeat-dose TK of odevixibat were evaluated in a 7 day, 14 days, (non-GLP), 39 week (GLP) and a 13 weeks (non-GLP) oral toxicity study in beagle dogs (dose levels 1000, 30-1000, 3-150 mg/kg/day as a suspension in 20% v/v propylene glycol, and 3-300 mg/kg as solid in gelatin capsules, respectively). Two-four times lower odevixibat exposures (Cmax and AUC) were observed for the gelatine capsule formulation relative to the suspension formulation at the 30 mg/kg dose level. In general, exposure (Cmax as well as AUC0-24) increased proportional or sub-proportional to dose. The elimination half-life was between 2 and 11 h. Some accumulation (0.5-4.5) was observed after repeated dosing. No gender differences were observed.PK parameters in the marmoset were analysed in a single dose study following oral administration of 18.5 mg/kg or IV administration of 7.4 mg/kg b.w. A biphasic elimination was shown following IV administration. The t1/2, CL, and Vss were 8.6 hours, 7.5 mL/min/kg and 0.9 L/kg, respectively. Maximal exposure was reached 4 h after oral dosing and elimination seemed monophasic, probably due to the low absorption. Oral bioavailability was 0.9%. The repeat-dose TK of odevixibat were evaluated in a 7-day tolerability and oral toxicity study (dose levels 259 mg/kg/). In this study, Cmax was reached 1-3 h after dosing, and no accumulation was observed. DNAUC in the 7-day study was approximately 4 times lower than in the single-dose study after oral administration, indicating a subproportional increase to dose.

Distribution

The extent of plasma protein binding of odevixibat was evaluated in mouse, rat, rabbit, dog, marmoset, and human plasma using ultracentrifugation and LC-MS/MS. Odevixibat was highly protein-bound (>99% in most species and 98% in rabbit) Free concentrations were <0.4% in mouse and rat, 0.6% in dog and human, 0.8% in marmoset and 2% in the rabbit. A minimal level of accumulation of odevixibat inside the blood cells was observed for nonclinical species and humans (blood to plasma ratio 0.48-0.60).

Tissue distribution of odevixibat was investigated using quantitative whole-body autoradiography (QWBA) following a single iv administration of 2.5 µmol/kg [14C]-odevixibat (albino and pigmented rats) or a single oral dose of 5 µmol/kg (albino rats only).

Following IV exposure, odevixibat was distributed throughout the body. After 5 minutes, high concentrations were observed in bile and liver, followed by blood; in other tissues (including CNS) the levels were below blood concentration. After 1 hour, the concentration of odevixibat-related material was decreased in all tissues, except in parts of the skin of the neck. No indication of melanin binding was observed in the pigmented rats.

Following oral exposure, odevixibat was poorly absorbed, and most of the radioactivity was found in the content of the gastro-intestinal tract (mostly in the gastric mucosa and in the wall of the small intestine). The concentration in blood was below the level of detection, and no radioactivity was observed in the CNS. Maximal levels were found after one hour in bile, skin, prostate gland, liver and renal cortex.

The effects of odevixibat on placental transfer was assessed by QWBA in pregnant rats following a single iv dose of 2.5 µmol/kg odevixibat on gestational day 18. Odevixibat-related material was found in the placenta and amnion membrane but transfer to the foetus was limited (only low concentrations were found in the foetal liver at 4 hours after administration). Transfer to milk was not investigated.

Metabolism

In vitro studies showed that 14C-A4250 is slowly metabolised by rat, mouse and human hepatocytes. Odevixibat metabolic turnover in all species was minimal and slow. Up to 6 metabolites were detected, of which 3 were monohydroxylated (M2, M3 and M6). All metabolites observed in human hepatocytes were also observed in animals.

Due to the very low oral bioavailability of odevixibat, no in vivo metabolism studies were performed in animals. Following a clinically relevant dose of 5 µmol/kg, no radioactivity was detected in blood. The applicant, therefore, assumed that odevixibat would be predominantly excreted unchanged in faeces. Indeed, in humans following a 3 mg oral dose, no quantifiable radioactivity was detected in plasma and only very low amounts (<0.01%) in urine, whereas faeces contained >96% of total radioactivity as parent compound (within 48 hours). However, it is noted that intestinal metabolism in animals was not investigated.

Excretion

In rats, following administration of a single oral [14C]-A4250 dose at a target level of 4 mg/kg, excretion was almost exclusively via the faeces (88.6%), with the majority being excreted during the first 48 hours after dosing (87.8%). Excretion via urine is less than 0.1%. In humans, 83% is excreted via faeces. At least in humans, the majority (>96%) is excreted as the parent compound.

Other pharmacokinetic studies

In safety pharmacology studies, odevixibat formulated in sodium bicarbonate buffer solution, whereas odevixibat as a suspension in 20% v/v propylene glycol in purified water was used in the TK/toxicity studies. Nevertheless, exposure at doses of 10 and 100 µmol/kg (7.4, and 74 mg/kg) were comparable in safety pharmacology and toxicity studies. At the lowest dose (1 µmol/kg), exposure was in general below LOQ.

In an EFD study in rats with dose levels of 100-1000 mg/kg, exposure in pregnant dams was similar to that in non-pregnant rats. Both in the EFD study in rats as the EFD study in rabbits (dose levels 10-100 mg/kg), exposure increased in a dose-proportional to sub-dose proportional manner and there was no to minimal accumulation after repeated dosing.

In a PPND study in rats with dose levels 10-1000 mg/kg, mean plasma concentrations in pups on PND 4 and PND 20 represented 3.3% to 52.1% of concentrations in dams, irrespective of dose and occasion. However, odevixibat was also observed in 5 out of 17 control pup samples, at similar concentrations as in the low dose group. Although it was concluded that contamination probably occurred ex-vivo and control animals had not been inadvertently dosed, also the results of the dosed pups are unreliable due to the probable ex-vivo contamination.

In a juvenile toxicity study in rats with doses of 10-100 mg/kg/day, it was shown that peak and systemic exposure were markedly lower after repeated administration, relative to single-dose

exposure. This observation is not unexpected as the rat GI tract is known to be immature for the first 2 weeks of life, and after this period undergoes significant development, especially around weaning. The GI tract in humans is more significantly developed at birth than in rats, and as outlined in Downes et al., (Downes, 2017) TK data in juvenile rats between days 10 and 21 are unlikely to be a good indicator of likely clinical bioavailability. Given the absence of new toxicities or increased sensitivity in the juvenile rats, the provided study is supportive of an indication in a paediatric population from 6 months of age.

2.3.4. Toxicology

Single dose toxicity

Single-dose toxicity studies were performed in rats and mice, with a single dose of 2000 mg/kg. There were no major toxicities seen, although the interpretation of the studies is difficult due the lack of a control group and small number of animals.

Repeat dose toxicity

Repeated dose toxicity of odevixibat was investigated in mice, rats, dogs and marmosets.

Table 10: Overview of pivotal repeat-dose toxicity studies with odevixibat:

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg /day)	Major findings
TEA0013 GLP	CD-1 mice 12/sex/dose 18/sex/dose for TK	0, 10, 100, 300 mg/kg/day Oral gavage	13 weeks	F: 300 M: 100	**≥10**: ↓ liver and gallbladder weight (M) **=300**: 4 mortalities (M), ↓ BW (M), distended GI tract and gallbladder (M), necropsy/atrophy in GI tract and gallbladder (M)
TEA0001 GLP	Wistar rat 12/sex/dose 9/sex/dose for TK	0, 10, 100, 300 mg/kg/day Oral gavage	26 weeks	300	**≥10**: ↓ glu (M), ↓ total protein/albumin, Ca (F), ↓ liver weight (M) **≥100**: ↓ total protein, Ca, HDL (M)
8348308 GLP	Beagle dog 6/sex ctrl and high dose 4/sex low and mid dose 2/sex ctrl and high dose for recovery	0, 3, 30, 150 mg/kg/day Oral gavage	39 weeks + 4 weeks recovery	<3	**≥3**: ↓ spleen weight (<50% M, <30% F), gall bladder epithelial hyperplasia (M) and vacuoles **=150**: diarrhoea, vomiting, ↓ chol, HDL, HDLN **Recovery**: ↓ HDL (M), ↓ spleen weight (~20%)

BW: body weight, chol: cholesterol, HDL: High Density Lipoprotein Cholesterol, HDLN: Non High Density Lipoprotein Cholesterol, GI: gastrointestinal, glu: glucose

Table 11: Overview of supportive repeat-dose toxicity studies with odevixibat:

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg /day)	Major findings
Mouse					
TEA0012 Non-GLP	CD-1 mice 3/sex/dose phase I 5/sex/dose phase II 4/sex/dose for TK	0, 100, 300, 500, 750, 1000, 1500 mg/kg/day Oral gavage	3 or 14 days	1500	No treatment-related findings No increase in systemic exposure >300 mg/kg/day
Rat					
0804KR GLP	Wistar rat 4F/dose	0, 2, 200 mg/kg/day Oral gavage	5 days	200	No treatment-related findings
02263 GLP	Wistar rat 4/sex/dose 3/sex/dose for TK	0, 10, 100, 1000 mg/kg/day Oral gavage	7 days	1000	**≥10**: ↓ total protein/albumin (F) **=1000**: ↓ K (M)
0664AR GLP	Wistar rat 10/sex/dose 5/sex ctrl and high dose for recovery 2/sex low and mid dose for TK	0, 20, 200, 2000 mg/kg/day Oral gavage	28 days + 28 days recovery	20	**≥20**: ↓ Hb (F), RBC, HCT, retic, ↓ Ca (F), ↓ total protein/albumin (F) **≥200**: ↑ lym (M), ↑ APTT (M), hypertrophy in caecum **=2000**: ↓ BW (M), ↓ Hb (M), ↓ total protein/albumin (M), ↓ glu, chol, TG (F) **Recovery**: no findings
Dog					
8220870 GLP	Beagle dog 2/sex/dose	0, 50, 100, 200, 400, 1000 mg/kg/day (dose-escalation) Oral gavage	1, 3 or 4 days	400	**≥50**: diarrhoea, ↓ BW gain (F) **=1000**: vomiting, ↓ reticulocytes, dark caecum, red duodenum, thick thymus
8220869 GLP	Beagle dog 3/sex/dose	0, 30, 300, 1000 mg/kg/day Oral gavage	14 days	1000	**≥30**: diarrhoea **≥300**: vomiting, ↓ chol (M)
TEA0002 GLP	Beagle dog 3/sex/dose	0, 3, 30, 300 mg/kg/day Oral capsule	13 weeks	300	**≥3**: diarrhoea, ↓ chol, LDL, epithelial vacuolation gallbladder **≥30**: ↓ HDL **=300**: vomiting
Marmoset					
0011DT GLP	Marmoset 2/sex/dose	50, 100, 259 (dose-escalation); 0, 259 mg/kg/day (fixed dose) Oral gavage	7 days	100	**=259**: vomiting, diarrhoea, slight ↓ BW

APTT: activated partial thromboplastic time, BW: body weight, chol: cholesterol, glu: glucose, Hb: haemoglobin, RBC: red blood cell, HCT: haematocrit, HDL: high density lipoprotein, LDL: low density lipoprotein, lym: lymphocytes, retic: reticulocytes, TG: triglycerides

In repeat-administration studies across the rodent (mouse and rat) and non-rodent (dog and marmoset) species, odevixibat administration was generally well tolerated, with in-life findings (periodic diarrhoea, emesis, salivation, and reductions in body weight/weight gain and/or food consumption) and minor clinical pathology alterations (reductions in plasma proteins, albumin, total cholesterol, and/or lipoproteins) noted. No deaths attributed to odevixibat occurred in the mouse (female only), rat, dog, or marmoset. Mortality/moribundity in male mice was noted, starting on Day 52, in a 13-week GLP repeat-administration study at 300 mg/kg/day. Morbidity in rabbits is detailed later in this document. The GI tract was the primary target organ of toxicity in adult animals. Drug-related target organ toxicity included the GI tract (mouse, rat, and dog), gallbladder (mouse), kidney (rat), parotid gland acinar cells (rat), cardiovascular system (embryo-foetal rabbit), and the liver (adult and juvenile rats). Therefore, following both single and repeat administration, clinical symptomatology was primarily GI, with associated reductions in body weight and/or food consumption.

Genotoxicity

Table 12: Overview of genotoxicity studies with odevixibat:

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
02233 Gene mutations in bacteria Ames test Non-GLP	Salmonella strains TA1535, TA100, TA98 and TA1537 and E.coli WP2 uvrA (pKM101)	Up to 5060 µg/plate +/- S9 Plate incorporation method	Negative
0332BV Gene mutations in bacteria Ames test GLP	Salmonella strains TA1535, TA100, TA98 and TA1537 and E.coli WP2 uvrA/pKM101)	50.5, 168, 505, 1680, 5050 µg/plate +/- S9 Plate incorporation method 45.1, 150, 451, 1500, 4510 µg/plate +/- S9 pre-incubation method	Negative
02242 Gene mutations in mammalian cells Non-GLP	Mouse lymphoma cells, L5178Y tk locus Assay	Up to 51.8 µg/ml - S9 Up to 104 µg/ml + S9 4 hours incubation	Negative
0331MV Gene mutations in mammalian cells GLP	Mouse lymphoma cells, L5178Y tk locus Assay	73.2, 88.7, 104, 118, 133, 149, 162 µg/ml +S9 37.5, 45, 52.4 µg/ml -S9 3 hours incubation 30, 45, 59.9, 67.4, 74.9, 82.4, 89.9, µg/ml -S9 24 hours incubation	Negative
TEA0008 Chromosomal aberrations in vivo GLP	Rat, micronuclei in bone marrow	2000 mg//kg/day (twice) 7 males/dose	Negative

The genotoxicity of odevixibat has been studied in vitro and in vivo. An Ames test was performed to test for gene mutations in bacteria and a mouse lymphoma L5178Y tk locus assay to test for gene mutations in mammalian cells. A rat micronucleus assay was performed to test for chromosomal

aberrations in vivo. In the vivo study, the concentration odevixibat in plasma, 1 hour after dosing, ranges from 152 to 620 ng/ml (320 ng/ml mean)

Carcinogenicity

Overview of carcinogenicity studies performed with odevixibat is presented in Table 13.

Table 13: Carcinogenicity studies conducted with odevixibat

Study ID /GLP	Dose/Route	Exposure (AUC)	Species/No. of animals	Major findings
TEA0015 GLP	0 (water and 20% aq propylene glycol control groups), 10, 30 and 100 mg/kg/day Oral gavage	Not reported	Rat, Crl:WI(Han), 50/sex/dose + satellites 3/sex/dose	**≥ 10:**↓ HDL and/or LDL in M (ss), ↑ urothelium hyperplasia in M/F (ss trend); ↑ pelvis mineralisation in M (ss trend); ↑ liver basophilic foci in F (ss trend), ↓ fatty infiltrate in pancreas (ss trend) **100:** ↑ biliary hyperplasia, biliary cysts and centrilobular liver hypertrophy in F (ss trend)
TEA0016 GLP	0 (water and 20% aq propylene glycol control groups), 10, 30 and 100 mg/kg/day Oral gavage	Not reported	Mouse, Crl:CD-1 (ICR), 50/sex/dose + satellites 6/sex/dose	**≥ 10:**↓ food intake M (ss *vs* water controls); ↓ MCHC in M (ss *vs* both controls), ↑ RTC in M (ss *vs* both controls); ↑ aRTC in M (ss *vs* vehicle controls); ↑ RDW in F (ss *vs* water controls); ↑ spleen - extramedullary haematopoiesis; thymus - arteritis/periarteritis; thyroid - interstitial inflammatory cell infiltrate in F (ss trend); ↑ gall bladder cystic hyperplasia and increased basophilic amorphous content in M/F (ss trend) **≥30:** ↓ BW and BWG (M ss *vs* water controls/V nss); ↓ RBC, Hb and PCV in F (ss *vs* both controls); ↑ RTC and aRTC in F (ss *vs* both controls); ↑ neutrophils in F (ss *vs* water controls); ↑ eosinophils in M (ss *vs* vehicle controls) **100:** ↓ food intake F (ss *vs* water and vehicle controls); ↓ MCHC in F (ss *vs* water controls); ↑ epithelial hyperplasia in vagina (ss trend).

Tumour findings in Study TEA0015 (rat) are presented in the below table:

Tumour findings		Water controls	Vehicle controls	Low dose	Mid dose	High dose
Leiomyoma of duodenum	M	0	0	0	0	0
	F	0	0	0	1	2

Fibroadenoma of mammary gland	M	0	1	1	0	0
	F	11	1	1	0	0

Table 14: Study TEA0015; carcinogenicity evaluation in rat

The design for Study TEA0015 is presented below:

Group	No. of Animals		Animal ID		Odevixibat Dose Level (mg/kg/day)	Odevixibat Concentration (mg/mL)
	Males	Females	Males	Females		
Carcinogenicity assessment animals (main study)						
1	50	50	1-50	251-300	Water control	0
2	50	50	51-100	301-350	0 (vehicle)	0
3	50	50	101-150	351-400	10	2
4	50	50	151-200	401-450	30	6
5	50	50	201-250	451-500	100	20
Proof of exposure animals (satellites)						
6	3	3	501-503	513-515	0 (vehicle)	0
7	3	3	504-506	516-518	10	2
8	3	3	507-509	519-521	30	6
9	3	3	510-512	522-524	100	20

Note: An additional 5 males and 5 females were also provided by the animal supplier for health screening only. Histopathological review of selected organs from this screen confirmed that the batch of animals supplied for the study was suitable for use.

Treatment: odevixibat (A4250)

In this GLP-compliant study, groups of 50/sex/group Han Wistar rats were dosed with 0 (water control), 0 (vehicle control—20% v/v PG in purified water), 10, 30, or 100 mg/kg/day odevixibat, once daily, by gavage at a dose volume of 5 mL/kg body weight for at least 104 weeks, until the day before necropsy. Separate groups of animals (3/sex/group) received the same dosages, as above, for proof of exposure.

Exposure to odevixibat was detected at all dosage levels at 1 and 24 hours after dosing (Table 15). Exposure generally increased with increasing dose. There was no appreciable difference in exposures between blood sampling occasions or sex:

Table 15:

Dose level A4250 (mg/kg/day)	Mean plasma concentrations at 1 hour after dosing (ng/mL)				Mean plasma concentration at 24 hours after dosing (ng/mL)			
	Males		Females		Males		Females	
	Week 13	Week 26	Week 13	Week 26	Week 13	Week 26	Week 13	Week 26
10	15.2	28.2	15.5	11.0	23.5	8.89	7.30	10.8
30	32.2	50.9	29.8	23.9	7.90	3.61	5.37	8.53
100	69.2	80.2	28.7	29.3	12.3	12.1	15.2	7.15

Values are shown to 3 significant values.
Analytical range = 0.500 ng/mL to 200 ng/mL

Concentrations of odevixibat, slightly above the LLOQ (0.500 ng/mL), were detected in approximately half of the vehicle control plasma samples obtained during Weeks 13 and 26. The presence of odevixibat ranged from concentrations just above the LLOQ to values 8-fold higher (0.510 to 3.89 ng/mL). Although a causative mechanism could not be determined, odevixibat was detected at very low levels only and was considered not to impact the study outcome or any conclusions drawn from the data.

There were no clinical observations or effects on body weight and food intake that were related to administration of odevixibat. There were no test item-related ocular findings and no effects on haematology parameters that were considered to be of toxicological significance. Reductions in plasma cholesterol and lipoproteins (HDL and/or LDL) were noted in odevixibat-treated males at all dosage levels in comparison to water and vehicle controls; these changes were not considered toxicologically significant. There was no effect of odevixibat on survival of either sex over the course of the study and there was no test item-related increase in the incidence of any factor that may have been contributory to the death of the animals.

Table 16:

Group/ Sex	Odevixibat Dose Level (mg/kg)	Percentage Survival at Selected Weeks (%)				
		16	28	52	88	104
1M	0 (water)	100	98	96	76	66
2M	0 (vehicle)	100	100	98	84	68
3M	10	100	100	100	74	52
4M	30	100	98	96	80	68
5M	100	100	100	96	78	62
1F	0 (water)	100	96	94	78	56
2F	0 (vehicle)	100	100	100	82	72
3F	10	100	100	98	84	64
4F	30	100	100	96	86	70
5F	100	100	100	98	80	66

F: female; M: male
Treatment: odevixibat (A4250)

There were no macroscopic findings or neoplastic changes (i.e. incidence, location, or size of the palpable masses) that were considered to be related to administration of odevixibat.

There was an exposure-related increase in incidence of non-neoplastic lesions in the kidney (hyperplasia of the urothelium and associated mineralisation in the pelvis) and liver (biliary hyperplasia and basophilic foci of alteration). These changes showed no signs of advancing towards a proliferative lesion, were considered to be non-adverse and not to represent a neoplastic risk.

Table 17:

GROUP:		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
ODEVIXIBAT DOSE LEVEL (MG/KG/DAY):		0	0	10	30	100	0	0	10	30	100
NUMBER OF RATS EXAMINED:		50	50	50	50	50	50	50	50	50	50
Kidney											
Hyperplasia, urothelium	Minimal	4	9	10	12	15	28	31	27	31	21
	Slight	1	2	5	0	3	3	5	9	5	16
	Moderate	0	0	0	0	0	0	0	2	0	1
	Total	**5**	**11**	**15**	**12**	**18**	**31**	**36**	**38**	**36**	**38**
Mineralisation, pelvis	Minimal	1	1	3	7	10	23	33	24	29	24
	Slight	1	6	4	0	4	6	2	8	3	10
	Moderate	0	2	1	0	0	0	1	0	0	1
	Total	**2**	**9**	**8**	**7**	**14**	**29**	**36**	**32**	**32**	**35**
Liver											
Biliary hyperplasia	Minimal	1	4	6	3	3	5	5	6	6	10
	Slight	2	2	0	3	6	2	3	1	4	6
	Moderate	1	0	0	1	0	1	1	0	0	1
	Total	**4**	**6**	**6**	**7**	**9**	**8**	**9**	**7**	**10**	**17**
Foci of alteration (basophilic)	Minimal	9	5	6	10	9	16	18	14	20	13
	Slight	0	2	0	4	1	6	6	15	14	14
	Moderate	0	1	0	1	0	2	2	6	7	8
	Marked	0	0	0	0	0	0	0	3	2	4
	Severe	0	0	0	0	0	0	0	0	0	1
	Total	**9**	**8**	**6**	**15**	**10**	**24**	**26**	**38**	**43**	**40**

Treatment: odevixibat (A4250)

Odevixibat administered once daily by gavage to the rat at dosage levels up to 100 mg/kg/day did not affect survival and there was no odevixibat-related increase in the incidence of any factor that may have been contributory to the death of the animals. There were no clinical signs, effects on body weight or food intake, ophthalmoscopic findings, or changes in haematological parameters related to odevixibat. Slight decreases in plasma cholesterol and related parameters (HDL and/or LDL) in males (all dosages) were considered non-adverse. Odevixibat administration at dosages of up to 100 mg/kg/day did not cause the formation of neoplastic lesions. There was an increase in the incidence of non-neoplastic lesions in the kidney (hyperplasia of the urothelium and associated mineralisation in the pelvis) and liver (biliary hyperplasia and basophilic foci of alteration). These non-adverse changes showed no signs of advancing towards a proliferative lesion and were, therefore, not considered to represent a neoplastic risk. On this basis, the NOEL for tumour formation in this study was considered to be 100 mg/kg/day, the highest dosage administered to both males and females. At the NOEL during Week 26 at 1 hour post-dose, confirmation of plasma exposure was 80.2 and 29.3 ng/mL for males and females, respectively.

Study TEA0016; carcinogenicity evaluation in mice

The design for Study TEA0016 is presented below:

Table 18:

GROUP	NO. OF ANIMALS		ANIMAL ID		ODEVIXIBAT DOSE LEVEL (mg/kg/day)	ODEVIXIBAT CONCENTRATION (mg/mL)
	MALES	FEMALES	MALES	FEMALES		
Carcinogenicity assessment animals (main study)						
1	54	54	1-54	271-324	Water control	0
2	54	54	55-108	325-378 & 589[a]	Vehicle control	0
3	54	54	109-162	379-432	10	1
4	54	54	163-216	433-486	30	3
5	54	54	217-270	487-540 & 590[a]	100	10
Proof of exposure animals (satellites)						
6	6	6	541-546	565-570	Vehicle control	0
7	6	6	547-552	571-576	10	1
8	6	6	553-558	577-582	30	3
9	6	6	559-564	583-588	100	10

[a] Female 342 (Group 2) and Female 526 (Group 5) were removed from the study due to non-test item related deaths and were replaced with Females 589 and 590, which were dosed from Days 12 and 22, respectively.

Note: An additional 5 males and 5 females were also provided by the animal supplier for health screening only. Histopathological review of selected organs from this screen confirmed that the batch of animals supplied for the study was suitable for use.

Treatment: odevixibat (A4250)

In this pivotal (GLP-compliant) study (TEA0016), groups of 54/sex/group CD-1 mice were administered 0 (water control), 0 (vehicle control—20% v/v PG in purified water), 10, 30, or 100 mg/kg/day odevixibat once daily by gavage (10 mL/kg body weight) for at least 104 weeks, until the day before necropsy. Satellite animals (6/sex/group) received the same dosages and were sampled for proof of exposure during Weeks 13 and 26.

Exposure to odevixibat was detected in all dosage levels at 1 hour after dosing and generally, for the 30 and 100 mg/kg/day groups, at 24 hours after dosing. Exposure generally increased with increasing dose. There was no appreciable difference in exposure between blood sampling occasions or sex:

Table 19:

Dose level A4250 (mg/kg/day)	Mean plasma concentrations at 1 hour after dosing (ng/mL)				Mean plasma concentration at 24 hours after dosing (ng/mL)			
	Males		Females		Males		Females	
	Week 13	Week 26	Week 13	Week 26	Week 13	Week 26	Week 13	Week 26
10	34.2	45.2	25.2	30.2	BQL	BQL	BQL	0.667
30	50.8	54.9	75.1	55.3	1.64	0.457	0.485	9.57
100	150	107.8	99.2	192	1.48	5.40	28.8	2.43

BQL = Below quantifiable limit (0.500 ng/mL)
Individual values of BQL were taken as zero for the purposes of calculations. For this reason, group mean values may appear lower than the lower limit of quantification.
Values are shown to 3 significant values.
Analytical range = 0.500 ng/mL to 200 ng/mL

Concentrations of odevixibat that were slightly above the LLOQ (0.500 ng/mL) were detected in 2 mice in the vehicle control group in plasma samples obtained during Week 26: Female 565 at 1 hour after dosing (0.500 ng/mL) and Male 544 at 24 hours after dosing (0.711 ng/mL). The presence of odevixibat in the 1-hour sample was 40-fold lower than the lowest concentration measured in dosed animals at the same time point (21.9 ng/mL); the 24-hour sample concentration was similar to that seen in dosed animals at the same time point (0.602 to 15.8 ng/mL). Since odevixibat was detected in only 2 control

animals and at very low levels, these observations were not considered to impact the study outcome or any conclusions drawn from the data.

There were no clinical observations related to administration of odevixibat. Reductions in body weight gain were seen for both sexes given either 30 and 100 mg/kg/day (between 13% and 25% compared to concurrent control groups). In general, there was inconsistent correlation with food intake in males, and only slightly lower food intake seen for females given 100 mg/kg/day. There were no test item-related ocular findings or effects on haematology parameters.

There was no effect of odevixibat on survival of either sex over the course of the study and there was no test-item related increase in the incidence of any factor that may have been contributory to the death of the animals:

Table 20:

Group/ Sex	Odevixibat Dose Level (mg/kg)	Percentage Survival at Selected Weeks (%)				
		16	28	52	88	104
1M	0 (water)	100	100	96	67	50
2M	0 (vehicle)	96	93	87	69	44
3M	10	98	98	91	74	52
4M	33	100	98	98	78	61
5M	100	94	93	83	65	46
1F	0 (water)	100	100	93	70	46
2F	0 (vehicle)	98	96	87	65	43
3F	10	100	100	93	59	41
4F	30	100	94	85	63	46
5F	100	100	100	98	65	43

F: female; M: male
Treatment: odevixibat (A4250)

Other than microscopic changes in the gallbladder, there were no other macroscopic or neoplastic findings (i.e. incidence, location, or size of the palpable masses) that were considered to be related to administration of odevixibat. There was an odevixibat-related increase in the incidence of non-adverse, non-neoplastic lesions in the gallbladder (cystic hyperplasia and basophilic amorphous contents) at all dosage levels and in both early decedents and terminal sacrifice animals. Cystic hyperplasia was seen in a combined total of 6 control animals (sexes combined) and was seen for 12 to 26 animals in each odevixibat group. Basophilic amorphous content was seen in a combined total of 9 control animals (sexes combined) and was seen for 24 to 39 animals in each odevixibat group. The incidence of both findings was statistically significant for both sexes and at all dosages. Incidence was slightly higher in terminal sacrifice animals, suggesting a late onset. These appeared to be reactive changes without evidence of proliferative advancement and were considered to be non-adverse and without neoplastic risk.

Odevixibat when administered once daily by gavage to the mouse at dosage levels up to 100 mg/kg/day did not affect survival. There were no test item-related ocular findings and no test item-related changes in haematology parameters. Odevixibat administration at dosages of up to 100 mg/kg/day did not cause the formation of neoplastic lesions. There was an increase in the incidence of non-neoplastic lesions in the gallbladder (cystic hyperplasia and basophilic amorphous contents) for both sexes at all dosage levels. These apparently late-onset, non-adverse changes showed no signs of advancing towards a proliferative lesion and were, therefore, not considered to represent a neoplastic risk. On this basis, the NOEL for tumour formation in this study was considered to be 100 mg/kg/day, the highest dosage

administered to both males and females. At the NOEL on Week 26 at 1 hour post-dose, confirmation of plasma exposure was 108 and 192 ng/mL for males and females, respectively.

Table 21:

GROUP:		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
Odevixibat dose level (mg/kg/day):		0	0	10	30	100	0	0	10	30	100
Number of mice examined (decedents):		29	30	26	22	29	29	32	33	29	32
Gallbladder											
Cystic hyperplasia	Minimal	0	0	0	1	4	1	1	4	8	8
	Slight	0	0	3	4	2	0	0	5	2	3
	Moderate	0	0	0	0	0	0	1	0	0	0
	Total	**0**	**0**	**3**	**5**	**6**	**1**	**2**	**9**	**10**	**11**
Basophilic amorphous contents	Minimal	0	0	1	1	7	1	0	2	2	4
	Slight	0	0	8	7	9	3	2	12	12	15
	Moderate	1	0	1	2	3	0	0	4	4	1
	Total	**1**	**0**	**10**	**10**	**19**	**4**	**2**	**18**	**18**	**20**
Number of mice examined (terminal kill)		25	24	28	32	25	25	22	21	25	22
Cystic hyperplasia	Minimal	1	0	4	6	7	1	1	6	11	7
	Slight	0	0	5	9	4	0	0	6	5	5
	Moderate	0	0	0	2	0	0	0	1	0	0
	Total	**1**	**0**	**9**	**17**	**11**	**1**	**1**	**13**	**16**	**12**
Basophilic amorphous contents	Minimal	0	0	1	4	3	0	0	6	3	1
	Slight	0	0	11	12	10	2	0	8	16	14
	Moderate	0	0	2	5	4	0	0	3	2	1
	Total	**0**	**0**	**14**	**21**	**17**	**2**	**0**	**17**	**21**	**16**

Treatment: odevixibat (A4250)

Reproduction Toxicity

Reproductive and developmental toxicity of odevixibat was investigated in rats and rabbits. It included a segment I fertility study in rats, segment II studies in rats and rabbits, a segment III study in rats, and the juvenile animal study with rats (including dose-range finding studies). In rats, in the FEED and EFD studies no effects on fertility and development were seen up to and including the highest tested dose of 1000 mg/kg/day. The delayed ossification of several bones (i.e. squamosal, metacarpal, sternebrae and caudal vertebral arches) and thick ribs observed in the EFD study in odevixibat-treated animals are considered non-adverse and rather related to the early necropsy timepoint (GD 20 instead of GD 21). On the contrary, two available DRF studies in non-pregnant and pregnant New Zealand White rabbits and the pivotal EFD study in rabbits revealed maternal toxicity at dose levels ≥ 30 mg/kg/day, manifested as reduced faecal output, reduced food consumption and body weight, with one dose at 30 mg/kg/day and one dose at 100 mg/kg/day in the EFD study sacrificed in extremis after aborting/delivering early. Increased incidence of the front pow hyperflexion was seen in the DRF and the pivotal study, suggesting the relationship with the treatment. In the DRF study, this effect was not observed in controls; however, in the pivotal study, it was also seen in 2 (2) foetuses (litters) of the controls (0.9%). The effect may have thus been related to the teratogenicity of the vehicle (20%

propylene glycol); however, in the DRF study, the incidences in the odevixibat-treated groups significantly exceeded historical control ranges (4.7%, 8.2% and 6.3%, resp., vs 0.57% in historical controls) whereas the effect was not seen in concurrent controls. Thus, the relationship with odevixibat treatment seems more plausible.

Starting from 10 mg/kg/day cardiovascular effects were seen in the foetuses of the pivotal study (primarily ventricular diverticulum (described as a "five-chambered heart"), small ventricle and dilated aortic arch), compared to 0 in controls. Although no clear dose-response was seen, the observed effects, particularly five-chambered heart, are rare, were seen across all treated groups and the observed incidence was outside the historical control data range. In view of this, these effects are considered to be related to odevixibat treatment. A number of external (primarily neural tube defects) and skeletal (primarily sternebrae defects) malformations were seen in the pivotal study in both controls and the treated animals at incidences exceeding historical control data. It is therefore possible that these effects were related to the teratogenicity of the vehicle (20% propylene glycol). Based on the observed cardiovascular effects at all dose levels in the rabbit study, the NOAEL for prenatal developmental toxicity cannot be established and is considered < 10 mg/kg/day. This dose level corresponded to AUC0-24 of 4.57-6.28 ng x h/mL, comparable with the anticipated exposure in humans administered the therapeutic dose of odevixibat, with the therapeutic margin at the maternal NOAEL ≤1.0-fold the MRHD. It is known that rabbits are sensitive to changes in the GI tract microbiota and are also known for their coprophagous behaviour which in combination with the decreased faecal output could have resulted in higher local exposure to odevixibat. However, the coprophagous behaviour was not specifically recorded in the study, and the reduced faecal output appeared to be related to the reduced food consumption.

Based on these results, section 5.3 of the SmPC states that odevixibat had no effect on the reproductive performance, fertility, embryo-foetal development, or prenatal/postnatal development studies in rats at the exposure multiple of 133 of the anticipated clinical exposure (based on total plasma odevixibat AUC0-24), including juveniles (exposure multiple of 63 of the anticipated human exposure). The presence of odevixibat in breast milk was not measured in animal studies. Exposure was demonstrated in the pups of lactating dams in the pre- and post-natal developmental toxicity study with rats (3.2-52.1% of the odevixibat plasma concentration of the lactating dams). It is therefore possible that odevixibat is present in breast milk.

Toxicokinetic data

In the EFD study in rat, the therapeutic margin at the maternal NOAEL was at least 47-fold the maximum recommended human dosage (MRHD) (Table 1). At this dose there was a slight increase in delayed ossification when the foetuses were examined on GD 20. Ossification delays, such as those noted, disappear with continued development and have no toxicological consequence.

In the EFD study in rabbits, the maternal (conservative) NOAEL was the low dosage of 10 mg/kg/day, while the NOAEL for embryo-foetal toxicity was <10 mg/kg/day. The therapeutic margin at the maternal NOAEL was therefore ≤ 1.0-fold the MRHD (Table 1). Based on evaluation of the rat and rabbit embryofoetal studies (DART Expert Report 30SEP2020 the developmental and reproductive toxicology (DART) expert report authors considered the teratogenic risk for odevixibat in humans low. However, at present, in the absence of an embryofoetal NOAEL in the rabbit and the variability of the exposure values, the association of odevixibat treatment and the incidence of cardiovascular anomalies cannot be excluded, but more information on these events will be collected in the post-authorisation phase in the agreed safety studies.

Following a single administration on PND 14 at the 100 mg/kg/day dosage in the pivotal juvenile toxicity study, the (free) therapeutic margin of safety was 2550- and 3610-fold relative to the human MRHD for males and female rats, respectively. On the last day of dosing (Day 63; similar to human adulthood) the (free) therapeutic margin of safety in male and female rats at the 100-mg/kg/day dosage was 38- and 15-fold, respectively (see table 22)

Table 22:

Study and species	**Dose level (mg/kg)**	**Total (free) Cmax (ng/ml)**		**EM total (free)**		**Total (free) AUC_{0-24} (ng·h/L)**		**EM**	
		m	**f**	**m**	**f**	**m**	**f**	**m**	**f**
13 week mouse TEA0013	100 mg/kg	188 (0.752)	323 (1.29)	171 (114)	294 (429)	1440 (5.76)	1350 (5.40)	58 (38)	54 (36)
1 month rat 0664AR	2x10 mg/kg	32 (0.13)	21 (0.084)	29 (20)	19 (13)	611 (2.48)	601 (2.44)	24 (17)	24 (16)
26 week rat TEA0001	300 mg/kg	464 (1.86)	362 (1.45)	422 (282)	329 (220)	4040 (16.4)	2150 (8.74)	162 (109)	86 (58)
13 week dog TEA0002	300 mg/kg	6 (0.04)	7 (0.04)	5 (6)	7 (6)	39 (0.23)	50 (0.30)	1.56 (1.56)	2 (2)
39 week dog 8348308	3 mg/kg (LOAEL) 150 mg/kg (NOAEL appl)	1 (0.006) 45 (0.27)	1 (0.006) 47 (0.28)	0.91 (0.91) 41 (41)	0.91 (0.91) 43 (42)	10 (0.060) 91 (0.54)	5 (0.030) 120 (0.72)	0.4 (0.4) 3.64 (3.64)	0.2 (0.2) 4.8 (4.8)
EFD rat AB21161	1000 mg/kg		77 (0.31)		70 (47)		799 (3.24)		32 (22)
EFD rabbit AB21159	10 mg/kg (F0) <10 mg/kg (F1)		0.405 (0.008) 0.405 (0.008)		0.37 (1.2) <0.37 (1.2)		6.28 (0.12) 6.28 (0.12)		0.25 (0.83) <0.25 (0.83)
PPND Rat AB22204	1000 mg/kg		114 (0.456)		104 (69)		1274 (5.18)		51 (35)
Juv tox rat TEA0010	100 mg/kg			2550	3610				

Pnd 14 Pnd 63		4210 (16.8) 62 (0.25)	5960 (23.8) 26 (0.10)	38	15	30000 (122) 345 (1.40)	57000 (232) 376 (1.53)	1200 (813) 14 (9.3)	2280 (1545) 15 (10)
Human	*0.12 mg/kg/day*	*1.1 (0.0066)*		*na*		*25 (0.15)*		*na*	

**Following the maximum recommended clinical dosage, the highest observed Cmax values in human plasma were 1.1 ng/mL total and 0.0066 ng/mL unbound. The highest observed AUC0-24 values in human plasma were 25 ng·h/L total and 0.15 ng·h/L unbound.*

Interspecies comparison

The TK of odevixibat were characterised during nonclinical safety studies. Following oral administration, odevixibat was rapidly absorbed with a time to maximal plasma concentration (Tmax of generally 1 to 4 hours; 1 to 8 hours in gravid and juvenile rats) in all nonclinical species evaluated (mouse, rat, rabbit, dog, and marmoset). In general, mouse, rat, and dog exposures (both AUC and Cmax) in toxicology studies increased in an approximately dose-proportional, or less than dose-proportional, manner and remained consistent with repeated dosing (≤3-fold accumulation), thereby demonstrating little evidence for a change in clearance with time. In general, gravid rats and rabbits displayed similar toxicokinetics to their non-gravid counterparts. At 1 hour following oral odevixibat administration to rat dams on LD 4 in the pre- and postnatal development studies (non-GLP [Study AB22203] and GLP [Study AB22204]), drug exposure in pups (PND 4) was highly variable (3 to 52%) compared to the maternal plasma concentration and was generally less than proportional to dosage.

Local Tolerance

Odevixibat is intended to be given orally in humans. The local tolerance in the intestine has been evaluated in the standard toxicity studies by oral administration of high doses of odevixibat. Assessing local tolerance using other routes of administration, e.g. subcutaneous, intravenous, inhalation, intravitreal (ophthalmic), have not been deemed relevant and have not been performed. This was accepted by the CHMP.

Other toxicity studies

Unlike therapeutic protein products (e.g. antibodies, peptides), small molecules such as odevixibat are not expected to generate an immune response. Thus, antigenicity studies have not been performed. This was accepted by the CHMP.

The risk of immunotoxicity has been evaluated based on results from the standard toxicity studies. No obvious signs in related organs have been detected in response to odevixibat treatment (e.g. changes in thymus, spleen, lymph nodes, bone marrow). Altered haematology and incidence of infection have not been detected. Neither IBAT specifically nor bile acids in general are expected to perturb immunological responses. No signs of immunological reactions have been seen in clinical trials thus far. Based on the outcome from the standard toxicity studies, the minimal systemic exposure, and the general profile and mechanism of action of odevixibat, the risk of immunotoxicity has been considered low and dedicated immunotoxicity studies have not been performed. Due to the lack of adverse effects on the immune system, the lack if dedicated immunotoxicity studies was accepted by the CHMP.

Odevixibat has a molar extinction coefficient >1000 L/mol/cm within the range of natural light (290-700 nm). Per International Conference on Harmonisation (ICH) S101 guidance, a phototoxicity study [Study 20243334] was performed to determine the effects of repeat administration of odevixibat on the eyes and skin of pigmented rats. There was no evidence of ocular (confirmed by histopathology) or cutaneous phototoxicity after administration of odevixibat at oral dosages up to 1000 mg/kg/day that were followed approximately 4 hours later by a single exposure to UVR/Sham UVR.

No dedicated studies on impurities have been performed. Whilst the proposed levels of some of the impurities are higher than those seen in the batches used in the toxicity study, taking into account the significantly higher doses used in these studies the absolute amounts of the specified impurities are significantly higher than the levels associated with the proposed specifications at the maximum clinical dose of 7.2 mg/day. Therefore, the proposed specification levels are considered qualified.

2.3.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Odevixibat			
CAS-number (if available): 501692-44-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	log K_{ow} = 5.2 (at pH for neutral molecule)	Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.2 (at pH for neutral molecule)	potentially B
	BCF	P.M.	B/not B
Persistence	ready biodegradability	P.M.	P/not P
	DegT50	P.M.	P/not P
Toxicity	NOEC algae NOEC crustacea NOEC fish	P.M.	T/not T
	CMR	not investigated	potentially T
PBT-statement :	P.M.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, refined on the basis of public literature	0.00008	µg/L	< 0.01 threshold

The applicant has calculated the PECsw based on a dose of 8.4 mg/patient/day. However, in the SmPC a maximum dose of 7.2 mg/patient/day is given. Therefore, the calculations of the applicant can be considered as the worst case. Furthermore, the current application is for the indication of PFIC only, as the PECsw for PFIC is 0.00008 µg/L, well below the action limit of 0.01 µg/L, a further assessment is not deemed necessary.

Odevixibat was considered a potentially PBT and hence, the applicant provided a document with an expert opinion on the issue. The expert concluded that the partitioning value of the dissociated molecule at pH 7 (logDow value of 2.99) is the preferred value to use in the PBT screening assessment. The applicant concluded that, as this value is below the PBT assessment trigger value of 4.5, no further PBT assessment is considered warranted. The CHMP concluded that overall, the neutral

molecule screens as a potential PBT/vPvB substance, but as the neutral form is predominantly present at very low pH values, the log Dow¬ at environmentally relevant pH values is not close to the trigger value of >4.5. Therefore, it can be agreed that a further PBT/vPvB assessment is not deemed necessary.

2.3.6. Discussion on non-clinical aspects

Pharmacokinetics: The PK and metabolism of odevixibat were studied in mouse, rat, dog, and human tissues in vitro and in mouse, rat, dog, marmoset, and human in vivo. Odevixibat TK were determined in general toxicology studies conducted in mice, rats, dogs, and marmosets and in rat and rabbit (embryo-foetal development studies at doses ranging from 10 to 300 mg/kg/day). In the single-dose PK study, on day 89, abnormal unexplained high exposures (Cmax, AUC) were observed in both males and females at the low dose (12-50x exposure at day 1 and day 177). Also, Tmax was much higher on day 89 (both in 10 and 100 mg/kg dose groups) than on day 1 and day 177. This is due to high 8-hour and 24-hour post-dose concentrations. Without these data, the concentration-time curve of day 89 looks similar to those of day 1 and day 177. Since the majority of the data consistently show that odevixibat is poorly absorbed, the aberrant observations do not impact the integrity or the outcome of the study.

Toxicology: Repeated dose toxicity of odevixibat was investigated in mice, rats, dogs and marmosets. Odevixibat was well-tolerated in general in mice, rats and dogs. Toxicity target organs were GI tract in mice and dogs. In rats, no target organs were identified. Other effects were related to the pharmacological action of odevixibat as an IBAT inhibitor. A decrease in spleen weight was seen after 39 weeks of treatment in males and females in all dose groups with exposures below those in humans, which was persistent until the end of the 4-week recovery period. However, a relation to treatment is unlikely due to the lack of dose-response, high inter-animal variation, lack of any macroscopic or microscopic correlate, and spleen weights that were within the historical control range of the test site.

Carcinogenicity: Carcinogenicity was tested in two 104-week rat and mouse studies up to a dose level of 100 mg/kg/day. A number of neoplastic changes for which statistically significantly increased incidences were observed, were reported in both studies. In rats, those included leiomyoma of duodenum and mammary fibroadenoma in females and adrenal phaeochromocytomas and pituitary adenomas/adenocarcinomas in males; in mice, skin/subcutis fibromas/fibrosarcoma's in females and pituitary adenomas/adenocarcinomas in males. These lesions either occurred at a low incidence/seen only in one sex, or showed no dose-response relationship, or were commonly occurring in the ageing animals and thus not related to treatment. As duodenum leiomyoma is quite a rare tumour occurring at the site where local exposure to odevixibat can be expected to be significant, however, leiomyoma is a smooth muscle tumour; thus, it is not likely that the direct exposure of this tissue would occur in the absence of significant epithelial erosion/ulceration. Furthermore, no treatment-related microscopic lesions were in other sections of gastro-intestinal tract, where also high local concentration of odevixibat could be expected. This suggests that the observed effect is not treatment-related and is thus not considered to be clinically relevant.

Considering the pharmacology of the compound as an inhibitor of bile salt reabsorption, the findings of cystic hyperplasia of the gall bladder in mice and liver biliary hyperplasia in rats are of particular interest. The applicant has provided additional literature data demonstrating that odevixibat at dose level of 16 mg/kg/day reduced the elevated serum bile acids and the bile duct proliferation in the MDR2 knockout mice. It was suggested by the applicant that odevixibat may have a beneficial antiproliferative effect on cholangiocytes by reducing the bile duct load, and that the effects seen in carcinogenicity studies were high-dose phenomena seen in healthy animals having normal bile duct physiology, as opposed to the PFIC patients. Overall, the applicant's argumentation is endorsed by the

CHMP. It is also noted that the severity of the observed lesions was low in both species (minimal/slight) and did not appear to increase with the increased exposure. In rats, bile duct hyperplasia is known to occur upon aging and has a low chance of progression to neoplasia or significant alteration of hepatic function. According to the review of Hailey et al., minimal "typical" biliary epithelial hyperplasia alone or with very minimal associated inflammatory cell infiltrate and/or hepatocellular changes may be considered non-adverse in the rat in nonclinical safety studies. In mice, gallbladder hyperplasia is usually caused by irritation of gallbladder mucosa due to xenobiotic exposure. Furthermore, the effects in both species occurred at exposure multiple of 114 (rat) or 35 (mouse) of the anticipated clinical exposure, therefore it is agreed by the CHMP that they do not represent a safety concern in clinical settings.

Reproductive and developmental toxicity of odevixibat was investigated in rats and rabbits. It included a segment I fertility study in rats, segment II studies in rats and rabbits, a segment III study in rats, and the juvenile animal study with rats (including dose-range finding studies). No adverse effects were noted in rats. Rabbits seem to be sensitive for odevixibat-related developmental toxicity effects. Teratogenic effects (cardio-vascular system) were observed in the absence of clear maternal toxicity. Exposure levels measured in the study were much lower than in rats at the same dose levels and comparable to the expected clinical exposure. Decreased faecal output and coprophagous behaviour of the rabbits could have resulted in higher local exposure to odevixibat. In addition, it is known that rabbit as species is sensitive to changes in the GI tract microbiota. The applicant was asked to elaborate on the potential mechanism of the findings in the rabbit developmental toxicity study, considering all the above noted issues and discussing their clinical relevance. The applicant stated that based on available data it is currently not possible to envisage the mechanism of the observed effects; however, he suggested that the teratogenic risk of odevixibat in humans is low based on the following main considerations: 1) the absence of the dose-response relationship; 2) the spontaneous occurrence of the observed malformations in rabbits; 3) possible issues with the treated does due to the body weight loss seen in the 10 and 100 mg/kg/day does on days 0-6 (pre-treatment); and 4) exposure margin of 10.5 based on free odevixibat plasma concentration. However, although is the CHMP agrees with the applicant that no clear evidence of the dose-response relationship was seen in the study, the observed findings occurred across all dose levels and concerned different females and different foetuses, making an association with the test item probable. Furthermore, based on the provided historical control data, the observed findings are very rare, and some were not reported at all. Regarding the reduced body weight in the 10 and 100 mg/kg/day does, it is concluded by the CHMP that the body weight reduction occurred on GD6-9 of the treatment, thus when the treatment was initiated. The applicant further calculated the exposure margins of 3.08 and 10.5 based on the total and free fraction odevixibat plasma AUC_{0-24} in humans of 2.04 and 0.012 ng x h/mL, respectively. However, the chosen AUC_{0-24} values disagree with the simulated AUC_{0-24} and C_{max} values, which have submitted by the applicant based on the results of the PK modelling as a response to the first round of questions and accepted by the CHMP. The new AUC_{0-24} and C_{max} values for the total odevixibat which have been included in the updated SmPC Section 5.3 are 5.99 ng x g/mL and 0.623 ng/mL. It is therefore logical to use the same values to calculate the exposure margins. Furthermore, considering the very high degree of protein binding by odevixibat in plasma, the comparison based on total exposure, rather than exposure to the unbound fraction, is considered more appropriate. Using these values, the exposure margins of 1.1 and 1.6 are calculated based on AUC0-24 and Cmax of the total odevixibat. Therefore, it is concluded that the observed cardiovascular malformations in rabbit foetuses are caused by odevixibat treatment and adequate statement has been included in the SmPC, section 5.3.

2.3.7. Conclusion on the non-clinical aspects

Overall, the nonclinical programme was well designed and performed. The toxicology programme revealed primarily effects related to the pharmacological action of odevixibat. Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use are teratogenic effects seen in rabbits. Odevixibat caused cardiovascular defects in developing rabbit foetuses (primarily ventricular diverticulum, small ventricle and dilated aortic arch) at exposure multiples of 1.1 and 1.6 of the anticipated clinical exposure, based on AUC0-24 and Cmax of total odevixibat, respectively, and an adequate statement has been included in the SmPC to inform the prescribing physician.

From a non-clinical point of view, the marketing authorisation of Bylvay can be granted.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 23: List of Clinical Pharmacology Studies and Clinical Studies with PK Samples

STUDY ID (COUNTRIES)	STUDY DESIGN	OBJECTIVES	POPULATION/ NO. SUBJECTS/ GENDER/MEAN AGE (RANGE)	DOSE REGIMENS
Phase 1				
A4250-001 (UK)	Single-centre, 2-part, double-blind, placebo- controlled study in healthy subjects Part 1: SAD Part 2: MAD	Safety, tolerability, PK, and PD in healthy subjects. Odevixibat alone Odevixibat in combination with cholestyramine	Healthy adults Part 1: 39 (22F/17M) range 20-56 years Part 2: 55 (33M/22F) range 19-60 years	Part 1 SAD: placebo, 0.1, 0.3, 1, 3, and 10 mg Part 2 MAD: (7 days): 1 mg QD, 3 mg QD, and 1.5 mg BID, 3 mg QD in combination with 1 g cholestyramine (at different intervals between the 2 drugs)
A4250-004 (US)	Open-label, randomised, 3-way crossover, food-effect, and sprinkle study	To determine the single dose PK of odevixibat when administered after high-fat meal, when sprinkled on applesauce, and when fasting in healthy adult subjects	Healthy adults 17 (12M/5F) 41 (20-55) years	Single oral administration of 9.6 mg odevixibat, 3-way crossover
A4250-007 (UK)	A single-centre, open-label, non-randomised single oral dose ADME study	To assess the mass balance recovery, metabolite profile, and metabolite identification of ^{14}C-odevixibat	Healthy adults 6M/0F 44 (31-52) years of age	Single oral administration of 3 mg ^{14}C-odevixibat capsule containing ≤4.3 MBq (116 µCi), in the fasted state
A4250-013 (US)	Open-label, 2-part, fixed-sequence crossover DDI study	Part A: To determine the effect of odevixibat on the PK of midazolam (CYP3A4 substrate) Part B: To determine the effect of a P-gp inhibitor (itraconazole) on the PK of odevixibat	Healthy adults Part A: 22 (12M/10F) 43 (22-54) years of age Part B: 21 (6M/15F) 43 (19-54) years of age	Part A: Single 2 mg midazolam alone Single 2 mg midazolam + 7.2 mg odevixibat QD for 4 days Part B: Single 7.2 mg odevixibat Single 7.2 mg odevixibat + 200 mg itraconazole QD for 4 days
Phase 2/3				
A4250-003 (Sweden, Denmark, France, and Germany)	Multi-centre, single- and multiple-dosing open-label study in up to 24 children with cholestatic pruritus	To assess safety and tolerability of odevixibat in children with cholestasis. To explore changes in serum total bile acids, evaluate changes in VAS-itching score and effects on liver biochemistry, p-C4, and FGF19 after 4-week treatment period	Children ≥12 months and <18 years of age 24 patients (20 unique +4 re-entered) 15M/9F 6.5 (1-17) years of age	10, 30, 60, 100, and 200 µg/kg/day
A4250-005 (Belgium, France, Germany, Italy, Netherlands, Poland, Sweden, UK, US, Australia, Canada. Israel, Saudi Arabia, Turkey)	Double-blind, randomised, placebo-controlled efficacy and safety in children with PFIC types 1 and 2	Efficacy and safety study Sparse samples were collected for PK.	Children with PFIC types 1 and 2 62 (31M/31F) 4.25 (0.5-15.9) years of age	40 µg/kg/day and 120 µg/kg/day of odevixibat compared to placebo

2.4.2. Pharmacokinetics

The pharmacokinetics of odevixibat was evaluated in three Phase 1 studies in healthy adults and one Phase 2 study in paediatric patients with cholestatic pruritus. These studies were conducted to support dose selection and to characterise the single-dose and multiple-dose pharmacokinetics in children (**A4250-003**) and adults (**A4250-001**), to evaluate the impact of food (**A4250-004**) and to assess the interaction potential of odevixibat (**A4250-013**). In the Phase 3 study **A4250-005** sparse PK sampling was performed; these PK samples were included in the population PK analysis **ALBI-PMX-A4250-1167_PPK**.

Further the applicant conducted an ADME study (**A4250-007**) to assess the mass balance recovery and the metabolite profile of odevixibat. Several *in vitro* studies were conducted to assess the role of different transporters and cytochrome P450 (CYP) enzymes on the fate of odevixibat and the interaction potential of odevixibat.

Methods

In the phase 1 studies, rich sampling schemes were implemented to collect pharmacokinetic samples. Generally sampling was dense in the first 4 hours after administration (at least 1 sample/hour) and less frequent up to 24 hours after administration. Further, PD samples were collected to monitor the pharmacodynamic effects of odevixibat.

A LC-MS/MS assay (method **QBR111522QB0**) was used to quantify odevixibat concentrations in human plasma in the concentration range of 0.05-50.0 ng/mL. This assay was appropriately validated, an acceptable within-run and between run accuracy and precision was shown. Although the concentration of odevixibat was undetectable in about half of the clinical PK samples, the assay is considered suitable for the detection of odevixibat as the observed C_{max} of the highest administered odevixibat dose was around 0.5 ng/mL (about 10-fold higher than the lowest quantifiable concentration (0.05 ng/ml)) and at least 2 QC sample levels fell within the range of concentrations measured in study samples.

Several bioanalytical methods were developed to monitor the pharmacodynamic effects of odevixibat. The concentrations of the fibroblast growth factor 19 (FGF19) hydroxy-4-cholensten-3-one (C4) , total and individual bile acids, autotaxin/LPA were determined in various matrices (plasma, urine, faeces, whole blood and serum) and standard liver function test measurements (ASAT, ALAT, GGT, AFT, dBili, tBili) were conducted. These assays were generally appropriately validated, an acceptable within-run and between run accuracy and precision was shown.

Non-compartmental methods have been used to determine the pharmacokinetic parameters of odevixibat in the phase 1 studies. However, because the plasma levels of odevixibat were often not quantifiable, the pharmacokinetic parameters could not be determined for all subjects.

The population PK analysis **ALBI-PMX-A4250-1167_PPK** of odevixibat was performed based on Phase 1 studies in healthy adult subjects (A4250-001, A4250-004, and A4250-013) and Phase 2/3 studies in paediatric patients (A4250-003 and A4250-005). Due to the limited availability of detectable PK samples, the population model is mainly driven by data from studies A4250-004 and A4250-013. Population PK modelling and simulations were performed using NONMEM.

A total of 105 adult and 53 paediatric subjects were included in the population PK analysis. As the concentration of odevixibat was not detectable in about half of the study samples, the model accounted for the samples BLQ, using the likelihood method M3, as published by Beal SL, 2001[1].

[1] Beal SL. Ways to fit a model with some data below the quantification limit. J Pharmacokinet Pharmacodyn. 2001;28:481-504.

The PK of odevixibat was described using a one-compartment model with linear elimination. The population PK model included a first- and second-rate constant of absorption to characterise double peak absorption profiles (Ka1 and Ka2, respectively). Covariates included in the final model were bodyweight on CL/F, P-gp inhibitors and liver impairment on CL/F, body weight on V/F, dosage form and formulation on relative bioavailability (Frel), and formulation on Ka1.

Quality-of-fit of the base and final PK models was evaluated using a standard model discrimination process including statistical criteria such as minimum objective function value (OFV) as well as pertinent graphical representations of goodness-of-fit (e.g. observed vs predicted(PRED), CWRES vs PRED or time).

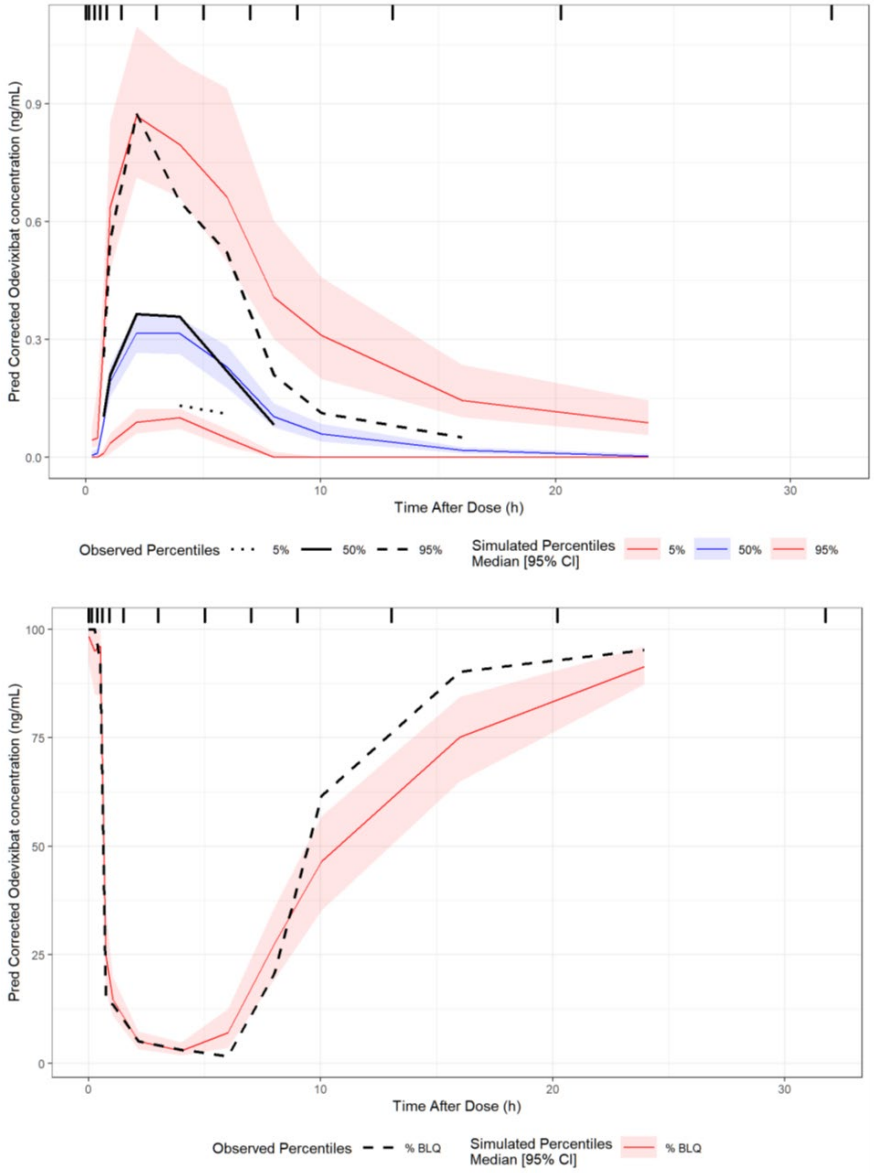
The methodology used to construct the data set is considered acceptable and PK model appears to describe the observed data reasonably well. Typical values of PK parameters derived with the final population PK model of odevixibat are presented in Table **26**24. The typical apparent clearance (CL/F), volume of distribution (V/F) and elimination half-life (t1/2) of odevixibat in a typical 70-kg subject were 2180 L/h, 2510 L and 0.798 h (corresponding to 47.9 min), respectively. The VPC plot of the concentration-time profiles of odevixibat in the overall population, including the probability of undetectable concentrations, is presented in Figure 44.

Table 24: Population PK Analysis of Odevixibat: Parameter Estimates of the final model, population PK study ALBI-PMX-A4250-1167_PPK

Parameter	Estimate	BSV	Shrinkage
CL/F (L/h)	2180 × (WT/70)0.75 × (1 - 0.369) if Concomitant Administration of P-gp Inhibitors × (1 - 0.606) if Mild Liver Impairment (Child-Pugh B)	32.9%	16.9%
V/F (L)	2510 × (WT/70)1	32.6%	32.0%
Ka1 (h-1)	0.332 × (1 -0.869) if Formulation A (powder blend in capsule)	33.1%	34.5%
Ka2 (h-1)	2.24	NA	NA
Lag1 (h)	0.586	NA	NA
Lag2 (h)	3.94	NA	NA
F1 (Ka1 and Ka2)	0.879	NA	NA
Frel	1, Fixed × (1 - 0.340) if Sprinkle dosage form × (1 - 0.432) if Formulation A (powder blend in capsule)	NA	NA
Error Model	Proportional: 0.261 Additive (ng/mL): 0.0242	NA	NA

CL/F = apparent clearance, V/F = apparent volume of distribution; Ka1 = first (slow) rate of absorption; Ka2 = second (rapid) rate of absorption; Lag1 = first absorption lag time; Lag2 = second absorption lag time; F1 = fraction of drug that is absorbed via the first route (Ka1, Lag1); Frel = relative bioavailability; BSV = between-subject variability.

Figure 4: Visual Predictive Check Concentration-Time Profiles of Odevixibat in Overall Population (upper panel) and Probability of Undetectable Concentrations of Odevixibat lower panel), population PK study ALBI-PMX-A4250-1167_PPK



Physical-chemical properties

Odevixibat has a low but pH-dependent solubility, with ionization constants pKa 3.84 and 9.64 and has a low permeability; thus, it can be classified as a BCS IV-drug. Odevixibat has 2 chiral centres and is manufactured as a single stereoisomer with the S,R-configuration.

Absorption

Low bioavailability of odevixibat was observed in clinical studies. In the mass balance study **A4250-007** about 83% of the administered oral dose was recovered in 216 hours. An average of 0.002% of the total radioactivity was recovered from the urine, and 82.886% was recovered from the faeces. Also, in single and multiple-dose studies **A4250-001** and **A4250-003,** the relative bioavailability is

estimated to be low. In many of the study samples, no quantifiable plasma concentrations of odevixibat were obtained, and no PK parameters were calculated in these two studies.

The SmPC presents noncompartmental pharmacokinetic data obtained in DDI study A4250-013, in healthy adult volunteers (see Table 25: Summary of Odevixibat Pharmacokinetic Parameters following a single oral dose of 7,2mg odevixibat in healthy adult [PK Evaluable Population] study A4250-013 below). In this study a second peak could be observed around 4 hours after administration of odevixibat, thus following administration of the first meal.

Table 25: Summary of Odevixibat Pharmacokinetic Parameters following a single oral dose of 7,2mg odevixibat in healthy adult [PK Evaluable Population] study A4250-013

Plasma PK Parameter	**Odevixibat (N=21)**
AUC0-t (h*ng/mL)	2.04 (42.8); 21
AUC0-inf (h*ng/mL)	2.45 (30.4); 19
Cmax (ng/mL)	0.435 (40.6); 21
Tmax (h)	2.50 (1.00-5.00); 21
t1/2 (h)	2.36 (2.00); 19
CL/F (L/h)	3060 (955); 19
Vz/F (L)	9940 (7280); 19

AUCs and Cmax are presented as geometric mean (geometric CV%); Tmax is presented as Median (Min, Max); other parameters are presented as mean (SD).

In vitro study, **XT168064** showed that odevixibat is a substrate for the gastrointestinal efflux transporter P-gp, but not for BCRP.

The exposure of odevixibat was calculated for the 40 and 120 µg/kg/day dose levels in the target population, paediatric patients with PFIC (study **A4250-005**), using the population model. The mean C_{max} of odevixibat in paediatric patients treated with the 40 and 120 µg/kg/day dose were 0.211 and 0.623 ng/mL, respectively, and their mean AUCs were 2.26 and 5.99 ng*hr/mL, respectively.

Descriptive statistics of exposure parameters of odevixibat in patients with PFIC1 and PFIC2 in **A4250-005** are presented in Table 26.

Table 26: Summary of Exposure Parameters of Odevixibat in Paediatric Patients with PFIC1 or PFIC2 in A4250-005 by Dose, based on population PK modelling

PARAMETERS	**40 µg/kg/day (n=17)**	**120 µg/kg/day (n=16)**
CL/F (L/hr) Mean (CV%) Median [min, max]	 398 (70.0) 351 [29.0, 1130]	 438 (85.8) 318 [46.0, 1240]
V/F (L) Mean (CV%) Median [min, max]	 614 (50.8) 576 [304, 1610]	 799 (87.8) 536 [267, 3070]
Ka1 (h-1)		

Mean (CV%) Median [min, max]	0.312 (19.6) 0.332 [0.186, 0.422]	0.326 (9.2) 0.333 [0.221, 0.346]
Cmax (ng/mL) Mean (CV%) Median [min, max]	 0.211 (49.4) 0.165 [0.0912, 0.435]	 0.623 (34.2) 0.526 [0.409, 1.06]
Tmax Mean (CV%) Median [min, max]	 4.66 (27.8) 4.40 [1.70, 8.50]	 4.79 (18.2) 4.40 [4.40, 7.60]
AUC (ng.hr/mL) Mean (CV%) Median [min, max]	 2.26 (155.9) 1.01 [0.530, 15.5]	 5.99 (96.9) 3.10 [2.41, 25.0]
t1/2 (hr) Mean (CV%) Median [min, max]	 2.44 (176.8) 0.798 [0.453, 18.4]	 2.73 (174.7) 0.798 [0.796, 19.7]

AUC: area under the curve; CL/F: apparent clearance; Cmax: maximum concentration; CV: coefficient of variation;

hr: hour(s); Ka1: first (slow) rate of absorption; max: maximum; min: minimum; t1/2: elimination half-life; Tmax: time to maximum concentration; V/F: apparent volume of distribution

Three different odevixibat formulations have been used in the clinical studies, formulation A, B, and C. The main differences were the drug substance crystallinity and the strengths of the formulations; formulation C is identical to the to-be-marketed formulation. In the population PK study, differences in absorption have been observed between early formulation A relative to formulation B and C. As this formulation has only been used in the early SD/MD dose-finding study **A4250-001** and not in the Phase 2 or 3 studies, the difference is not considered relevant for the interpretation of the clinical safety and efficacy data.

The effect of food on odevixibat was studied by assessing the PK of a single dose of odevixibat (9.6 mg) in a randomized, 3-way crossover design in 17 healthy adults under fasting and fed (high-fat, high-calorie meal, 800 - 1 000 calories with approximately 50% of total caloric content of the meal from fat) conditions and when sprinkled on applesauce (study **A4250-004**). Exposure to odevixibat was lower in both the fed state (decrease of 72% and 62% in C_{max} and AUC_{0-24}, respectively) and when dosed as a sprinkled formulation on applesauce (decrease of 39% and 36% in C_{max} and AUC_{0-24}, respectively) when each condition was compared to fasted state exposure. The decrease in the bioavailability of odevixibat following administration with food, did not correlate with differences in changes from baseline in the concentration of the PD marker, C4. Taking into account the lack of PK/PD relationship and need for sprinkling the odevixibat capsule contents on food for younger children, it is agreed to recommend that odevixibat can be administered with food.

Distribution

The odevixibat plasma protein binding was high, >99.7% at 4 µM and >99.97% at 40 µM (unbound fraction <0.3%). In different studies, different V/F values were reported. V/F varied between 614 L

(paediatric target population, based on population modelling) and 9940 L (adult subjects' study A4250-013; reported in the SmPC). The Applicant has presented descriptive statistics on V/F and body weight adjusted V/F derived with the population PK analysis for the odevixibat PK studies (A4250-001,-003, -004, -005, and -013). The results of the body weight adjusted V/F are consistent between studies. Based on these data the following statement, agreed by the CHMP, was included in the SmPC: The mean body weight adjusted apparent volumes of distribution (V/F) in paediatric patients for the 40 and 120 µg/kg/day dose regimens are 40.3 and 43.7 L/kg, respectively.

Elimination

Based on population PK modelling, the mean half-life in paediatric patients was about 2.4 hours. The half-life is highly variable and could often not be determined using the non-compartmental data, due many undetectable samples in the terminal elimination phase. In different studies, different CL/F values were reported, probably due to differences in body weight. CL/F varied between 398 L/hr (paediatric target population, based on population modelling) and 3060 L/hr (adult subjects' study A4250-013; reported in the SmPC). The Applicant has presented descriptive statistics on Cl/F and body weight adjusted Cl/F derived with the population PK analysis for the odevixibat PK studies (A4250-001,-003, -004, -005, and -013). The results of the body weight adjusted Cl/F are consistent between studies. Section 5.2 of the SmPC was updated accordingly.

The elimination pathways odevixibat were evaluated in mass balance study **A4250-007**. About 83% of the administered oral dose was recovered in 216 hours. An average of 0.002% (0 to 0.1%) of the total radioactivity was recovered from the urine and 82.886% (75.39 to 90.76%) was recovered from the faeces. Metabolic profiling data of the faecal samples obtained in mass balance study A4250-007 show that odevixibat is minimally metabolised in humans. In faeces >96% of the radioactivity was identified as the parent compound, suggesting minimal metabolism of odevixibat. *In vitro* study **ALB-005** with human hepatocytes identified three minor metabolites: M2, M3 and M6.

Dose proportionality and time dependencies

Due to the low and variable absorption it is not possible to estimate the dose proportionality (C_{max}/dose and AUC/dose) accurately. However, the mean C_{max} and AUC_{0-t} tended to increase with increasing doses. No accumulation of odevixibat is observed after multiple-dose administration, due to the short elimination half-life of the drug.

Special populations

Many PFIC patients have some degree of hepatic impairment because of the nature of the disease. Hepatic metabolism of odevixibat is not a major component of the elimination of odevixibat. Analysis of data from a placebo-controlled study in patients with PFIC Types 1 and 2 did not demonstrate a clinically important impact of mildly impaired hepatic function (Child Pugh A) on the pharmacokinetics of odevixibat. Although, body weight adjusted CL/F values were lower and body weight adjusted V/F values were larger in paediatric patients with PFIC with Child Pugh B compared to healthy subjects, the safety profile was comparable between the patient groups. Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

No clinically significant differences in the pharmacokinetics of odevixibat were observed based on mild renal impairment, age, sex or race. No subjects with moderate and severe renal impairment were included in the studies.

Further, the applicant used the population model to simulate the pharmacokinetics in paediatric patients < 1 year-old. Simulations predict that the C_{max} values in paediatric patients will remain below 1.06 ng/mL in most paediatric patients< 1 year old. As no PK samples are available for these infants, it is not possible to evaluate the appropriateness of the model, in children <1year.

Pharmacokinetic interaction studies

The role of different transporters and cytochrome P450 (CYP) enzymes on the fate of odevixibat was explored *in vitro*. Odevixibat concentrations in the range of 0.01-30 µM have been tested. Odevixibat has a very low bioavailability and is minimally metabolised. Therefore, the risk of metabolic interactions is minimal. In vitro tests showed that odevixibat was a substrate for the gastrointestinal efflux transporter P-gp and suggest that odevixibat could potentially inhibit CYP3A4 in the gut.

Based on the *in vitro* tests, odevixibat was not anticipated to be an inducer of CYP1A2, 2B6, and 3A4 nor an inhibitor of CYP1A2 or 2C19, 2C9, 2D6, 2C8, at clinically relevant concentrations.

Further, the *in vitro* tests showed that odevixibat is not a substrate for the transporter BCRP and it was not anticipated to inhibit any of the transporters tested (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2, MATE1, and MATE2-K.

Study **A4250-013** was conducted to investigate drug interactions with itraconazole, an inhibitor of P-gp and midazolam, a sensitive substrate of CYP3A4. This study showed a 50-60% increase of odevixibat exposure upon concomitant coadministration with the P-gp inhibitor itraconazole. Concomitant administration with the CYP3A4 substrate midazolam resulted not in an increase, but instead in a 30% decrease of midazolam exposure and a 20% decrease of its 1-OH-midazolam metabolite.

2.4.3. Pharmacodynamics

The pharmacodynamics (PD) of odevixibat were evaluated in Studies A4250-001 and A4250-003 by assessment of changes from baseline in serum bile acids, faecal bile acids, fibroblast growth factor 19 (FGF19), 7α-hydroxy-4-cholesten-3-one (C4) and autotaxin levels. A reduction in bile acid absorption is expected to result in lower levels of FGF19 and higher levels of C4. Autotaxin levels have been correlated with cholestatic pruritus.

Mechanism of action

Odevixibat is a small molecule that acts as a potent, selective inhibitor of the ileal bile acid transporter (IBAT). IBAT is a key regulator of the bile acid pool and a key element in enterohepatic circulation (Dawson 2003).

Odevixibat, administered orally, acts locally in the gut where it binds reversibly to IBAT to decrease the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acids. 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.

Primary and Secondary pharmacology

Study A4250-001 (healthy subjects)

Part 1 – single ascending dose

Mean decreases in FGF19 and mean increases in C4 from pre-dose to both post-dose time points (4 hours and 24 hours) were generally observed for each odevixibat dose level (0.1, 0.3, 1, 3, and 10 mg) compared with placebo but with high inter-subject variability. No meaningful dose-related trend was observed.

Overall and for each odevixibat dose level, mean decreases in plasma total bile acids from Day 1 pre-dose were recorded at 4 and at 24 hours post-dose, but with high inter-subject variability. No differences could be seen between dose levels.

Part 2 – multiple ascending dose

Cohorts 1 to 3 (Odevixibat 1 mg QD, 3 mg QD, and 1.5 mg BID Versus Placebo)

For FGF19, mean decreases from Day 1 pre-dose were observed for all odevixibat dose levels at all post-dose time points on Days 1 and 7, and at pre-dose on Day 7. For C4, comparable mean increases from Day 1 pre-dose were observed for all odevixibat dose levels at all post-dose time points on Days 1 and 7, with greater mean increases observed on Day 7. Pairwise treatment comparisons with placebo showed the adjusted arithmetic means were statistically significant for 3 mg odevixibat (FGF19 and C4 on both study days) and for 1.5 mg odevixibat BID (FGF19 on both study days and C4 on Day 7).

Mean decreases from Day 1 pre-dose in plasma levels of total bile acids were observed for odevixibat-dosed subjects in all cohorts, but with a high degree of variability. Pairwise treatment comparisons with placebo showed the mean decreases were statistically significant for 3 mg odevixibat QD and 1.5 mg odevixibat BID at isolated time points and were of similar magnitude.

Increases in mean changes from Day 1 pre-dose in concentrations of total bile acids in faecal homogenate and increases in the amount excreted over 24 hours post-dose during Day 7, were recorded for both placebo and odevixibat (at all dose levels), but with high variability. However, greater mean increases were observed for odevixibat-dosed subjects than for placebo-dosed subjects.

Cohorts 2, and 4 to 7 (Odevixibat/Cholestyramine versus Odevixibat Alone and Placebo)

There was a sustained decrease in FGF19 and an increase in C4 levels compared to baseline following repeat dosing of odevixibat alone (Cohort 2) or in combination with either Questran (Cohort 4) or CRC (Cohorts 5 and 7). Co-administration of odevixibat 3 mg QD with Questran appeared to result in a greater decrease in FGF19 mean AUC_{0-12} and in a greater increase in C4 mean AUC_{0-12} compared to administration of 3 mg odevixibat alone.

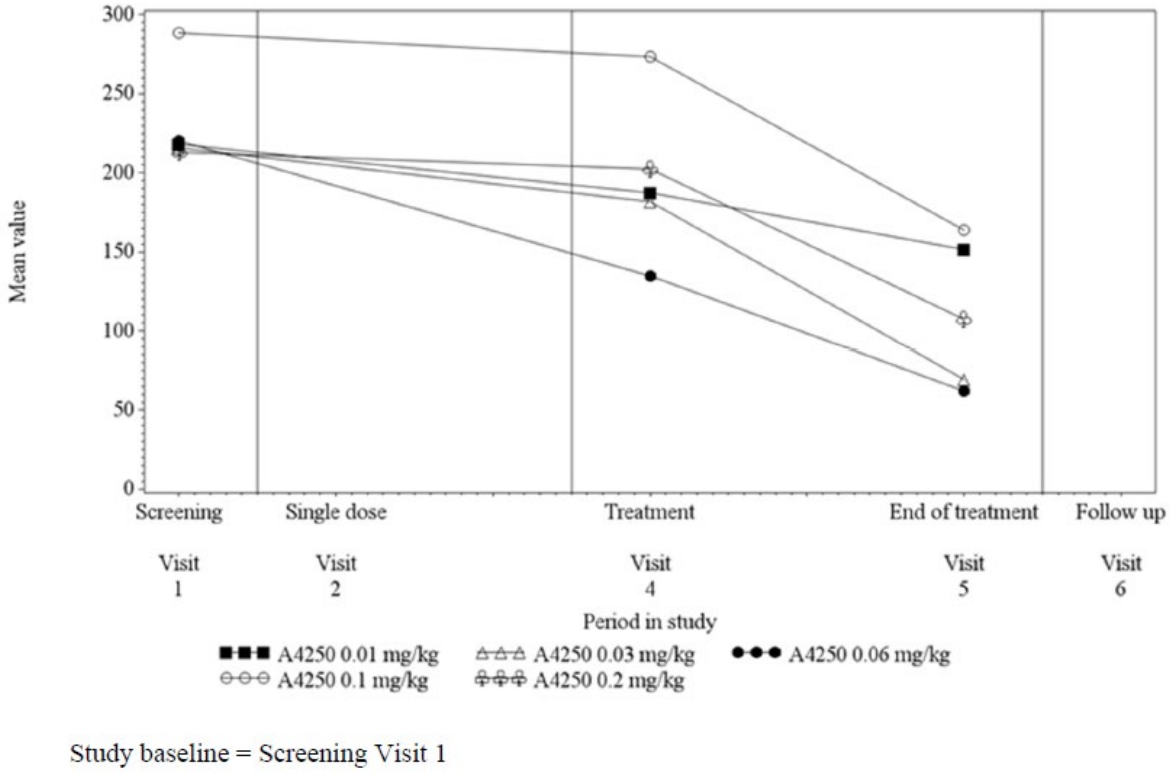
The odevixibat/Questran and odevixibat/CRC combinations did not appear to have had an additive effect on AUC(0–12) estimates of plasma total bile acids, irrespective of the timing of CRC administration concerning odevixibat dosing.

Mean increases from Day 1 pre-dose in the concentration and amount of total bile acids in faecal homogenate to Day 7 post-dose (24-hour collection period) were recorded for both odevixibat/Questran and odevixibat/CRC combinations, and placebo dose groups, but with high variability.

Study A4250-003 (paediatric patients with cholestatic pruritus)

A reduction in serum bile acid levels was observed after 4 weeks of daily treatment with odevixibat in all dose groups, with the smallest mean reduction being 30.9% in the 0.01 mg/kg dose group and the largest being 62.8% in the 0.06 mg/kg dose group. Further dose escalation did not show any additional decrease in total serum bile acids. Figure 5 illustrates the changes observed by cohort.

Figure 5: Total Serum Bile Acids (µmol/L)—Mean Values by Dose Group and Study Period (Full Analysis Set).



Study baseline = Screening Visit 1

Individual patient responses varied from a 98% reduction of total serum bile acids in some patients to almost unchanged levels in others. Numerically, patients with PFIC trended toward a greater response than patients with other diagnoses. The best response in the subgroup of patients with PFIC was at 30 µg/kg/day.

Mean increases from baseline to end of treatment in C4 were observed in all dose groups. Mean decreases in FGF19 were seen in all dose groups except the 0.1 mg/kg dose group. Mean decreases in plasma autotaxin were observed in all dose groups. No obvious dose-dependency for C4, FGF19, and autotaxin was seen (Table).

Table 27: Mean (StDev) Change from Baseline to End of Treatment for C4, FGF19, and Plasma Autotaxin (Full Analysis Set).

Measure	Odevixibat					Total
	0.01 mg/kg	0.03 mg/kg	0.06 mg/kg	0.1 mg/kg	0.2 mg/kg	
C4 (ng/mL)	7.5 ± 8.18 (n=4)	13.2 ± 23.44 (n=6)	9.9 ± 11.06 (n=4)	1.6 ± 2.02 (n=6)	5.8 ± 5.01 (n=3)	7.7 ± 13.18 (n=23)
FGF19 (pg/mL)	-27.8 ± 29.42 (n=2)	-46.8 ± 102.29 (n=5)	-48.5 ± 91.99 (n=4)	7.1 ± 97.06 (n=5)	-60.4 ± 67.53 (n=3)	-30.7 ± 83.34 (n=19)
Plasma autotaxin (ng/mL)	-196.3 ± 443.12 (n=4)	-795.5 ± 701.24 (n=6)	-85.3 ± 865.16 (n=4)	-336.7 ± 348.23 (n=6)	-416 ± 627.92 (n=3)	-389.2 ± 604.83 (n=23)

C4: 7α-hydroxy-4-cholesten-3-one; FGF19: fibroblast growth factor 19; StDev: standard deviation.

Secondary pharmacology

A dedicated QT study was not conducted. Non-clinical data indicated a low potential for adverse effects on the cardiovascular system, including cardiac conduction as assessed by ECG. This was supported by the ECG findings performed in Phase 1 studies conducted in healthy volunteers.

Odevixibat did not affect the hERG potassium channel at the tested concentration (1 µM), which is 7700-fold higher than the IC_{50} (0.13 nM) in the human IBAT transfected cell assay (0062SZ).

The clinical data in conjunction with the minimal systemic exposure to odevixibat, resulting only in transient nanomolar plasma concentrations (where quantifiable), indicates odevixibat does not carry a significant risk for induction of arrhythmias or QTc prolongation.

Dose-response analysis

Dose-response relationships were explored based on nonclinical results and biomarkers (bile acids, FGF19, and C4) in healthy subjects and children with cholestatic pruritus to support dosing of odevixibat.

Dose-Response Analysis of Odevixibat in Nonclinical Study

Odevixibat resulted in a significant inhibitory effect on the intestinal absorption of bile acids in ApoE knockout mice. Based on an animal-to-human conversion factor, the ED50, ED90, and ED95 of odevixibat were 0.00439, 0.0395 and 0.0834 mg/kg, respectively. Dose levels in study A4250-003 provided an adequate coverage of dose levels relative to above parameters, with the lowest dose (Cohort 1, 0.01 mg/kg) approximately 2-fold higher than the ED50 and the highest dose (Cohort 6, 0.2 mg/kg) approximately 2-fold higher than the ED95.

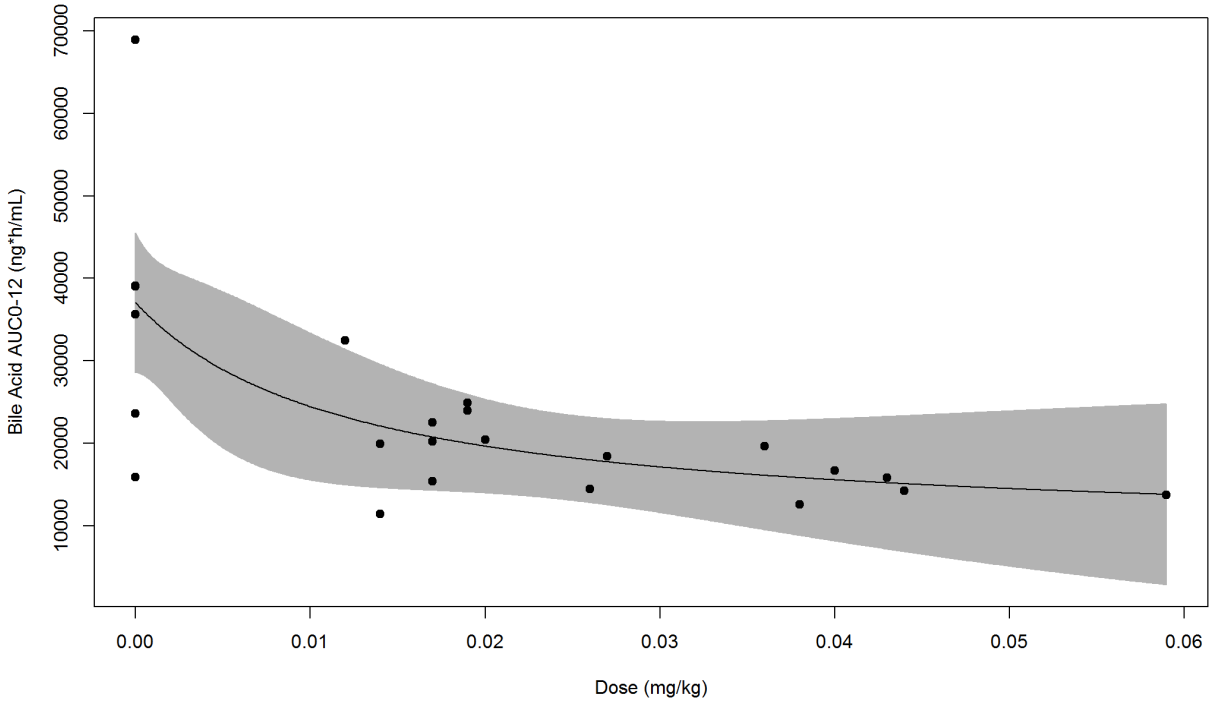
Dose-Response Analysis of Odevixibat in Healthy Subjects (A4250-001)

Bile acids

Among the different models tested, an Emax model was associated with a better fit of the AUC0-12 for bile acids vs dose. A gradual dose-dependent reduction in the AUC0-12 of bile acids was observed on Day 7 (

Figure **6**).

Figure 6: Study A4250-001 (Multiple Ascending Dose; Day 7); Dose-Response Relationship of AUC_{0-12} for Bile Acids.

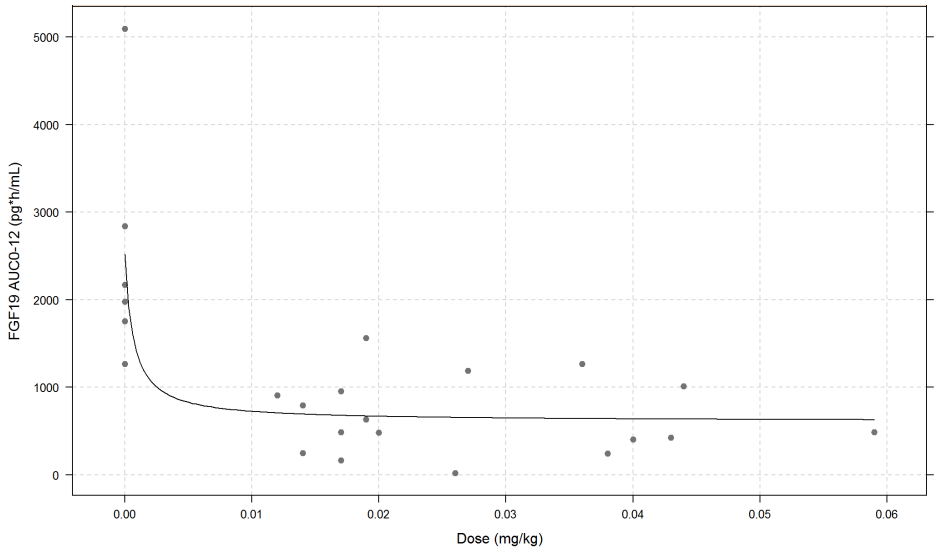


The model-estimated ED50 was 0.0123 mg/kg but was associated with a high uncertainty. The corresponding ED90 and ED95 are 0.111 and 0.234 mg/kg, respectively. Dose levels in study A4250-003 provided an adequate coverage of dose levels relative to these parameters.

FGF19

An Emax model best fit the data. A very steep dose-response relationship was observed on Day 7 (Figure 7). The estimated ED50 was very low (0.000649 mg/kg), suggesting a plateau of effect at doses greater than 0.01 mg/kg.

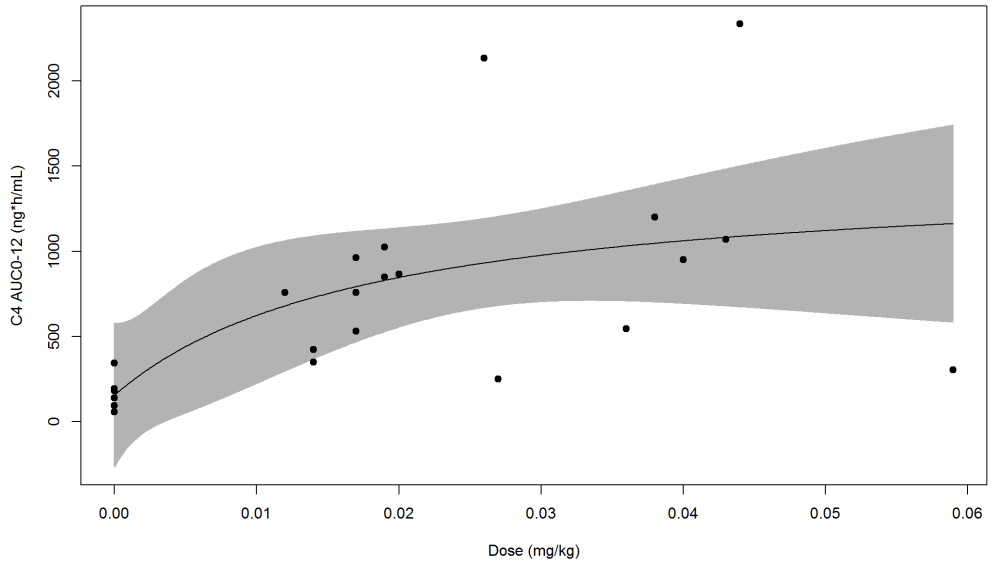
Figure 7: Study A4250-001 (Multiple Ascending Dose; Day 7); Dose-Response Relationship of AUC_{0-12} for FGF19.



C4

An Emax model provided the best fit to the data. A gradual dose-dependent increase in the AUC0-12 of C4 was observed on Day 7 (Figure 87).

Figure 8: Study A4250-001 (Multiple Ascending Dose; Day 7); Dose-Response Relationship of AUC_{0-12} for C4



The estimated ED50 was 0.0181 mg/kg. The corresponding ED90 and ED95 are 0.162 and 0.344 mg/kg, respectively. Dose levels in study A4250-003 provided an adequate coverage of dose levels relative to these parameters.

Dose-Response Analysis of Odevixibat in Children with Cholestatic Pruritus (A4250-003)

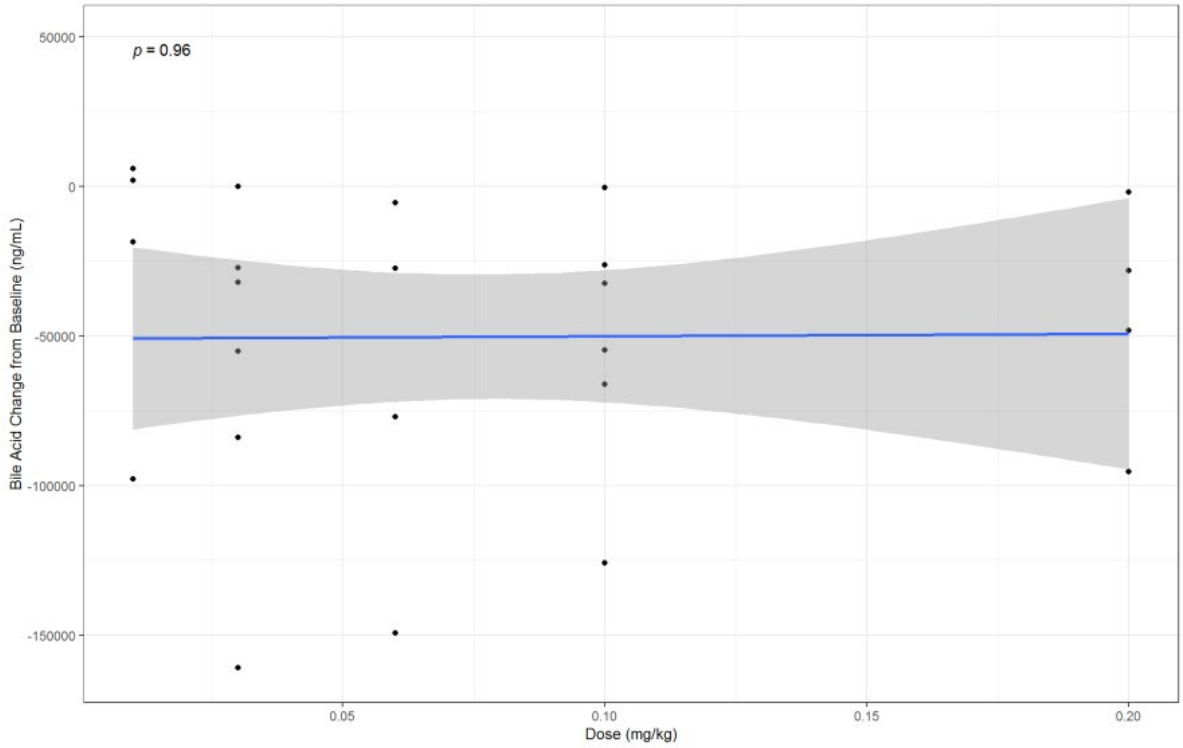
Bile Acids

Linear models were associated with a better fit to the data. Results for the dose-response analysis of bile acids derived with a linear model are presented in

Figure **9**.

. For both the change from baseline bile acids and the percent change from baseline bile acids, a statistically significant treatment effect (intercept) was observed but the slope for the relationship was not statistically significant.

Figure 9: A4250-003 (Visit 5); Dose-Response Relationship for Change from Baseline of Bile Acids.



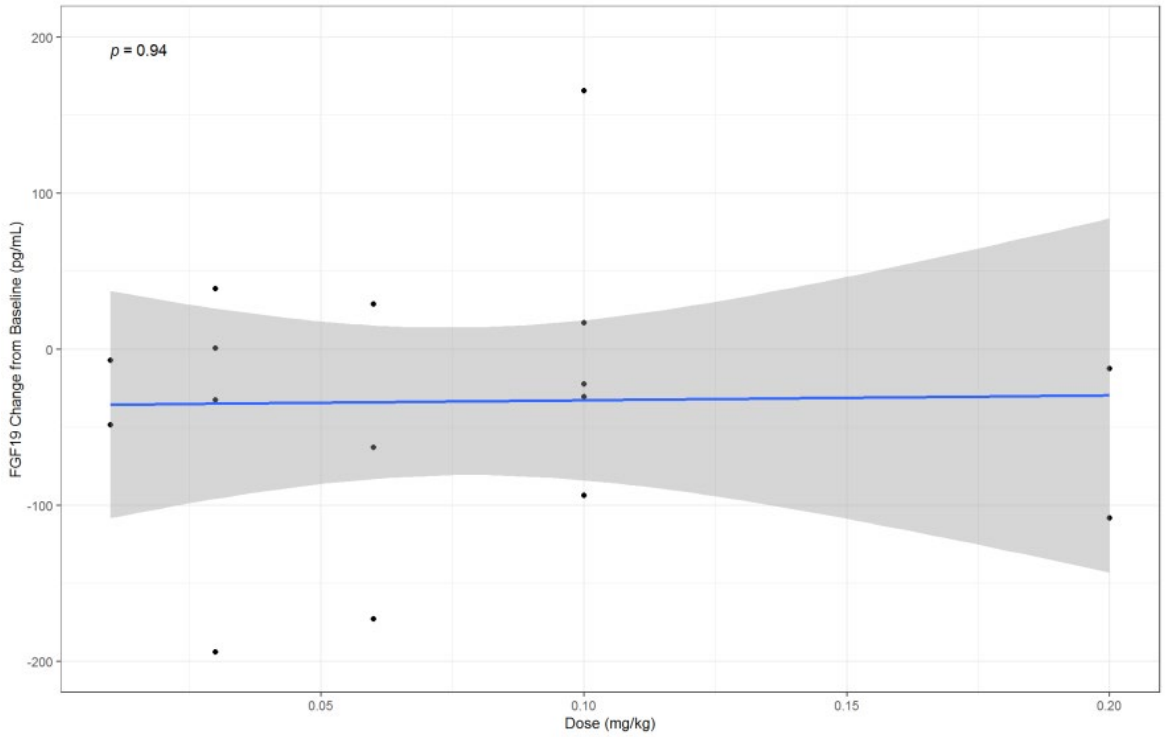
FGF19

Linear models provided the best fit to the data for all endpoints. Results for the dose-response analysis of FGF19 derived with a linear model are presented in

Figure **10**.

. Slopes and intercepts for the change from baseline and percent change from baseline were not statistically significant. Thus, no treatment effect and no dose-response relationships were observed.

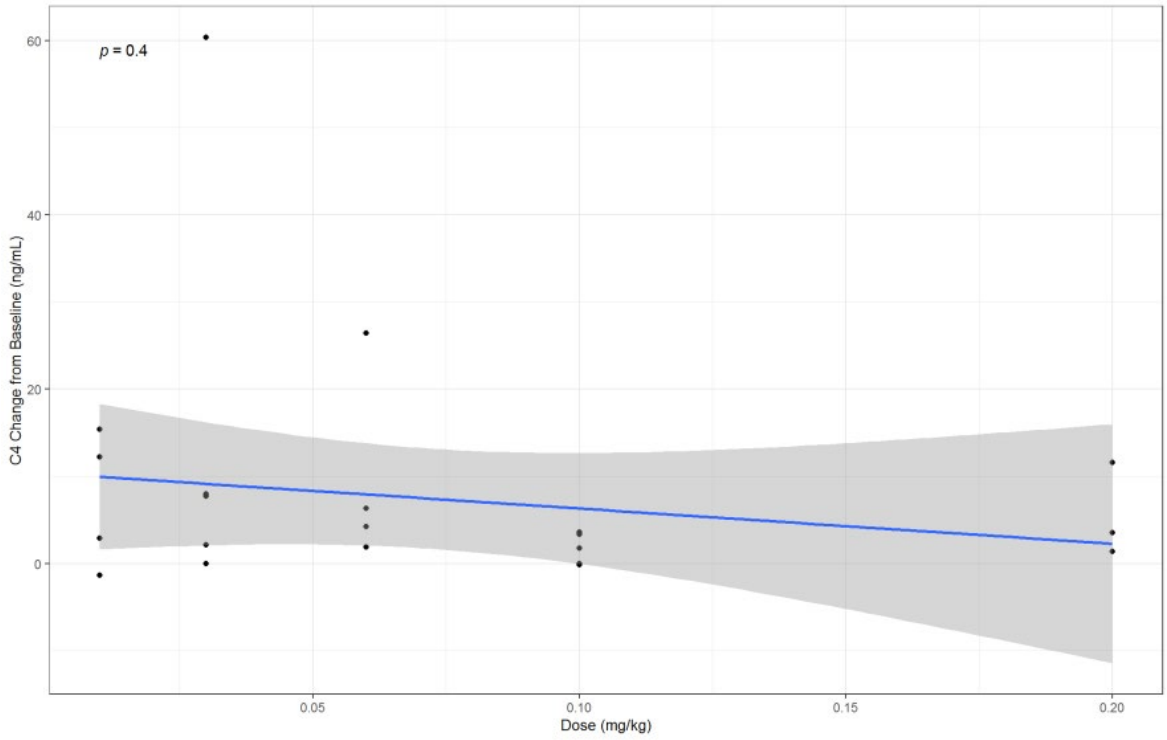
Figure 10: A4250-003 (Visit 5); Dose-Response Relationship for FGF-19.



C4

Linear models provided the best fit to the data. Results for the dose-response analysis of C4 derived with a linear model are presented in Figure 11. For both the change from baseline C4 and the percent change from baseline C4, a statistically significant treatment effect (intercept) was observed but the slope for the relationship was not statistically significant.

Figure 11: A4250-003 (Visit 5); Dose-Response Relationship for C4.



2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Methodology: Although an appropriately validated and sufficiently sensitive bioanalytical method was used to analyse the concentration of odevixibat in plasma, about 50% of the study samples were undetectable, and no ISR was conducted in studies A4250-001, A4250-005 and A4250-007 due to the small number of quantifiable results for odevixibat; which is considered acceptable. The non-compartmental pharmacokinetic parameters could not be determined for all subjects because the plasma levels of odevixibat were often not quantifiable in the terminal elimination phase. As the population PK analysis developed by the applicant accounted for the samples BLQ, the population model is considered more appropriate for assessing the PK of odevixibat than the non-compartmental studies. The population PK model accounted for the samples BLQ, using the likelihood method M3, as published by Beal. Data excluded from the primary analysis was detailed and sensitivity analyses confirmed that the exclusion of these data did not impact the results. The methodology used to construct the data set is considered acceptable, and PK model appears to describe the observed data reasonably well. The PK of odevixibat was described using a one-compartment model with linear elimination and two different rate constants of absorption (Ka1 and Ka2, with their respective lag times) to characterize double peak profiles. The base model included fixed exponents for the effect of body weight on CL/F and V/F (0.75 and 1, respectively), which is supported. PK parameters were estimated with good precision, and shrinkage values were adequate.

Covariates included in the final model, in addition to bodyweight on CL/F and V/F, were P-gp inhibitors and liver impairment on CL/F, dosage form and formulation on relative bioavailability, and formulation on Ka1. The rationale for covariate selection was adequately justified. The inclusion of covariates in the final model resulted in a decrease in between-subject variability (BSV) for CL/F and Ka1 but an increase in BSV for V/F. However, V/F was only dependent on body weight.

In order to allow assessment of the precision of parameter estimates, the applicant provided %RSE values for all parameters in the final model. Most parameters were estimated with good precision. A notable exception is the high RSE of 95.6% for the covariate effect $Frel_{FORMABC21}$ (to describe the different bioavailability of early formulation A, which was only used in SD/MD dose-finding study A4250-001). Nonparametric bootstrap resampling analysis showed comparable estimates to those derived in the original analysis. However, the 95% CI for the effect of formulation on Frel includes zero. The applicant explained that the reason for including the covariate effect of formulation was that it was highly statistically significant in the formal covariate analysis. Further, in the small number of subjects administered early formulation A, odevixibat concentrations were markedly lower than with other formulations. Given the small number of Formulation A concentrations in the popPK analysis, the 95% CI from the bootstrap analysis was considerably wide and should be interpreted with caution. It may have been more appropriate to fix this parameter to a plausible value or remove it from the model, but the issue was not further pursued.

VPCs of the final model suggest that the predictive ability of the model is limited. In the overall population, there is a tendency for underprediction of median peak concentrations and variability is not well captured. VPCs stratified by study show reasonably poor prediction of paediatric data in study A4250-003, with clear over-prediction of median concentrations. This is further seen in the VPCs by disease type, since all patients included in the dataset were paediatric. Finally, VPCs stratified by degree of liver impairment indicate poor model prediction in patients with liver impairment. Although the predictive ability of the model is limited, it is questionable whether the model can be improved without additional collection of PK samples. As limited PK data are currently available in children and concentrations were very low and often undetectable, the poor predictions are accepted.

Several bioanalytical methods were developed to monitor the pharmacodynamic effects of odevixibat. For each method validation report submitted, data were presented to confirm calibration curve (CC) performance, intra- and inter-assay accuracy and precision using quality control (QC) samples. However, not all methods have been fully validated; some were qualified or partially validated. Upon request from the CHMP, the applicant provided detailed performance characteristics of the total bile acid assay, which shows that intra- and inter- assay reproducibility were within the accepted range. Further, routine technology has been used to determine liver function tests, which is considered acceptable.

Updated stability data were submitted. Long-term stability of C4 in human plasma has been shown for 388 days at -20°C and 380 days at -80°C (project LGC301045QB40); study samples of studies A4250-004 and -005 have been analysed within the validated stability period. However, it should be noted that the stability of C4 in human plasma under this analytic project was assessed with acceptance criteria of < + 30% CV and RE; EMA guideline on method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**), states that *the mean concentration of QC samples should be within ±15% of the nominal concentration*. Further, LPA samples from study A4250-005 were analysed outside of the 552-day stability period. Both samples are presented in the report for information only and were analysed initially within the stability period but gave concentrations above the analytic range. It is acceptable that repeat analysis of 2 samples was conducted outside the stability window.

In method QBR116156QB02 for determination of bile acids in human plasma or faeces, all QC samples and calibration standards were prepared in a surrogate matrix (phosphate buffered saline), because the analytes are endogenous in both human plasma and faeces. Precision and accuracy of the method was determined using this surrogate matrix, these data demonstrate that the %CV and %RE for each analyte calibration curve, were within <20%, the acceptance criterion for precision and accuracy of the method. It is accepted that samples from study A4250-001, were measured using a non-validated assay and was not used for analysis of samples from other studies.

No ISR was performed for determination of FGF-19 (study A4250-001) and determination of LPA (studies A4250-003, A4250-005), but the applicant has provided adequate reasoning for the failure to perform incurred sample reanalysis (ISR).

Absorption: Odevixibat is a low permeability drug designed for minimal systemic absorption and intended to act locally in the gut where it binds reversibly to the ileal bile acid transporter (IBAT) to decrease the reuptake of bile acids from the ileum and their return to the liver. The low solubility and low permeability have been appropriately demonstrated *in vitro.*

A low bioavailability was observed in the submitted single and multiple-dose studies **A4250-001** and **A4250-003**. In mass balance study **A4250-007** about 83% of the administered oral dose was recovered in 216 hours. An average of 0.002% of the total radioactivity was recovered from the urine, and 82.886% was recovered from the faeces. In about 50% of the study samples, odevixibat was undetectable. These data indicate that there is very limited absorption of odevixibat following oral administration. In the SmPC, the pharmacokinetic results from study **A4250-013** are presented. In this study, healthy adults received a single oral dose of 7200 µg odevixibat, the highest recommended dose of odevixibat. Upon request from the CHMP, the applicant provided an estimate of the relative bioavailability in humans, which is < 1% based on pop PK data on study **A4250-005** and non-compartmental data of study **A4250-013**. The exposure of odevixibat was calculated for the 40 and 120 µg/kg/day dose levels in the target population, paediatric patients with PFIC (study **A4250-005**), using the population model. The mean C_{max} of odevixibat in paediatric patients treated with the 40 and 120 µg/kg/day dose were 0.211 and 0.623 ng/mL, respectively, and their mean AUCs were 2.26 and 5.99 ng*hr/mL, respectively. However, differences were observed between observed and simulated post hoc patient data of study **A4250-005**. The applicant clarified the differences, between observed

and simulated post hoc patient data of study A4250-005. For many study subjects no measurable concentrations could be reported due to sparse sampling and the lack of samples around C_{max}. The pop PK model includes rich concentration time profiles and can be used to describe the pharmacokinetics of odevixibat more accurately. The model-based concentration time data for the paediatric PFIC population, are mentioned in the updated SmPC, this is considered acceptable.

Food effect study **A4250-004** showed that concomitant administration of a high-fat resulted in decreases of approximately 72% and 62% in C_{max} and AUC_{0-24}, respectively, compared to administration under fasted conditions. When odevixibat was sprinkled on apple sauce, decreases of approximately 39% and 36% in C_{max} and AUC_{0-24}, respectively, were observed compared to administration under fasted conditions However, this effect on the pharmacokinetics did not correlate with differences in changes from baseline in the concentration of the PD marker C4. Taking into account the lack of PK/PD relationship and need for sprinkling the odevixibat capsule contents on food for younger children, it is agreed by the CHMP to recommend that odevixibat can be administered with food. As no safety markers were studied and the drug is intended to act locally in the GI tract, a higher bioavailability is not desired; therefore, the current advice to take the drug with food is supported by the CHMP.

Distribution: The volume of distribution differed between the dense sampling study **A4250-013** and the population PK study. In study **A4250-013** , the apparent volume of distribution (Vz/F) was 9940 L, following a single oral dose of 7200 µg odevixibat in healthy adults. This differs from the V/F reported in the population PK model, a V/F of 2510 L and 614 L were reported for the overall population and paediatric population, respectively. These differences can be explained by the use of different calculation methods and body weight differences. As V/F is body weight dependent, the applicant presents the body weight normalised volume of distribution in the SmPC, which is acceptable to the CHMP.

Elimination: The consistency of the half-life and clearance (CLss/F) across studies is difficult to assess based on non-compartmental data, due to many undetectable samples in the terminal elimination phase. As the population model did account for the samples below the detection limit, it is preferred to present the model estimates in the SmPC.

The clearance differed between the dense sampling study A4250-013 and the population PK study. In study A4250-013, the average apparent total clearance (CLss/F) was 3060 L/h and a mean half-life (t1/2) 2.36 hours. This value differs from CL/F reported in the population PK model, CL/F of 2180 L/h and 398 L/h were reported for the overall population and paediatric population, respectively. These differences can be explained by the use of different calculation methods and body weight differences. As CL/F is body weight dependent the applicant presents the body weight normalised clearance in the SmPC, which is acceptable to the CHMP.

Variability and dose proportionality: Due to the low bioavailability of odevixibat, the variability of the PK parameters is relatively high. It is not possible to estimate the dose proportionality (C_{max}/dose and AUC/dose) accurately. However, the mean C_{max} and AUC_{0-t} tended to increase with increasing doses. Odevixibat has a short elimination half-life, and no accumulation is observed. The agreed SmPC mentions that the Cmax and AUC0-t increase with increasing doses in a dose-proportional manner; however due to the high between-subject-subject variability of approximately 40%, it is not possible to estimate the dose proportionality accurately.

Transport: Odevixibat is identified as a substrate of P-gp and P-gp transporters are encoded by the MDR1 gene which is known to have allelic variants that have been shown to influence protein expression and P-glycoprotein. It is possible that genetic polymorphism may contribute to the variability of absorption. As the bioavailability is low in all subjects and the drug interaction study with

itraconazole has shown that the impact on P-gp inhibition is small, the CHMP agrees that there is no need to investigate the role of polymorphism of MBR1.

Special populations: The population PK analysis was used to evaluate the influence of intrinsic factors on the pharmacokinetics of odevixibat. Weight and hepatic impairment were identified as relevant covariates. No clinically significant differences in the pharmacokinetics of odevixibat were observed based on age, sex or race.

Limited systemic PK data are available in order to compare subjects with hepatic dysfunction to subjects with normal hepatic function as none of the paediatric subjects, included in the Phase 3 study **A4250-005** had a normal hepatic function. Upon request from the CHMP, the applicant presented a comparison of the PK results of the Phase 3 study **A4250-005** and data from studies **A4250-004** and **A4250-013** in healthy adult subjects with normal liver function, to assess the impact of hepatic impairment. The body weight adjusted pharmacokinetic parameters of odevixibat were comparable between paediatric patients with PFIC with Child Pugh A and healthy subjects. Body weight adjusted CL/F values were lower and body weight adjusted V/F values were larger in paediatric patients with PFIC with Child Pugh B compared to healthy subjects. The mean body weight adjusted CL/F and V/F values were 10 L/h/kg and 51 L/kg in subjects with moderate hepatic dysfunction and 34 L/h/kg and 34 L/kg in subjects with normal hepatic function, respectively. According to the applicant, model predicted parameters for Child-Pugh B may have been skewed by two individual patients with Child Pugh B with unexpectedly high concentrations. It is agreed that, due to the limited number of measurable samples, this may have impacted the PK model. Although no clinically relevant tolerability differences have been observed between paediatric subjects with moderate hepatic impairment and healthy adults, it remains difficult to interpret the PK model correctly due to the limited amount of data which may be skewed for unknown reasons.

Mild renal impairment does not have any significant effect on the PK of odevixibat. This is consistent with the minimal renal elimination of odevixibat observed in mass balance study **A4250-007**, 0.002% of the total radioactivity was recovered from the urine. The applicant confirmed that there are no data in patients with moderate or severe renal impairment, or ESRD and has updated the SmPC to reflect this. Given the minimal absorption and minimal renal elimination of odevixibat, no dosage adjustment is required for patients with mild or moderate renal impairment and no additional monitoring is warranted.

The pivotal Phase 3 study (**A4250-005**) included paediatric patients (aged ≥6 months) with a body weight above 5 kg. However, Section 4.2 of the SmPC specifies doses for patients with a 4 kg or higher body weight. The applicant explained that, based on the dosing schedule in the SmPC, a child weighing 4 kg would receive doses that are within the dose ranges allowed in higher weight bands and have demonstrated both safety and efficacy. Further, inclusion of the lower of weight of 4 kg in the SmPC would allow symptomatic children weighing 4 kg to receive treatment. The SmPC is considered acceptable to the CHMP.

The population model was used to simulate the pharmacokinetics in paediatric patients < 1 year old. Simulations predict that the C_{max} values in paediatric patients will remain below 1.06 ng/mL in most paediatric patients< 1 year old. As no PK samples are available for these infants it is not possible to check the goodness of fit of the model in children <1year. The applicant proposes to indicate odevixibat for the use in children aged 6 months and older with PFIC, based on clinical efficacy and safety data. The use of PK modelling simulations in the youngest age group, without the goodness of fit data in this age group, is considered acceptable as the bioavailability of odevixibat is very low, and collection of PK samples is difficult in this age group. The extrapolation approach for paediatric patients aged <1 year assumes similar exposure-response relationships for safety between patients <1 year of age and children (1-17 years of age). An assessment based on clinical efficacy and safety data is

appropriate for this age group. However, simulations indicated that, at a dose of 120 µg/kg/day, 0.9% and 9.0% of paediatric patients (aged 6 to <12 months) with mild and moderate liver impairment, respectively, would be expected to achieve C_{max} values above 1.06 ng/mL , the level demonstrated to have an acceptable safety profile in clinical studies. The applicant considers that these proportions are very low and, therefore, a dose adjustment for paediatric patients <1 year is not warranted. The applicant further justified that, based on simulations, the 120 µg/kg/day dosing regimen of odevixibat is expected to result in C_{max} values below 2 ng/mL patients with PFIC < 1 year of age, which is about 3-fold lower than the NOAEL for dogs.

Interactions: The role of different transporters and cytochrome P450 (CYP) enzymes on the fate of odevixibat was explored *in vitro*. Odevixibat concentrations have been tested in the clinically relevant concentration range of 0.01-30 µM. Odevixibat has a very low bioavailability and is minimally metabolised. Therefore, the risk of metabolic interactions is minimal. *In vitro* tests showed that odevixibat was a substrate for the gastrointestinal efflux transporter P-gp and suggested that odevixibat could potentially inhibit CYP3A4 in the gut. Concomitant administration with the P-gp inhibitor itraconazole resulted in a 50-60% increase of odevixibat exposure. These results are consistent with odevixibat being a substrate of P-gp. However, the magnitude of the increase indicates that this interaction is not clinically relevant. Concomitant administration with the CYP3A4 substrate midazolam resulted in a 30% decrease of midazolam exposure and a 20% decrease of its 1-OH-midazolam metabolite. Because the impact was small and did not follow the classical pattern for inhibition of CYP3A4, the interaction at the gut level is not considered clinically important.

Because treatment with odevixibat results in decreased recirculation of bile acids also the absorption of fat-soluble vitamin deficiencies and lipophilic drugs may be affected. Therefore, the applicant monitored the vitamin status as a safety parameter in the clinical studies. In the agreed SmPC section 4.5, the results of the monitoring of fat-soluble vitamins have been provided and it is mentioned that the potential interaction with lipophilic drugs has not been investigated. This wording is agreed by the CHMP. Levels of fat-soluble vitamins will be monitored in a post-marketing setting.

The non-clinical studies indicate that odevixibat may be teratogenic at clinically relevant concentrations. Therefore, adequate contraception is required. However, no interaction study with oral hormonal contraception has been conducted. The applicant committed to conduct an interaction study with an oral hormonal contraceptive. The final study report is awaited in agreed due time. In the agreed SmPC section 4.5, it is mentioned that the potential interaction with oral contraceptives has not been investigated. Since the uptake of lipophilic oral contraceptives may be affected by odevixibat, a barrier contraceptive method should be used.

Pharmacodynamics

The PD of odevixibat were evaluated by assessment of changes from baseline in serum bile acids, faecal bile acids, FGF19, C4 and autotaxin levels (which have been correlated with cholestatic pruritus).

Primary pharmacology

Study A4250-001 (healthy adults): In Part 1 of the study, following a single dose of odevixibat to healthy subjects, greater mean decreases in plasma FGF19 and associated increases in plasma C4 levels were generally observed at all dose levels compared with placebo. However, there was no apparent dose-related trend for these changes. Mean plasma total bile acids levels increased post-dose at all levels, although a high degree of variability was observed. This trend towards a general increase in total bile acids is not consistent with the mode of action of odevixibat. The applicant considers that this could be due to the insufficient duration of effect of odevixibat with a single dose. In Part 2 of the study, following repeated administration of odevixibat for 7 days to healthy subjects, mean decreases

in FGF19 were observed for all dose levels with a corresponding increase in C4 plasma levels. These changes were most notable for the 3 mg once daily dose level.

Mean decreases in plasma total bile acids were observed at all dose levels, but not consistently. Compared with placebo, significantly greater mean changes in total bile acids on Day 7 were shown for the 3 mg once daily and 1.5 mg twice daily regimens but only at 24 h post-dose and pre-dose time points, respectively. Notably, odevixibat/cholestyramine combinations, no statistically significant results were recorded for any odevixibat dose level when Day 7 and Day 1 mean changes in total bile acids were compared. Overall, the data suggest that the effect of odevixibat on plasma total bile acids is highly variable.

For mean changes in concentrations of total bile acids in faecal homogenate and the amount excreted at 24 h post-dose during Day 7, mean increases from baseline were recorded for placebo and all odevixibat dose levels, but with high variability. Greater mean increases were observed for active-dosed subjects than for placebo-dosed subjects. Pairwise treatment comparisons with placebo showed that the adjusted arithmetic means (mean increases) were statistically significantly greater for 3 mg once daily and 1.5 mg twice daily but not for 1 mg once daily.

Results of the exploratory analysis in Part 2 of the study suggested that Questran, but not CRC, may have an additive effect on odevixibat in terms of FGF19 and C4 levels. The odevixibat/Questran and odevixibat/CRC combinations did not appear to have an additive effect on AUC(0–12) estimates of plasma total bile acids, irrespective of the timing of CRC administration concerning odevixibat dosing.

Study A4250-003 (paediatric patients with cholestatic pruritus): Reduction in total serum bile acids was highly variable. There was a trend for greater mean decreases with increasing doses up to 60 µg/kg/day. No further reductions were apparent at doses above this. The best response in the subgroup of patients with PFIC was at 30 µg/kg/day.

For the biochemical markers of bile synthesis, mean decreases in FGF19, mean increases in C4 and mean decreases in plasma autotaxin were observed, with no apparent dose-dependency. These PD trends are generally consistent with those observed in healthy adults in Study A4250-001.

Dose-Response Analysis of Odevixibat by weight (study A4250-003 and -005): It is agreed with the applicant that this may be due to a plateau already reached. In the analysis no dose relationship could be established, these results are in line with clinical observations, which support similar efficacy between the 40 µg/kg/day and 120 µg/kg/day two dose regimen. The lack of clear dose-response relationship is mentioned in SmPC section 5.2.

Secondary pharmacology

Lack of a dedicated QT study is considered acceptable. Non-clinical data indicated a low potential for QT prolongation with odevixibat at the very low systemic exposure observed in the clinical studies at the proposed dose.

Pharmacodynamic interactions

It is considered possible that odevixibat reduces the levels of conjugated UDCA in patients with PFIC while parent UDCA levels may be elevated. Nevertheless, in Study **A4250-005**, the majority of patients were on stable doses of UDCA and the beneficial effects of odevixibat were not compromised. UDCA and odevixibat can be administered concomitantly.

Genetic differences in PD response to odevixibat

Upon request from the CHMP, the applicant discussed the potential for genetic differences in the PD response to odevixibat. There are no known genetic mutations that result in changes to IBAT that produce resistance to inhibition by odevixibat. In addition, genetic variations in the CYP enzymes or

transporters are unlikely to impact the PD response to odevixibat since it undergoes minimal metabolism and inhibition of the P-gp transporter did not result in relevant increase of the odevixibat exposure (see transporters).

Dose-response analysis

The objective of this modelling exercise was to explore dose-response relationships based on non-clinical results and biomarkers (bile acids, C4, and FGF19) in healthy subjects as well as children with cholestatic pruritus to support dosing of odevixibat.

While bile acids, C4 and FGF19 presented dose-dependent relationships in healthy subjects following 7 days of dosing (Study **A4250-001**), a treatment effect independent of the dose was observed following 42 days of dosing in children with cholestatic pruritus (Study **A4250-003**).

2.4.5. Conclusions on clinical pharmacology

Odevixibat is a low permeability drug designed for minimal systemic absorption and intended to act locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids from the ileum and their return to the liver. It has been appropriately shown that odevixibat has low bioavailability and generally, the pharmacokinetics of odevixibat has been sufficiently characterised. As non-clinical studies indicate that odevixibat might be teratogenic at clinically relevant concentrations, the applicant has agreed to conduct an interaction study with oral hormonal contraception following the CHMP's request.

Based on the data submitted, the inclusion of appropriate information in the SmPC, especially on impact of hepatic impairment, the extrapolation to children <1 year and the between-study consistency of the pharmacokinetic data, the pharmacodynamic properties of odevixibat are considered demonstrated.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- Drug-drug Interaction study to investigate the interactions between odevixibat and oral contraceptives, due to observations in non-clinical studies that odevixibat might be teratogenic at clinically relevant concentrations.

2.5. Clinical efficacy

Table 28 provides an overview of the clinical studies that are conducted to substantiate the proposed indication in the treatment of PFIC in patients aged 6 months and over.

Table 28: Overview of Clinical Studies Designed to Support the Efficacy of Odevixibat in the Proposed Indication.

STUDY ID STUDY DATES[A] (STATUS)	STUDY CENTRES[B] (LOCATION)	PHASE STUDY DESIGN	STUDY POPULATION	DOSE REGIMEN/ DURATION	PRIMARY EFFICACY ENDPOINT	NO. OF PATIENTS TREATED	SEX MEDIAN AGE RACE
A4250-005 16MAY2018 – 28JUL2020	33 (US, Canada, Europe, Middle East, Australia)	Phase 3, double-blind, randomised, placebo-controlled	Paediatric patients with PFIC1 or PFIC2	Oral administration of 40 µg/kg or 120 µg/kg odevixibat or matching	Europe and RoW: Proportion of patients who experienced at least a 70% reduction in serum bile acids	Odevixibat: 40 µg/kg: 23 120	31M/31F 3.2 yrs 52W/2B/2A/ 6 Other

(Complete)				placebo daily for 24 weeks	concentration from baseline to the end of treatment or reached a level ≤70 µmol/L compared to placebo after 24 weeks of treatment US: Proportion of positive pruritus assessments at the patient level over the 24-week treatment period	µg/kg: 19 Placebo: 20	
pivotal[c] 28SEP2018 - Ongoing	33 (US, Canada, Europe, Middle East, Australia)	Phase 3, open-label extension study	Cohort 1: Patients with PFIC1 or PFIC2 who were treated in Study A4250-005 Cohort 2: Treatment naïve patients with any PFIC type	Oral administration of 120 µg/kg odevixibat daily for 72 weeks[d]	Europe and RoW: Change from baseline in serum bile acids after 72 weeks of treatment. US: Proportion of positive pruritus assessments at the patient level over the 72-week treatment period	Cohort 1: 53 Cohort 2: 16	35M/34F 4.1 yrs 60W/1B/2A/ 6 Other
A4250-003 25AUG2015 - 17MAR2017 (Complete)	6 (Europe)	Phase 2, multiple center, single- and multiple-dosing open-label study	Paediatric patients with cholestatic pruritus	Single oral dose of 10, 30, 60, 100, or 200 µg/kg odevixibat. Each patient then received daily dosing for 4 weeks after a 14-day washout	Change in total serum bile acids after 4 weeks of treatment	20 (4 of these were re-enrolled)[e]	15M/9F 6 years

A: Asian; B: Black; F: female; ID: identification; M: male; No.: number; PFIC: progressive familial intrahepatic cholestasis; RoW: rest of world; US: United States; W: white.

a. *Date of first patient dosed to last patient last visit.*

b. *Centers that enrolled patients are included.*

c. *Data included are through the data cut-off date of 15JUL2020.*

d. *After the 72-week treatment period, patients had the option to remain on treatment in an extension period until the drug is commercially available.*

e. *Re-enrolled patients were treated as unique patients in each cohort for analyses.*

2.5.1. Dose response study(ies)

A4250-003: An Exploratory Phase II Study to Demonstrate the Safety and Efficacy of A4250 in Children with Cholestatic Pruritus.

Study A4250-003 was a Phase 2 single and multiple-dose, dose-finding, open-label study to evaluate the safety and efficacy of odevixibat when administered for 4 weeks in paediatric patients diagnosed with cholestatic pruritus (including patients with PFIC, Alagille syndrome, biliary atresia, and sclerosing cholangitis).

Methods

The study included a screening period to determine eligibility (this period also included a 7-day washout for patients on prior bile acid resin or other prohibited medication), single administration treatment period with a 10-day follow-up period, and a 4-week treatment period. There was no randomisation or stratification in the study.

Study Participants

Inclusion Criteria

For inclusion in the study, patients had to fulfil the following criteria:

- Diagnosis of pruritus due to chronic cholestasis based on history and Investigator judgment
- This included but was not restricted to patients with PFIC, ALGS, BA, and sclerosing cholangitis
- Laboratory markers of cholestasis identified within 3 months before Visit 1
- Total serum bile acids at least 2 times above the 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

Exclusion Criteria

- 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 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 the Screening period

Treatments

The study was designed to have 6 dose cohorts with 4 patients to be evaluated in each cohort. Patients were permitted to re-enrol into a later cohort after completion and a washout period following treatment in their first cohort.

- Cohort 1: 0.01 mg/kg/day
- Cohort 2: 0.03 mg/kg/day
- Cohort 3: 0.06 mg/kg/day
- Cohort 4: 0.1 mg/kg/day
- Cohort 5: 0.2 mg/kg/day
- Cohort 6: 0.3 mg/kg/day (planned)

The study was originally designed to evaluate doses up to 300 µg/kg/day. However, two patients with Alagille syndrome in the 200 µg/kg/day cohort experienced elevations in LFTs >2 times baseline. Although the respective investigators deemed both cases to be unrelated to study treatment and in line with their historical LFT fluctuations, the Data and Safety Monitoring Board (DSMB) recommended that further dose escalation not occur as elevations in one of the patients were considered inconclusive by the DSMB. Continued dosing at the 200 µg/kg/day was allowed.

In the situation that despite odevixibat treatment, the patient deteriorated biliary diversion surgery or liver transplant could be engaged as a rescue treatment.

Objectives

The primary objectives of this Phase 2 exploratory study in patients treated with odevixibat due to cholestasis induced pruritus were as follows:

- Assess the safety and tolerability of odevixibat orally administered first as a single dose and then during a 4-week treatment period as determined by the occurrence of treatment-emergent serious adverse events (SAEs)
- Explore changes in total serum bile acids during a 4-week treatment period

Secondary safety objectives of this study included assessment of the safety and tolerability of odevixibat 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 as follows:

- Demonstrate the efficacy of odevixibat, 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

Outcomes/endpoints

The efficacy of treatment was assessed by measuring of serum bile acids levels, pruritus and sleep-related endpoints. Assessments of pruritus and sleep-related endpoints were based upon patients' reports through a paper diary that included daily questionnaires.

Safety assessments conducted during the study included physical examination, vital sign measurements, clinical laboratory evaluations (including haematology, chemistry, and urinalysis), and review of concomitant medications and AEs.

Randomisation and blinding (masking)

This is an open-label study. There was no randomization or stratification.

Statistical methods

In general, descriptive statistics were presented for all efficacy variables and endpoints, PK parameters, and safety variables, as appropriate.

Results

Baseline date

Baseline demographics and patients' characteristics are described in

Figure **13**.

Table 29: Summary of Demographic Characteristics (Safety Set).

Variable	Category	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	TOTAL (N=24)
		0.01 MG/KG (N=4)	0.03 MG/KG (N=6)	0.06 MG/KG (N=4)	0.1 MG/KG (N=6)	0.2 MG/KG (N=4)	
Gender information	N	4 (100.0%)	6 (100.0%)	4 (100.0%)	6 (100.0%)	4 (100.0%)	24 (100.0%)
Male		3 (75.0%)	1 (16.7%)	3 (75.0%)	4 (66.7%)	4 (100.0%)	15 (62.5%)
Female		1 (25.0%)	5 (83.3%)	1 (25.0%)	2 (33.3%)		9 (37.5%)
Age (years) at date of consent (based on month level birth date)	N	4 (100.0%)	6 (100.0%)	4 (100.0%)	6 (100.0%)	4 (100.0%)	24 (100.0%)
	Mean	9.8	6.5	6.3	4.7	6.3	6.5
	StDev	3.77	4.51	4.5	2.8	7.54	4.56
	Median	9	5.5	6	4	3.5	6
	Min	6	2	1	2	1	1
	Max	15	14	12	9	17	17
Height (cm)	N	4 (100.0%)	6 (100.0%)	4 (100.0%)	6 (100.0%)	4 (100.0%)	24 (100.0%)
	Mean	128.4	116.7	112.5	96.5	104.8	110.9
	StDev	23.91	25.4	31.35	14.04	42.96	27.39
	Median	124.85	114	112.25	92.9	92.5	107.25
	Min	105	87	75	82	70.5	70.5
	Max	159	156	150.6	117.2	163.5	163.5
Weight (kg)	N	4 (100.0%)	6 (100.0%)	4 (100.0%)	6 (100.0%)	4 (100.0%)	24 (100.0%)
	Mean	30.7	24.8	23	16.5	22.3	23
	StDev	15.33	4.87	11.91	6.05	23.77	14.18
	Median	26.8	20.55	21.6	14.07	12.2	17.8
	Min	16.9	11.8	10.28	11.7	7.3	7.3
	Max	52.3	52	38.6	26	57.6	57.6

BMI (on the basis of height and weight entered)	N	4 (100.0%)	6 (100.0%)	4 (100.0%)	6 (100.0%)	4 (100.0%)	24 (100.0%)
	Mean	17.6	16.7	17.4	17.2	16.2	17
	StDev	2.35	2.46	0.65	1.47	3.78	2.15
	Median	17.22	16.205	17.16	17.555	15.345	16.83
	Min	15.33	14.15	16.8	14.8	12.73	12.73
	Max	20.69	21.37	18.28	18.93	21.55	21.55

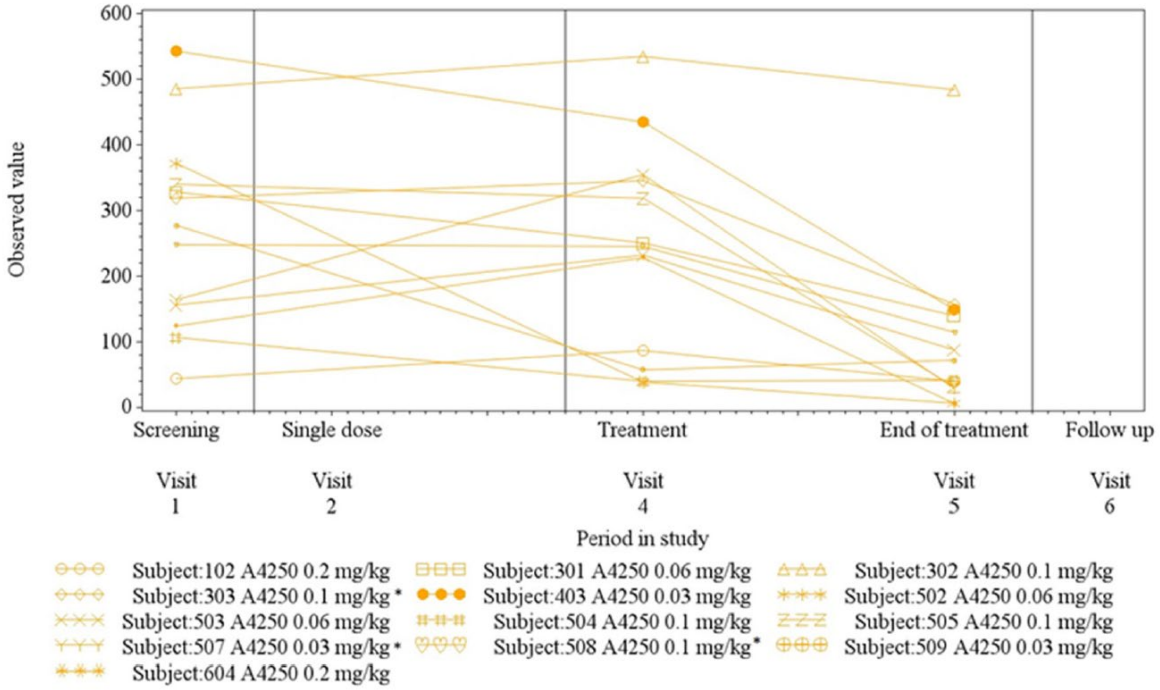
In the study cohorts 10 patients with PFIC (PFIC1-3, MyoB5) and 9 patients with either ALGS or BA were included.

Efficacy

Serum bile acids (SBAs)

Figure **12** depicts the change for total SBAs for the PFIC patients only.

Figure 12: PFIC Subgroup—Total Serum Bile Acids; Patient Profiles.



Re-enrolled patients with PFIC (Patient 301 re-enrolled as 303; Patient 502 re-enrolled as 507; and Patient 503 re-enrolled as 508).

Pruritus and Sleep-Related Patient Diary Data Endpoints

The diary data endpoints were analysed as the change in patient's individual weekly mean severity of self-reported symptoms from study Baseline (mean value from 7 days before Visit 2) to End of Treatment (mean value from the last 7 days of the 4-week treatment period). A summary of the mean effect of odevixibat on itching and sleep scales are presented in Table 30.

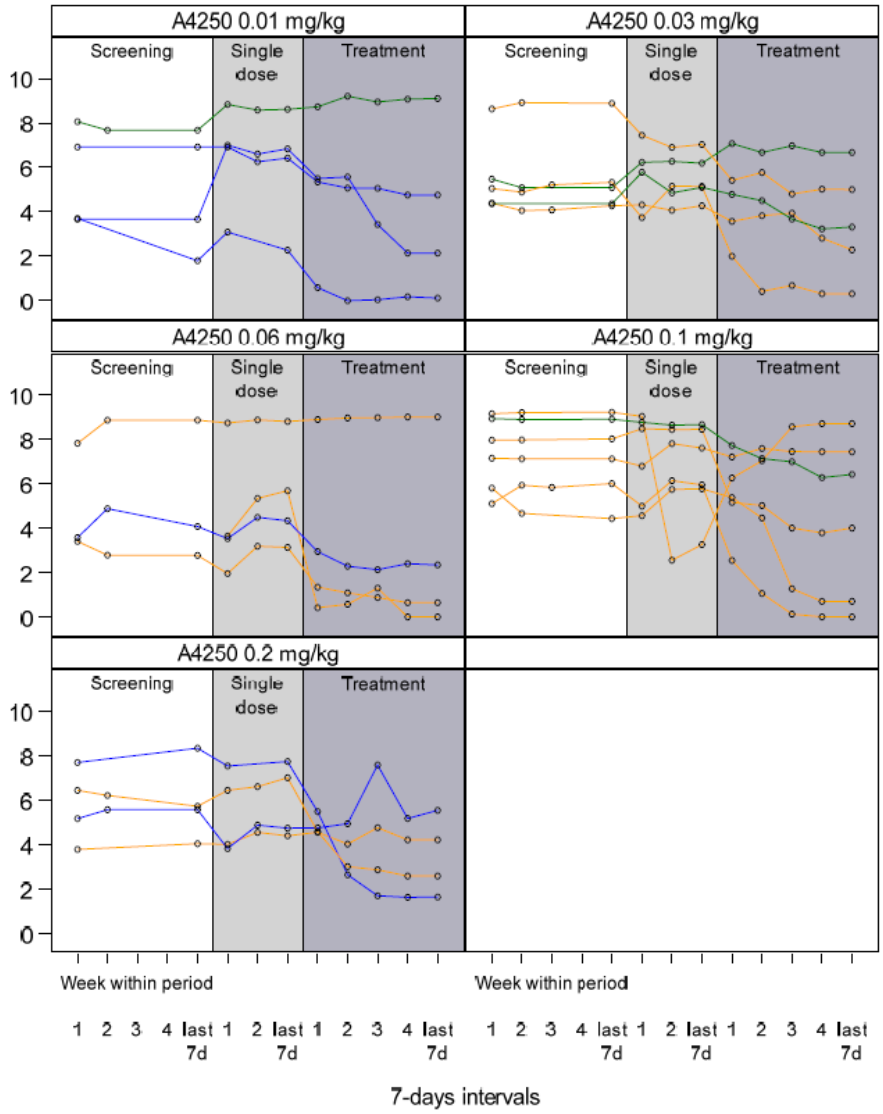
Table 30: Mean (StDev) Change from Baseline to End of Treatment for VASItch, PO-SCORAD Itching, Whitington, and the PO-SCORAD Sleep Disturbance Scales (Full Analysis Set).

MEASURE (SCALE)	0.01 MG/KG (N=4)	0.03 MG/KG (N=6)	0.06 MG/KG (N=4)	0.1 MG/KG (N=6)	0.2 MG/KG (N=4)
VAS-itch (0-10)	-1.5 ± 2.36	-2.0 ± 2.46	-1.9 ± 1.85	-2.8 ± 2.62	-2.3 ± 2.96
PO-SCORAD itching (0-10)	-1.0 ± 1.63	-2.1 ± 2.57	-1.2 ± 1.21	-2.7 ± 2.35	-2.4 ± 3.23
Whitington (0-4)	0 ± 0.72	-0.8 ± 0.71	-1.1 ± 1.0	-1.4 ± 1.24	-0.5 ± 0.8
PO-SCORAD sleep disturbance (0-10)	+0.1 ± 1.32	-1.8 ± 2.51	-1.4 ± 1.5	-2.9 ± 2.3	-2.1 ± 2.74

PO-SCORAD: patient-oriented scoring atopic dermatitis; StDev: standard deviation; VAS: visual analogue scale.

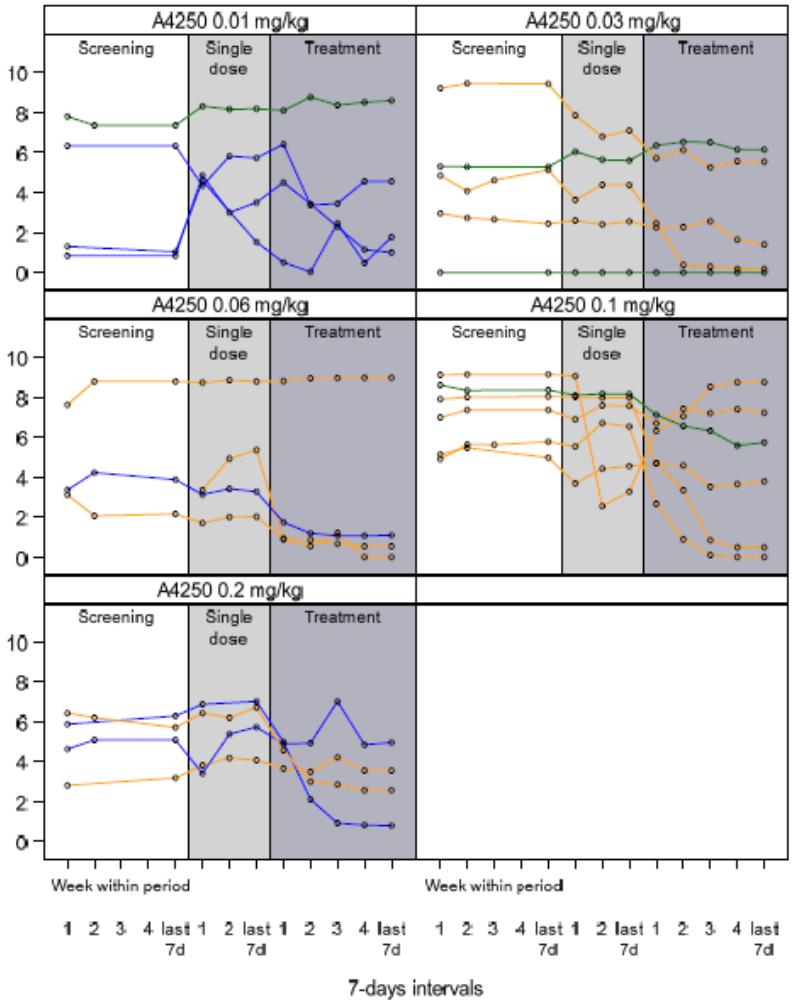
Figure **13**3 and 14 below show the PO-SCORAD Itching Score and PO-SCORAD sleep disturbance panel plots per patient included in the study. The panel plots for VAS-itch and Whitington scales showed similar graphs, although the Whitington scales were less outspoken. For all three scales, a correlation in the reduction of itching with decreasing SBAs could be demonstrated.

Figure 13: PO-SCORAD Itching Score—Panel Plot of Patient Profiles by Dose Group and Disease Type (Full Analysis Set).



Patients with PFIC are denoted in gold; Alagille syndrome in blue; and cholestasis or other disease type in green.

Figure 14: PO-SCORAD Sleep Disturbance Score—Panel Plot of Patient Profiles by Dose Group and Disease Type (Full Analysis Set).



Patients with PFIC are denoted in gold; Alagille syndrome in blue; and cholestasis or other disease type in green.

It should be noted that, after the study was conducted, the patient represented by the green line in panel 1 and 4 (0.01 and 0.1 mg/kg) in both figures above was considered a PFIC patient; as the patient had the Myo5B mutation.

2.5.2. Main study(ies)

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 (PEDFIC 1).

Methods

Study Participants

Inclusion Criteria

Based on Protocol Amendment 6 (dated 24 June 2019), patients who met all of the following criteria were eligible for enrolment in this study:

1. A male or female patient, with clinical diagnosis of PFIC1 or PFIC2, between the ages of ≥6 months and ≤18 years at Visit 1 with a body weight above 5 kg

2. Had clinical genetic confirmation of PFIC1 or PFIC2 through identification of biallelic pathogenic variants in either the ATP8B1 or ABCB11 genes

3. Had elevated serum bile acid concentration, specifically measured to be ≥100 µmol/L, taken as the average of 2 samples at least 7 days apart (Visits 1 and 2) prior to randomisation

4. Had a history of significant pruritus and a caregiver-reported observed scratching in the eDiary average of ≥2 (on 0 to 4 scale) in the 2 weeks prior to randomisation

5. Patient and/or legal guardian signed informed consent (and assent) as appropriate. Patients who

Exclusion Criteria

1. Pathologic variations of the ABCB11 gene that predicted complete absence of the BSEP protein
2. 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 suggestive of alternate non-PFIC related aetiology of cholestasis
3. Past medical history or ongoing presence of any other disease or condition known to interfere with the absorption, distribution, metabolism (specifically bile acid metabolism), or excretion of drugs in the intestine, including but not limited to, inflammatory bowel disease
4. Past medical history or ongoing chronic (i.e. >3 months) diarrhoea requiring intravenous fluid or nutritional intervention for treatment of the diarrhoea and/or its sequelae
5. Surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of screening period
6. Previous liver transplant or a liver transplant that was planned within 6 months of randomization
7. Decompensated liver disease, coagulopathy, history or presence of clinically significant ascites, variceal haemorrhage, and/or encephalopathy
8. International normalized ratio (INR) >1.4 (the patient could be treated with vitamin K intravenously, and if INR was ≤1.4 at resampling, the patient could have been randomised)

9. Serum ALT >10 × upper limit of normal (ULN) at screening
10. Serum ALT >15 × ULN at any time point during the last 6 months unless an alternate aetiology was confirmed for the elevation
11. Total bilirubin >10 × ULN at screening

Treatments

Patients received odevixibat at a dose of 40 µg/kg/day or 120 µg/kg/day, or placebo QD orally for 24 weeks. Odevixibat is administered orally. Odevixibat is supplied in 2 capsule sizes and 4 strengths: capsule size 0 (200 or 600 µg strength) that could be opened and sprinkled on food and capsule size 3 (400 or 1200 µg strength) to be swallowed intact but could be opened if unable to swallow the capsule. The specific dosing schedule can be found in the SmPC section 4.2.

Concomitant medication

Treatment with UDCA, rifampicin, and/or antihistamines was also allowed provided the patient was on a stable dosage at least 4 weeks before enrolment and no dosage changes were planned during the entire study period. Topical treatment was allowed without restriction. Other drugs/natural products with possible effects on GI motility (e.g. selective serotonin reuptake inhibiting drugs, tetracyclic antidepressants, fibre supplementation, yoghurt variants) were allowed provided there was stable usage of the product at least 4 weeks before enrolment until treatment discontinuation.

Objectives

Primary Objectives

The primary objective of the 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.

Secondary Objectives

The secondary objectives of the study were:

• To evaluate the effect of odevixibat on serum ALT concentration

• To evaluate the effect of odevixibat on growth

• To evaluate the effect of odevixibat on sleep disturbance

• To evaluate the effect of odevixibat on 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.

Outcomes/endpoints

Primary Efficacy endpoint

The primary efficacy endpoint was the proportion of patients experiencing at least a 70% reduction in serum bile acids concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment. Serum bile acids concentration at baseline was calculated as the average of the last 2 values prior to the first dose. The end value was calculated as the average of the values at Weeks 22 and 24 after the start of treatment.

Secondary Efficacy Endpoints

The proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument.

Additional secondary endpoints included changes from baseline to end of treatment in growth, sleep parameters (per ObsRO) and ALT.

Exploratory Efficacy Endpoints

Exploratory parameters, including GIC and GIS measures, ALT, AST, GGT, autotaxin, p-C4, Albireo PRO and ObsRO itching/scratching severity scores, additional Albireo PRO and ObsRO sleep parameters, PedsQL, PELD/MELD score, APRI score, and the FIB-4 score, were analysed descriptively.

Sample size

The study planned to enrol 60 to 70 patients in order to obtain at least 20 evaluable patients in each arm. For each primary endpoint, simulations with 5,000 iterations using 20 patients per arm were conducted to estimate the power after multiplicity adjustment, resulting in an SE of <0.7% for each estimated power.

Based on the Phase 2 study (A4250-003) data, both low and high dose groups were assumed to have the same positive treatment effects in both the serum bile acids and pruritus endpoints in the simulation. For serum bile acids, binomial distributions were used to simulate the proportion of responders to estimate the power. The simulated proportions were analysed using the CMH test to generate 1-sided p-values for the following comparisons: both odevixibat arms pooled vs placebo, low dose vs placebo, and high dose vs placebo. Assuming 60% responders in the odevixibat arms and 10% responders in the placebo arm, the power to claim significance for a particular odevixibat arm after multiplicity adjustment was approximately 94%. The probability to claim significance for at least 1 arm, and for both arms were approximately 99% and 91%, respectively. If the response rates were 50% in the odevixibat arms and 10% in the placebo arm, with 20 patients per arm, the probability to claim significance for a particular odevixibat arm after multiplicity adjustment was approximately 82%. The probability to claim significance for at least 1 arm, and for both arms was approximately 91% and 73%, respectively.

For the proportion of positive pruritus assessments at the patient level in pruritus scores, beta-binomial distributions were used for power simulations. The effect size was 1.0526 from the original sample size calculation using change from baseline as the endpoint. The same effect size was assumed for the current endpoint for the low and high dose vs the control. A difference of 15%, 20%, 25%, and 30% in the proportion of positive pruritus assessments was considered in power simulation. Within each difference, proportions of positive assessments in the placebo arm ranging from 15% to 35% were considered. Subsequently, the proportion of positive assessments in an active arm, the SD, and the corresponding beta binomial parameters were calculated to satisfy the assumed effect size. These parameters were used to simulate correlated binary results for each patient. The simulated proportions were analysed using ANCOVA to generate 1-sided p-values for the following comparisons: both odevixibat arms pooled vs placebo, low dose vs placebo, and high dose vs placebo. The simulation in each scenario was repeated for 5,000 iterations using the current sample size of 20 patients per arm. The simulated power to claim significance for a particular arm after multiplicity adjustment was quite consistent under different scenarios and was approximately 89%. The probability to claim significance for at least 1 arm, and for both arms was approximately 95% and 83%, respectively.

Randomisation

Randomisation was done in block size of 6 and stratified according to PFIC type (Type 1 or 2) and age group (6 months to 5 years, 6 to 12 years, and 13 to ≤18 years) to ensure an approximate balance between dose schemes (1:1:1). A separate randomisation list was prepared for the patients from Study A4250-003 regardless of stratification. Randomisation codes were assigned sequentially as patients became eligible for randomisation.

Blinding (masking)

This was a double-blind study and both investigators and patients were unaware of the treatment assignment during the study.

To ensure blinding of treatment assignment, the study drug and the matching placebo had the same shape and size. Labels on the study drug containers did not identify the randomised treatment assignment. Traceability of the treatment was ensured by the study drug number that corresponded to the randomisation arm and was assigned by the IWRS. Additionally, in order to maintain the blind, all serum bile acids results during the treatment period and at follow-up were blinded; samples were processed at a central laboratory.

The investigator could perform immediate unblinding through IWRS in emergency situations (i.e. where knowledge of the study drug was required to adequately manage a life-threatening situation). The investigator was to make every effort to discuss the rationale (status and outcome) for emergency unblinding with the medical monitor as soon as possible to review the individual patient details.

Once the randomisation code was broken for a patient, he/she was to be withdrawn from the study and all assessments and procedures at EOT were to be performed. As a follow-up, Visit 10 was performed according to the time schedule. Once a randomisation code was broken, the investigator was to inform the medical monitor in writing within 24 hours.

No emergency unblinding was conducted during the study.

Statistical methods

Patient populations

Full Analysis Set (FAS): All randomised patients who received at least 1 dose of study treatment. Patients were analysed as randomised. The FAS was the primary analysis set for efficacy analyses.

Safety Analysis Set (SAS): All randomised patients who received at least 1 dose of study drug. The safety analysis set was used for safety analyses.

Per-Protocol (PP) Analysis Set: All patients in the FAS who did not have any important protocol deviations.

Cochran Mantel Haenszel (CMH) Test

Statistical analysis was conducted using the Cochran-Mantel-Haenszel (CMH) test, stratified by PFIC type and age category, to compare the 2 odevixibat dose groups to placebo. Patients with missing data at the end of treatment were classified as non-responders. The proportion and corresponding 95% confidence interval (CI), odds ratio and corresponding 95% CI, and p-value for the CMH test are presented.

In the CMH test, data in a stratum will not be used in the calculation of the p-value if a row sum or column sum is 0 in the contingency table. To ensure that all data are used when this occurs, data will be pooled with the adjacent age stratum with a smaller number of subjects. If a row sum or column sum is still 0 after pooling data, all age groups will be pooled (i.e. the CMH test will be stratified by PFIC type only). If a row sum or column sum is still 0, the CMH test will not be stratified. Pooling strategy will also be conducted for a stratum with <4 patients.

Analysis of Covariance (ANCOVA) model

The ANCOVA model is usually used to test the main and interaction effects of categorical variables on a continuous dependent variable, controlling for the covariates. The ANCOVA model will be used to analyse the comparisons of the proportion of positive pruritus assessments at subject level over the 24-week treatment period between the treatment groups.

Multiplicity

For EU and RoW, the primary analysis will be related to the serum bile acid responder endpoint. For US, the primary analysis will be related to the pruritus endpoint. For each primary endpoint, a pooled analysis for the closed testing procedure will be 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 are pooled to compare with the placebo group first. If the 1-sided p-value is ≤0.025, the 1-sided p-values for low dose vs placebo and high dose vs placebo, respectively will be calculated. If both individual p-values are ≤0.025, a significant treatment effect will be declared on both dose groups. If only one of them is ≤0.025, a significant treatment effect will be declared on the corresponding dose group.

Adjusted p-values will also be reported when unadjusted p-values are presented directly from the model. The adjusted p-value for an individual dose is calculated as the maximum value of the unadjusted p-value for the pooled low and high doses and the unadjusted p-value for the individual doses.

Analyses of secondary and exploratory endpoints will provide supportive efficacy and safety information regarding the differences between the treatment groups. No adjustments will be performed for multiple comparisons when testing these secondary and exploratory endpoints.

Endpoints

For secondary efficacy parameters, including reduction of pruritus based Albireo PRO and ObsRO for pruritus (see below), serum bile acids concentrations, ALT, growth, PELD/MELD, Fibroscan, APRI, FIB-4, and Albireo PRO and ObsRO sleep parameters (see below), descriptive statistics are summarised for the FAS for observed values and changes from baseline for each visit. The summary of changes in serum bile acids, PRIand growth, are also provided based on the PP analysis set. The analysis of growth data is based on calculated values using the software or methods from the Centers for Disease Control and Prevention website for patients with age ≥ 2 years-old and from the WHO website for patients < 2 years-old. Note that for determination of z-scores for the analysis of growth data, an accurate age (date of birth or reported age in years/months) must be recorded at baseline.

Change in serum bile acids, ALT, and growth were analysed using a MMRM model, including terms for baseline, PFIC type, age category, treatment, visit, treatment-by-baseline interaction and treatment-by-visit interaction. For serum bile acids, the MMRM analysis may be performed based on log transformed values if deemed appropriate.

Liver related measurements

Paediatric end-stage liver disease (PELD) and MELD scores are used to estimate relative disease severity and the probability of survival for patients awaiting liver transplantation. The PELD score is based on the following test results: albumin, bilirubin, INR, growth [based on gender, height, and weight], and age at listing; 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).

Markers of fibrosis, the AST to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) index for liver fibrosis score, were also calculated at randomisation and at the end of treatment. The APRI score is a method to measure fibrosis of the liver.

Where available, Fibroscan, a specialized ultrasound of the liver measuring fibrosis and steatosis, was performed at randomisation and Week 24.

Obsro and PRO instruments for pruritus and sleep disturbance

Pruritus and sleep were measured in the study through a PRO instrument (for patients ≥8 years old) and an ObsRO instrument (completed by every patient's caregiver regardless of patient age). The PRO asked patients about their itching during the day and night-time hours and the ObsRO asked caregivers about the patient's scratching and other related behaviours observed during the daytime and night-time hours.

A threshold for meaningful change was established for the ObsRO pruritus score: a change of -1.00 on the ObsRO score from Baseline to Week 12 and from Baseline to Week 24 can be considered meaningful. This threshold can be applied to individual patients in order to categorise each patient as having experienced meaningful change or not. A meaningful change threshold for the PRO pruritus score could not be calculated due to the small number of patients completing the PRO measure.

A threshold for meaningful change was established for the ObsRO sleep disturbance domain score: a decrease of 0.40 (40%) reflects a substantial numeric decrease in the average percent of nights when patients require support due to their sleep disturbance. This threshold can be applied to individual patients in order to categorise each patient as having experienced meaningful change or not.

Subgroup Efficacy Analyses

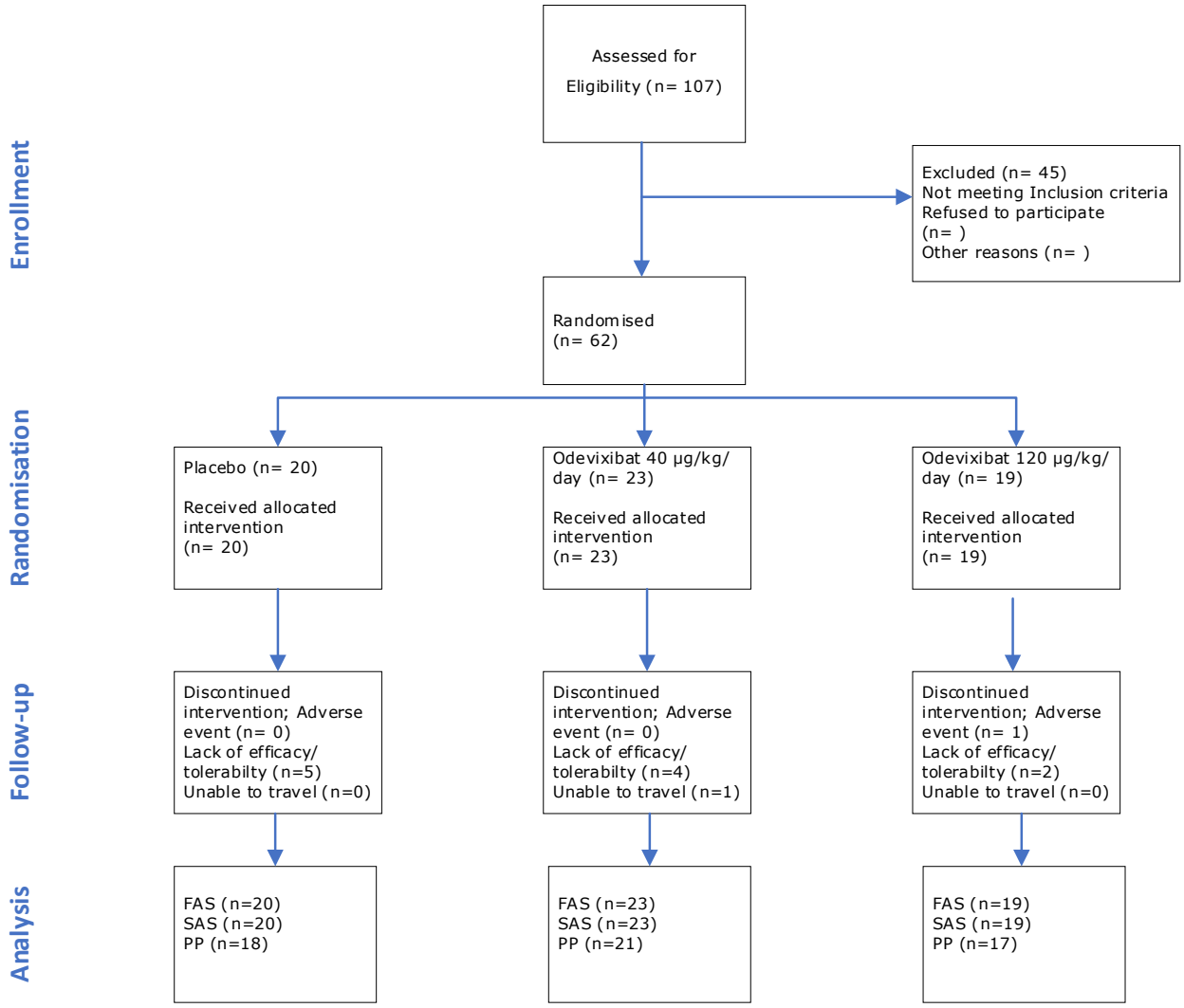
Subgroup efficacy analyses on the primary endpoint and selected secondary endpoints (changes from baseline to each visit in serum bile acid, ALT, and growth) were performed by age group (6 months to 5 years, 6 to 12 years, and 13 to 18 years), by PFIC type (1 and 2), region (US, Europe and RoW), sex (male and female), race (Caucasian and non-Caucasian), 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. 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.

Results

Participant flow

Figure 15 shows the participants flow in study A4250-005. In each arm, one patient who participated in the dose-finding study A4250-003 was included.

Figure 15: Participants flow in Study A4250-005.



Recruitment

Date first patient enrolled: 16 May 2018; Date last patient completed: 28 July 2020

Conduct of the study

The original protocol under which patients were first enrolled in the study was Protocol Amendment 1 (dated 06 December 2017). There were 5 global amendments during the study. Current protocol version is date 24 June 2019. No major protocol amendments were made. Due to COVID-19 pandemic, the applicant implemented contingency measures to ensure patients' safety and manage study conduct. No patients had to be discontinued or discontinued due to the impact of the COVID-19 pandemic.

Baseline data

The demographic and baseline disease characteristics were generally similar across the treatment groups Table 31 and Table 32).

Median height and weight were 88.7 cm and 12.5 kg, respectively in the overall study population. Consistent with PFIC patients having impaired growth, median height-for-age and weight-for-age z-scores were -1.70 and -0.95, respectively, indicating the patients were below their age-matched peers for growth. Review of z-scores across the treatment groups indicates that 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.

Table 31: Summary of Demographic Characteristics (A4250-005 Full Analysis Set).

PARAMETER	PLACEBO N=20	ODEVIXIBAT, ONCE DAILY DOSING			OVERALL N=62
		40 µg/kg N=23	120 µg/kg N=19	ALL DOSES N=42	
Sex, n (%)					
Female	8 (40.0)	12 (52.2)	11 (57.9)	23 (54.8)	31 (50.0)
Male	12 (60.0)	11 (47.8)	8 (42.1)	19 (45.2)	31 (50.0)
Age (years)					
n	20	23	19	42	62
Mean (SD)	3.75 (3.853)	3.86 (3.660)	5.24 (4.188)	4.48 (3.921)	4.25 (3.883)
Median	2.80	3.20	4.90	3.20	3.20
Min, Max	0.5, 15.0	0.6, 15.9	1.0, 13.2	0.6, 15.9	0.5, 15.9
Age Category 1, n (%)					
6 months to 5 years	16 (80.0)	17 (73.9)	14 (73.7)	31 (73.8)	47 (75.8)
6 to 12 years	3 (15.0)	5 (21.7)	4 (21.1)	9 (21.4)	12 (19.4)
13 to 18 years	1 (5.0)	1 (4.3)	1 (5.3)	2 (4.8)	3 (4.8)
Age Category 2, n (%)					
<8 years	18 (90.0)	20 (87.0)	14 (73.7)	34 (81.0)	52 (83.9)
≥8 years	2 (10.0)	3 (13.0)	5 (26.3)	8 (19.0)	10 (16.1)
Race, n (%)					
Caucasian[a]	17 (85.0)	18 (78.3)	17 (89.5)	35 (83.3)	52 (83.9)
Black/African American	0	2 (8.7)	0	2 (4.8)	2 (3.2)

Asian	1 (5.0)	0	1 (5.3)	1 (2.4)	2 (3.2)
Other	2 (10.0)	3 (13.0)	1 (5.3)	4 (9.5)	6 (9.7)
Ethnicity, n (%)					
Hispanic or Latino	1 (5.0)	0	0	0	1 (1.6)
Not Hispanic or Latino	19 (95.0)	23 (100.0)	19 (100.0)	42 (100.0)	61 (98.4)
Region, n (%)					
Europe	12 (60.0)	13 (56.5)	10 (52.6)	23 (54.8)	35 (56.5)
Rest of World (RoW)	5 (25.0)	8 (34.8)	6 (31.6)	14 (33.3)	19 (30.6)
United States (US)	3 (15.0)	2 (8.7)	3 (15.8)	5 (11.9)	8 (12.9)

CRF: case report form; max: maximum; min: maximum; SD: standard deviation.

Note: For patients enrolled at sites outside of France and Germany, age was calculated based on date of birth. For patients from France and Germany, only birth year was collected on the CRF, and age was calculated based on collected age years and months. a The study population from Middle Eastern countries was included under race category Caucasian.

Table 32: Summary of Baseline Disease Characteristics (Full Analysis Set).

PARAMETER	**PLACEBO N=20**	**ODEVIXIBAT, ONCE DAILY DOSING**			**OVERALL N=62**
		40 µg/kg N=23	**120 µg/kg N=19**	**ALL DOSES N=42**	
Years Since PFIC Diagnosis[a]					
n	20	23	19	42	62
Mean (SD)	2.84 (3.627)	2.28 (2.605)	3.66 (3.824)	2.91 (3.247)	2.89 (3.344)
Median	1.05	1.50	1.60	1.55	1.45
Min, Max	-0.1, 13.3	0.0, 9.0	-0.1, 11.9	-0.1, 11.9	-0.1, 13.3
PFIC type, n (%)					
Type 1	5 (25.0)	7 (30.4)	5 (26.3)	12 (28.6)	17 (27.4)
Type 2	15 (75.0)	16 (69.6)	14 (73.7)	30 (71.4)	45 (72.6)
Pathologic Variants Identified for:					
ATP8B1	5 (25.0)	7 (31.8)	5 (26.3)	12 (29.3)	17 (27.4)
ABCB11	15 (75.0)	16 (69.6)	14 (73.7)	30 (71.4)	45 (72.6)
BSEP Subtype for PFIC2					

Type 1	6 (40.0)	2 (12.5)	4 (28.6)	6 (20.0)	12 (26.7)
Type 2	9 (60.0)	14 (87.5)	10 (71.4)	24 (80.0)	33 (73.3)
History of Significant Pruritus per Investigator Report, n (%)	19 (95.0)	22 (95.7)	19 (100.0)	41 (97.6)	60 (96.8)
Serum Bile Acid Level >100 µmol/L within 6 Months Prior to Screening, n (%)					
Yes	12 (60.0)	16 (69.6)	14 (73.7)	30 (71.4)	42 (67.7)
No	2 (10.0)	6 (26.1)	2 (10.5)	8 (19.0)	10 (16.1)
Not applicable	6 (30.0)	1 (4.3)	3 (15.8)	4 (9.5)	10 (16.1)
Baseline Use of:					
UDCA	18 (90.0)	19 (82.6)	13 (68.4)	32 (76.2)	50 (80.6)
Rifampicin	17 (85.0)	13 (56.5)	11 (57.9)	24 (57.1)	41 (66.1)
UDCA and/or rifampicin	19 (95.0)	21 (91.3)	15 (78.9)	36 (85.7)	55 (88.7)

BSEP: bile salt export pump; max: maximum; min: maximum; PFIC: progressive familial intrahepatic cholestasis; SD: standard deviation; UDCA: ursodeoxycholic acid.

Note: Percentages are calculated based on the number of patients with non-missing data.

a Years since PFIC diagnosis was calculated based on date of diagnosis of PFIC and date of informed consent.

At baseline, serum bile acid levels were ≥250 µmol/L (≥102 µg/mL) in 25 (40%) of the 62 patients, including 15 (36%) of 42 patients who received odevixibat and 10 (50%) of 20 patients who received placebo. 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.

Medical and Surgical History

The medical and surgical history of patients were similar across treatments. The conditions reported were typical of patients with PFIC, primarily vitamin deficiencies, jaundice, pruritus and poor growth. Overall, 8 (13%) patients reported prior biliary tract surgeries (all reported to have undergone biliary diversion).

Prior and Concomitant Therapy

Overall, 38 (61%) of the 62 patients reported using **prior medications,** mostly vitamins. None of the patients reported prior PFIC-related medications.

All 62 patients took at least one **concomitant medication** during the treatment period. Most patients received concomitant medications for the treatment of pruritus and vitamin supplementation. Note that for patients receiving medication for pruritus, the dose/regimen was not to change. Generally, the types and use of these medications were similar across the treatment groups, except that a higher percentage of patients in the placebo group reported use of other bile acids and derivatives (UDCA)

and other antibacterials (rifampicin). Concomitant treatment with UDCA and rifampicin was permitted provided the patient was on a stable dosage at least 4 weeks before enrolment and no dosage changes were planned during the entire study period.

In the placebo group, UDCA was administered concomitantly in 90% of patients compared with 83% and 68% of patients treated with odevixibat 40 and 120 µg/kg/day, respectively. Concomitant administration of rifampicin was reported in 90% of patients who received placebo compared with 57% and 63% of patients treated with odevixibat 40 and 120 µg/kg/day, respectively.

Numbers analysed

A total of 62 patients were randomised into the study and received their assigned treatment and were included in the SAS and FAS; 56 patients were randomised and had no important protocol deviations documented and were included in the PP analysis set (Table 33).

Table 33: Analysis Populations (Randomised Patients).

Analysis population	**Placebo n=20 n (%)**	**Odevixibat, once daily dosing**			**Overall n=62 n (%)**
		40 µg/kg n=23 n (%)	**120 µg/kg n=19 n (%)**	**ALL DOSES n=42 n (%)**	
Safety Analysis Set (SAS)	20 (100)	23 (100)	19 (100)	42 (100)	62 (100)
Full Analysis Set (FAS)	20 (100)	23 (100)	19 (100)	42 (100)	62 (100)
Per Protocol Analysis Set (PP)	18 (90)	21 (91)	17 (90)	38 (91)	56 (90)

Outcomes and estimation

Primary Efficacy Endpoints

The FAS results for the primary efficacy endpoint, the proportion of patients with at least a 70% reduction in serum bile acids concentration from baseline or reaching a level ≤70 µmol/L (28.6 µg/mL), are summarised in

Table **34**. A significant difference between placebo and odevixibat was observed in the decrease from baseline in serum bile acids after 24 weeks of treatment.

A post hoc analysis comparing the results for the 40 and 120 µg/kg/day groups was also conducted. The results showed that there was not a statistically significant difference in the proportion of serum bile acid responders between the 2 odevixibat dose groups (CMH stratified by PFIC type, 2-sided, p = 0.1083).

Table 34: Analysis of the Number (%) of Patients Experiencing at Least a 70% Reduction in Serum Bile Acids Concentration from Baseline to End of Treatment or Reaching a Level ≤70 µmol/L after 24 Weeks of Treatment (Full Analysis Set, Study A4250-005).

STATISTIC	PLACEBO N=20	ODEVIXIBAT, ONCE DAILY DOSING		
		40 µG/KG N=23	120 µG/KG N=19	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 unadjusted p-value[d]		0.0003	0.0174	0.0015
1-sided adjusted p-value[e]		0.0015	0.0174	-

CI: confidence interval; NC: not calculable; PFIC: progressive familial intrahepatic cholestasis.

a. *Clopper-Pearson exact CI is reported for the percentage of responders, and the exact unconditional CI is reported for the proportion difference without adjusting for stratification factors.*

b. *Miettinen-Nurminen (score) CI is reported adjusting for stratification factors.*

c. *The exact CI is reported based on Vollset, Hirji, and Elashoff adjusting for stratification factors.*

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

e. *For an individual dose, the adjusted p-value was calculated as the maximum value of the unadjusted p-value for odevixibat all doses and the unadjusted p-value for the individual dose.*

Note: For the primary endpoint, a closed test procedure was used to compare odevixibat all doses combined and placebo, and then odevixibat 40 µg/kg vs placebo and odevixibat 120 µg/kg vs placebo.

Secondary endpoints

Pruritus assessment

The proportion of positive pruritus assessments for AM and PM scores combined at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument are summarised in Table **35**. There was a significant difference in the proportion of positive pruritus assessments after 24 weeks of odevixibat treatment compared to placebo.

Table 35: Analysis of the Proportion of Positive Pruritus Assessments (AM and PM Scores Combined) at the Patient Level over the 24-Week Treatment Period – Albireo ObsRO Instrument (Full Analysis Set).

STATISTIC	PLACEBO N=20	ODEVIXIBAT, ONCE DAILY DOSING		
		40 µg/kg N=23	120 µg/kg N=19	ALL DOSES N=42
n	20	23	19	42
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)[a]	30.10 (9.119)	58.34 (8.580)	51.81 (9.459)	55.08 (7.639)
LS Mean Difference (SE) (Odevixibat – placebo)[a]		28.23 (9.182)	21.71 (9.892)	24.97 (8.240)
95% CI[a]		(9.83, 46.64)	(1.87, 41.54)	(8.45, 41.49)
One-sided Unadjusted p-value[a]		0.0016	0.0163	0.0019
One-sided Adjusted p-value[b]		0.0019	0.0163	
p-value for normality test[c]				0.0070
p-value for homogeneity test of variances[d]				0.3164

ANCOVA: analysis of covariance; CI: confidence interval; LS: least squares; ObsRO: observer-reported outcome; max: maximum; min: minimum; PFIC: progressive familial intrahepatic cholestasis; SE: standard error.

a. The analysis was based on an 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.

b. For an individual dose, the adjusted p-value is calculated as the maximum value of the unadjusted p-value for odevixibat all doses and the unadjusted p-value for the individual dose.

c. Shapiro-Wilk test is performed for each treatment arm to derive the p-value. Then 3 p-values are combined to obtain the overall p-value based on Fisher's combined probability test.

d. Based on Levene's test.

Note: A closed test procedure was used to compare odevixibat all doses combined (average effect) and placebo first, and then odevixibat 40 µg/kg/day vs placebo and odevixibat 120 µg/kg/day vs placebo.

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

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, is provided in Table 36.

Table 36: Analysis of the Number (%) of Patients Achieving a Positive Pruritus Assessment (AM and PM Scores Combined) for More Than 50% of the Time during the 24-Week Treatment Period – Albireo ObsRO Instrument (Full Analysis Set).

STATISTIC	PLACEBO N=20	ODEVIXIBAT, ONCE DAILY DOSING		
		40 µg/kg N=23	120 µg/kg N=19	ALL DOSES N=42
Responders, n (%)	4 (20.0)	17 (73.9)	9 (47.4)	26 (61.9)
95% CI[a]	(5.73, 43.66)	(51.59, 89.77)	(24.45, 71.14)	(45.64, 76.43)
Proportion Difference without Adjusting for Stratification Factors (Odevixibat – Placebo)		0.539	0.274	0.419
95% CI[a]		(0.2247, 0.7601)	(-0.0337, 0.5478)	(0.0861, 0.6231)
Proportion Difference Adjusting for Stratification Factors (Odevixibat – Placebo)		0.467	0.287	0.320
95% CI[b]		(0.2290, 0.7045)	(0.0344, 0.5401)	(0.1062, 0.5331)
Odds Ratio (Odevixibat/Placebo)		16.22	3.14	6.21
95% CI[c]		(2.540, 106.320)	(0.718, 18.700)	(1.539, 27.429)
One-Sided Unadjusted p-valued		0.0002	0.0391	0.0016

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.

Results for the analysis of the proportion of patients achieving positive pruritus assessment for >50% of the time during 24-week treatment period for AM scores and PM scores were consistent with the overall results for AM and PM scores combined.

Changes from Baseline to Weeks 12 and 24 (Secondary Endpoint) and over Time in Growth Parameters

Review of baseline z-scores across the treatment groups indicated that 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.

Table 37 shows the change from baseline to week 24 in z-scores for height and weight.

Table 37: Summary of Change from Baseline to Weeks 12 and 24 in Growth Parameters (Full Analysis Set).

PARAMETER TIME POINT	PLACEBO N=20		ODEVIXIBAT, ONCE DAILY DOSING					
			40 µg/kg N=23		120 µg/kg N=19		ALL DOSES N=42	
	n	MEAN (SE)	n	MEAN (SE)	n	MEAN (SE)	n	MEAN (SE)
Height (z-score)								
Baseline	20	-2.26 (0.339)	23	-1.45 (0.269)	19	-2.09 (0.372)	42	-1.74 (0.226)
Change to Week 12	18	-0.03 (0.127)	22	0.01 (0.108)	16	-0.06 (0.100)	38	-0.02 (0.075)
Change to Week 24	12	-0.16 (0.104)	17	0.05 (0.105)	15	0.00 (0.163)	32	0.03 (0.093)
Weight (z-score)								
Baseline	20	-1.52 (0.319)	23	-0.74 (0.267)	19	-1.19 (0.345)	42	-0.94 (0.214)
Change to Week 12	18	0.13 (0.066)	22	0.20 (0.078)	16	0.00 (0.100)	38	0.12 (0.063)
Change to Week 24	12	0.10 (0.102)	18	0.29 (0.106)	15	0.15 (0.124)	33	0.22 (0.080)
BMI (z-score)								
Baseline	20	0.10 (0.308)	23	0.41 (0.190)	19	0.28 (0.273)	42	0.35 (0.160)
Change to Week 12	18	0.18 (0.148)	22	0.23 (0.114)	16	0.08 (0.147)	38	0.17 (0.090)
Change to Week 24	12	0.26 (0.156)	17	0.36 (0.113)	15	0.20 (0.203)	32	0.29 (0.112)

Exploratory endpoints

Changes from Baseline to Weeks 12 and 24 in ALT and in Other Hepatic Biochemical Parameters, including AST, Total Bilirubin and GGT to Weeks 4, 12 and 24

Table 38 provides mean (SE) baseline results and changes to Weeks 4, 12 and 24 for hepatic biochemical parameters. Overall, a significant improvement in hepatic parameters was observed in the patients treated with odevixibat. Results for the PP analysis set were similar to the results for the FAS.

Table 38: Hepatic Biochemical Parameters: Mean (±SE) Baseline Values and Changes from Baseline to Weeks 4, 12 and 24 (Full Analysis Set).

VARIABLE TIME POINT	PLACEBO N=20		ODEVIXIBAT, ONCE DAILY DOSING					
			40 µg/kg N=23		120 µg/kg N=19		ALL DOSES N=42	
	n	MEAN (SE)	n	MEAN (SE)	n	MEAN (SE)	n	MEAN (SE)
ALT (U/L)								
Baseline	20	76.9 (12.6)	23	127.7 (34.6)	19	89.1 (20.0)	42	110.2 (21.0)
Change to Week 4	19	-0.8 (5.3)	22	-34.9 (36.2)	18	41.6 (33.8)	40	-0.5 (25.5)
Change to Week 12	18	1.7 (10.5)	22	-25.9 (23.4)	18	-13.8 (19.4)	40	-20.5 (15.4)
Change to Week 24	11	3.7 (5.0)	17	-27.9 (18.0)	15	-25.3 (22.5)	32	-26.7 (14.0)
AST (U/L)								
Baseline	20	90.2 (11.59)	23	114.2 (17.24)	19	96.0 (16.13)	42	106.0 (11.87)
Change to Week 4	19	-3.3 (5.49)	22	-2.7 (13.11)	18	40.7 (26.92)	40	16.8 (14.32)
Change to Week 12	18	0.7 (10.34)	22	-14.5 (11.23)	18	-15.2 (15.77)	40	-14.8 (9.28)
Change to Week 24	11	4.7 (5.84)	17	-36.7 (12.21)	15	-27.0 (19.41)	32	-32.1 (11.02)
Total Bilirubin (µmol/L)								
Baseline	20	53.3 (12.97)	23	52.2 (10.13)	19	57.0 (18.05)	42	54.4 (9.75)
Change to Week 4	19	-7.2 (5.23)	22	-4.7 (6.36)	18	-15.3 (10.77)	40	-9.5 (5.95)

Change to Week 12	18	7.1 (11.69)	22	-6.0 (10.40)	18	-21.5 (14.10)	40	-12.9 (8.52)
Change to Week 24	11	-9.6 (15.16)	17	-23.7 (9.23)	15	-19.3 (13.62)	32	-21.7 (7.92)
GGT (U/L)								
Baseline	20	16.6 (1.49)	23	19.6 (1.87)	19	18.5 (1.62)	42	19.1 (1.25)
Change to Week 4	19	0.2 (0.61)	22	-0.1 (0.76)	19	1.3 (1.27)	41	0.5 (0.72)
Change to Week 12	17	2.3 (1.62)	22	-3.2 (1.09)	17	0.2 (0.95)	39	-1.7 (0.78)
Change to Week 24	11	1.5 (0.99)	17	-3.4 (1.58)	15	-0.8 (0.91)	32	-2.2 (0.95)

GGT: Gamma-Glutamyl Transferase; AST: aspartate transaminase; ALT: alanine transaminase

Changes in liver pathology

APRI and FIB-4

For the APRI and FIB-4, data for the change from baseline to Week 24 analysis were available for 31 of the 62 patients, including 23 of the 42 patients who received odevixibat and 8 of the 20 patients who received placebo. The APRI scores for individual patients varied considerably over time. For all groups, mean (SE) changes from baseline to Week 24 for the APRI score were small: -0.14 (0.072) for the 40 µg/kg/day group, 0.04 (0.233) for the 120 µg/kg/day group, and 0.04 (0.134) for the placebo group.

Similar to the APRI, mean (SE) changes from baseline to Week 24 for the FIB-4 were small.

Liver Fibrosis/Steatosis

Limited data were available for this analysis due to the unavailability of the required equipment (e.g. Fibroscan) at all sites. No notable differences between the treatment groups were observed.

PELD/MELD

Consistent with the results observed for improvements in hepatic biochemical parameters, treatment with odevixibat over 24 weeks led to an improvement in PELD/MELD scores with minimal changes observed in the placebo group. Mean changes from baseline to Week 24 for this parameter were -1.79 for the overall odevixibat group and were -2.43 and -1.10 in the odevixibat 40 and 120 µg/kg/day groups, respectively, compared with -0.66 in the placebo group.

Number of Patients Undergoing Biliary Diversion Surgery or Liver Transplant

None of the 62 patients underwent biliary diversion surgery or liver transplant during the study.

Other additional secondary endpoints performed.

Several other secondary and exploratory analysis on the FAS were performed that will not be discussed in the overview; details can be found in the day 60 clinical assessment report. The results all pointed in the same positive direction (e.g. improvement of symptoms reduction of SBAs, improvement of QoL) and are consistent with the primary and secondary endpoint

Ancillary analyses

Study 005

Subgroup analyses

The applicant has performed several subgroup analyses on the primary endpoint in study 005. The point-estimate for these analyses was in favour of odevixibat treatment over placebo. For some subgroups limited data was available e.g. PFIC1 patients (see below). Based on the subgroup by region it is noticed that none of the US patients was considered a responder to treatment.

Subgroup of PFIC 1 patients

It is anticipated that PFIC2 patients are the patients that directly benefit from treatment as the mutation prevents shuttling BAs across the membrane. In PFIC1 (and PFIC3) patients, the BSEP is intact, and the interplay with the other membrane proteins is important, and a more marginal treatment effect is expected. Nevertheless, these patients also have an unmet medical need.

For patients receiving odevixibat, the proportion of serum bile acid responders was higher for patients with PFIC2 (12 of 30 patients, 40.0%) compared to patients with PFIC1 (2 of 12 patients, 16.7%), although the comparison of each group to placebo had widely overlapping confidence intervals. Review of changes from baseline in serum bile acid levels for patients with PFIC1 who received odevixibat did show reductions in serum bile acids levels to Week 24 (Table 39). In line with the reduction of serum bile acids, 6/12 PFIC1 patients showed a clinical meaningful reduction of 1.0 point for pruritus score at Week 24, whereas in the placebo group 1/5 patients showed a clinical meaningful reduction. Further data on the reduction of pruritis showed that 10/12 patients showed reduction in pruritus, although in the placebo group also some patients showed reductions in pruritus though to a lesser extent.

Table 39: Change in serum bile acids to week 24 in PFIC1 patients (Study A4250-005).

		Placebo	40 ug/kg/day	120 ug/kg/day	All Doses
Visit	Statistics	N=5	N=7	N=5	N=12
Baseline	n	5	7	5	12
	Mean (SE)	200,10 (37,546)	265,36 (29,491)	170,10 (7,674)	225,67 (22,049)
	Median	186,5	251	166	190,75
	Min, Max	108,5, 328	163, 367,5	149,5, 188,5	149,5, 367,5
% Change from Baseline to Week 24	n	5	5	5	10
	Mean (SE)	30,14 (40,423)	-24,81 (22,902)	-30,63 (22,202)	-27,72 (15,068)
	Median	-21,32	-6,13	-28,34	-17,24
	Min, Max	-37,8, 171,9	-98,4, 28	-97,6, 23,6	-98,4, 28

Summary of main study

The following table (Table 40) summarises the efficacy results from the main study (A4250-005) supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy and the benefit-risk assessment (see later sections).

Table 40: Summary of efficacy for trial A4250-005

Title: 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 (PEDFIC 1).			
Study identifier	A4250-005 EudraCT Number: 2017-002338-21		
Design	Randomised, double-blind, and placebo-controlled Randomisation was 1:1:1 to the 2 dose levels of odevixibat and placebo.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo, n=20
	40 µg/kg/day		40 µg/kg/day, n=23
	120 µg/kg/day		120 µg/kg/day, n=19
Endpoints and definitions	Primary endpoint	Proportion of patients ≥ 70% reduction in	Proportion of patients experiencing a ≥ 70% reduction in fasting serum bile acid (sBA) concentration from baseline to end of therapy or reaching a level ≤ 70 µmol/L after 24 weeks
	Secondary endpoint	Proportion of positive pruritus	Proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument.
	Secondary endpoint	Proportion of positive pruritus assessment	Proportion of Patients Achieving a Positive Pruritus Assessment for >50% of the Time During the 24-Week Treatment Period.
	Secondary	Pruritis change from	Change from baseline to Week 12 and to Week 24 in serum bile acids.
	Secondary endpoint	Growth velocity (Z-scores)	Change from baseline to Week 12 and to Week 24 in Growth (z-scores).
	Exploratory endpoint	PELD/MELD	Change from baseline to Week 24 in PELD/MELD scores.

	Exploratory endpoint	AST to Platelet Ratio Index (APRI) score	Change from Baseline to Week 24 in AST to Platelet Ratio Index (APRI) score
	Secondary endpoint	OLT/SBD	proportion of patients undergoing biliary diversion surgery and/or liver transplant.
Database lock	Not applicable		

Results and Analysis

Analysis	**Primary Analysis**			
Analysis population and time point	Full analysis set (FAS)			
Descriptive statistics and estimate variability	**Treatment group**	**placebo**	**40 µg/kg/day**	**120 µg/kg/day**
	Number of subjects	**20**	**23**	**19**
	Proportion of patients ≥ 70% reduction in sBA: N (%)			
	Proportion of positive pruritus assessment >50% of time N (%)	4 (20.0)	17 (73.9)	9 (47.4)
	Growth velocity (Z-scores)	-0.16 (0.104)	0.05 (0.105)	0.00 (0.163)
	PELD/MELD Mean (SE)	-0.66 (1.14)	-2.43 (0.98)	-1.10 (1.23)
	APRI score Mean (SE)	0.038 (0.1343)	-0.140 (0.0718)	0.043 (0.2327)

Effect estimate per comparison	**Primary endpoint**: Proportion of patients ≥ 70% reduction in sBA.	**Comparison groups**	**40 µg/kg/day**	**120 µg/kg/day**
		Proportion Difference Adjusting for Stratification	0.441	0.216
		95% CI[a]	(0.2361, 0.6464)	(-0.0050, 0.4380)
		One-sided Adjusted p-value[b]	0.0015	0.0174
	Secondary endpoint:	**Comparison groups**	**40 µg/kg/day**	**120 µg/kg/day**

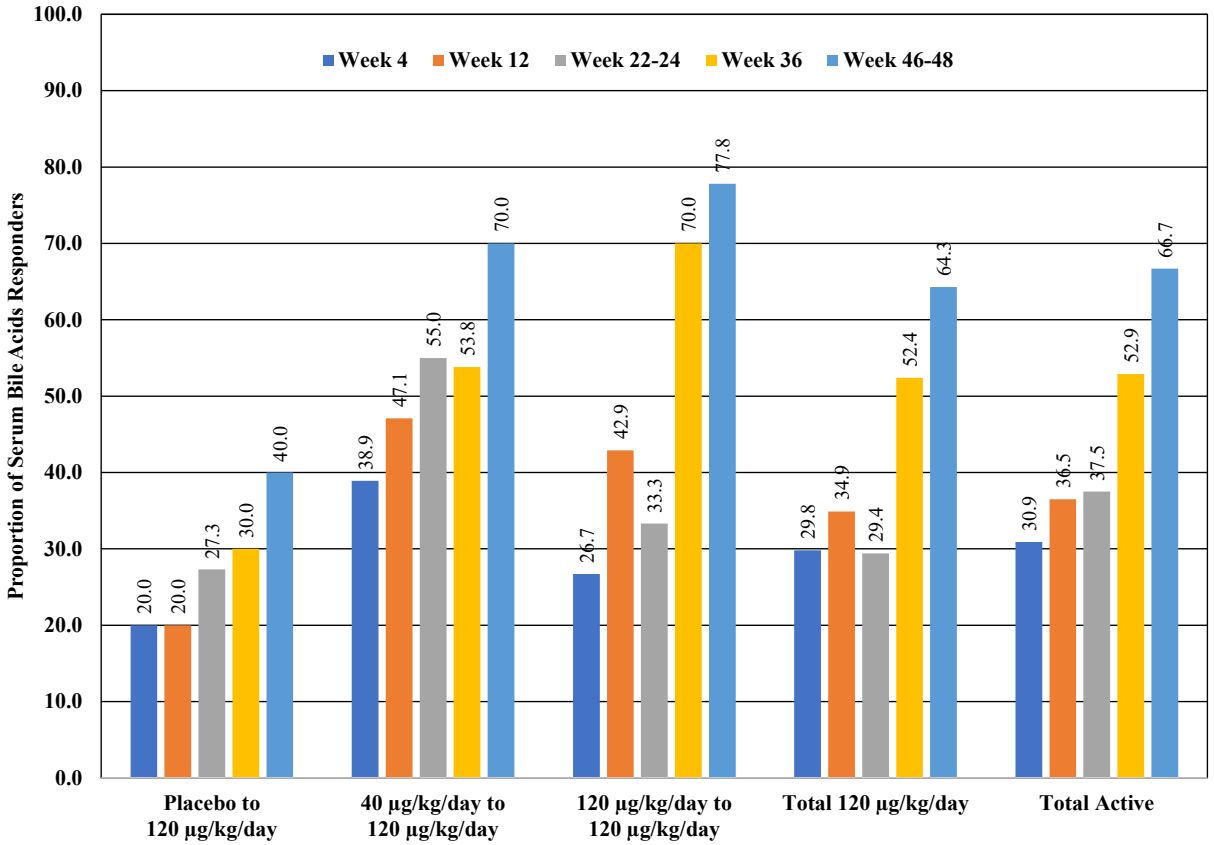
	Proportion of positive pruritus assessment.	LS Mean Difference (SE) (Odevixibat – Placebo)	28.23 (9.182)	21.71 (9.892)
		95% CI[b]	(9.83, 46.64)	(1.87, 41.54)
		One-sided Adjusted p-value[b]	0.0016	0.0163
	Secondary endpoint: Proportion of positive pruritus assessment >50% of time	**Comparison groups**	**40 µg/kg/day**	**120 µg/kg/day**
		Proportion Difference Adjusting for Stratification Factors (Odevixibat – Placebo)	0.467	0.287
		95% CI[b]	(0.2290,	(0.0344, 0.5401)
		P-value	0.0002	0.0391
Notes	Results in the PP were similar to the results in the FAS. Note that concomitant treatment with conventional therapies, including UDCA and rifampicin, was permitted during the study provided the dose remained stable			

Analysis performed across trials (pooled analyses and meta-analysis)

Integrated data patients treated with odevixibat in study 005 and 24 weeks in study 008

The applicant conducted an integrated analysis based on studies 005 and 008. The data showed that under continued odevixibat treatment for the primary endpoint, e.g. the proportion of patients reaching at least 70% in SBAs from baseline or a level ≤70 µmol/L showed further improvements (Figure16). Similar to the reduction in pruritus (Figure 17).

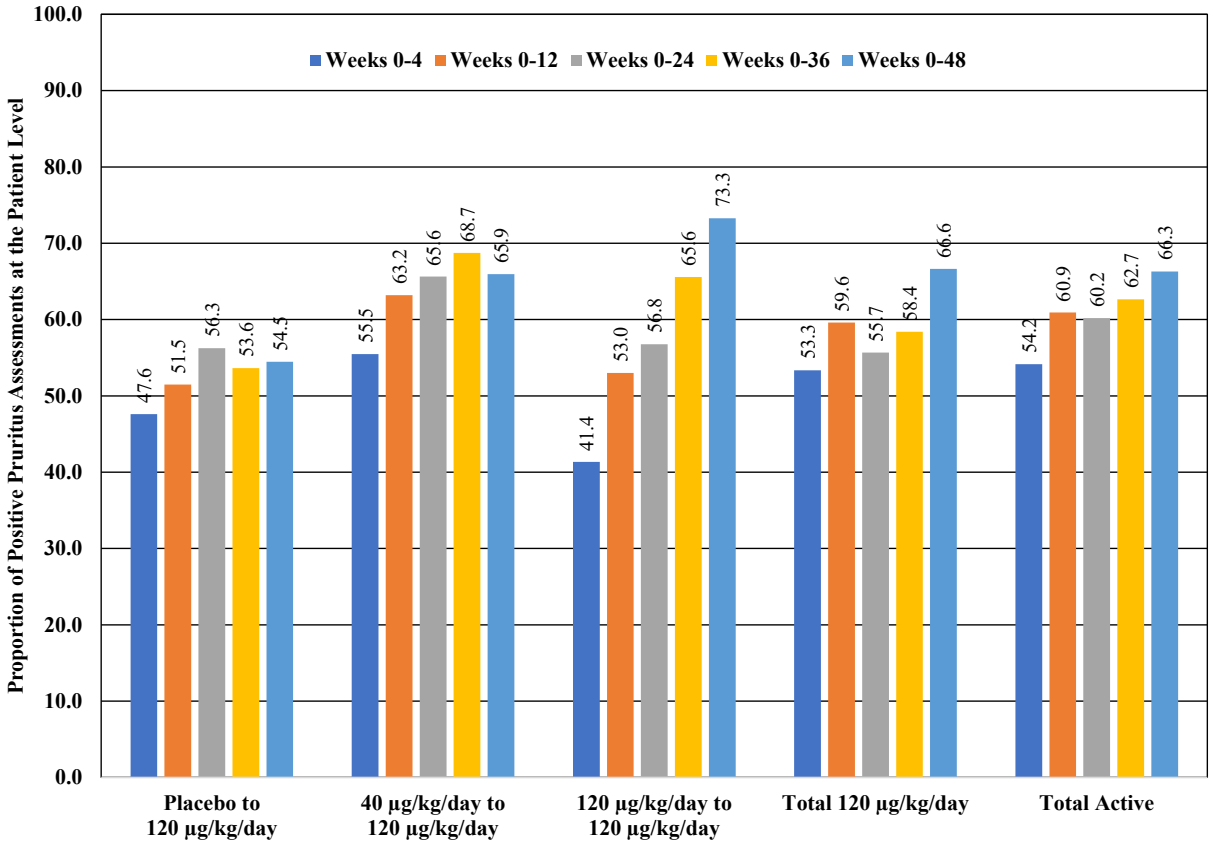
Figure 16: Proportion of Patients Experiencing at Least a 70% Reduction in Serum Bile Acid Concentration from Baseline or Reaching a Level ≤70 µmol/L Over Time on Treatment with Odevixibat by Treatment Group (Full Analysis Set, Pooled Phase 3 Studies)



No. Pts at Week:	Placebo to 120 µg/kg/day	40 µg/kg/day to 120 µg/kg/day	120 µg/kg/day to 120 µg/kg/day	Total 120 µg/kg/day	Total Active
4	15	18	15	47	68
12	15	17	14	43	63
22-24	11	20	15	34	56
36	10	13	10	21	34
46-48	5	10	9	14	24

Note: all data are presented from the first dose of treatment with odevixibat; data from Cohort 2 of Study A4250-008, which had limited data after Week 12, are included in the Total 120 µg/kg/day and Total Active groups.

Figure 17: Proportion of Positive Pruritus Assessments at the Patient Level Over Time During Treatment with Odevixibat by Treatment Group (Full Analysis Set, Pooled Phase 3 Studies)



No. Pts at Weeks:	Placebo to 120 µg/kg/day	40 µg/kg/day to 120 µg/kg/day	120 µg/kg/day to 120 µg/kg/day	Total 120 µg/kg/day	Total Active
0-4	18	20	15	52	75
0-12	16	20	15	47	70
0-24	11	20	15	34	56
0-36	10	19	14	27	46
0-48	6	15	11	17	32

Note: all data are presented from the first dose of treatment with odevixibat; data from Cohort 2 of Study A4250-008, which had limited data after Week 12, are included in the Total 120 µg/kg/day and Total Active groups.

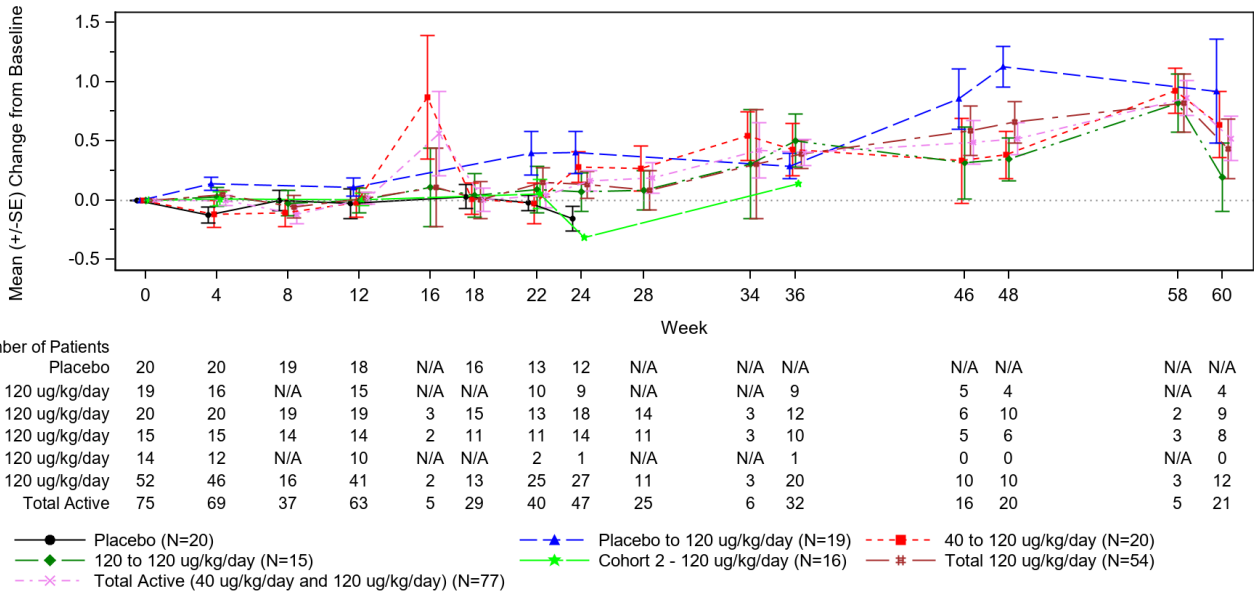
Anthropometrics

Figure 18 shows the pooled data on growth (Z-scores for height and weight) up to week 60 of odevixibat treatment.

Mean height z-score improved from a baseline value of -1.86 to -0.78 at Week 48, representing a mean (SE) change of 0.52 (0.134) and mean weight z-scores increased from a baseline value of -1.05 to -0.02 at Week 48, representing a mean (SE) change of 0.51 (0.144). Similar results were

observed for patients who had received 120 µg/kg/day throughout their treatment course with mean (SE) changes from baseline to Week 48 of 0.66 (0.177) and 0.39 (0.233) in height and weight z-scores, respectively, and for patients who had transitioned from 40 to 120 µg/kg/day (0.38 [0.200] and 0.61 [0.179]), respectively.

Figure 18: Mean (±SE) Change from Baseline in Height Z-scores (Full Analysis Set, Integrated Data).



Number of Patients																
Placebo	20	20	19	18	N/A	16	13	12	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Placebo to 120 ug/kg/day	19	16	N/A	15	N/A	N/A	10	9	N/A	N/A	9	5	4	N/A	4	
40 to 120 ug/kg/day	20	20	19	19	3	15	13	18	14	3	12	6	10	2	9	
120 to 120 ug/kg/day	15	15	14	14	2	11	11	14	11	3	10	5	6	3	8	
Cohort 2 - 120 ug/kg/day	14	12	N/A	10	N/A	N/A	2	1	N/A	N/A	1	0	0	N/A	0	
Total 120 ug/kg/day	52	46	16	41	2	13	25	27	11	3	20	10	10	3	12	
Total Active	75	69	37	63	5	29	40	47	25	6	32	16	20	5	21	

N/A: not applicable; SE: standard error.

Liver histopathology

Consistent with the results observed for improvements in hepatic biochemical parameters, long-term treatment with odevixibat led to improvement (decrease) in PELD/MELD scores. Mean changes from baseline after 48 weeks of treatment with odevixibat (either 40 µg/kg/day and 120 µg/kg/day dose) was -1.97 (0.817). Mean (SE) change in PELD/MELD scores for patients who received 120 µg/kg/day dose throughout their treatment course was -1.37 [1.265], and for those who transitioned from 40 µg/kg/day to the 120 µg/kg/day dose was -2.58 [1.067] at Week 48.

Minimal to no changes were observed in PELD/MELD scores during 24 weeks of treatment with placebo in Study A4250-005. After 48 weeks of odevixibat treatment, mean (SE) change from baseline in PELD/MELD scores for patients who had previously received placebo was 0.62 (1.464), although only 4 patients had data available at Week 48.

Clinical studies in special populations

Not applicable. PFIC is a paediatric disease.

Supportive study

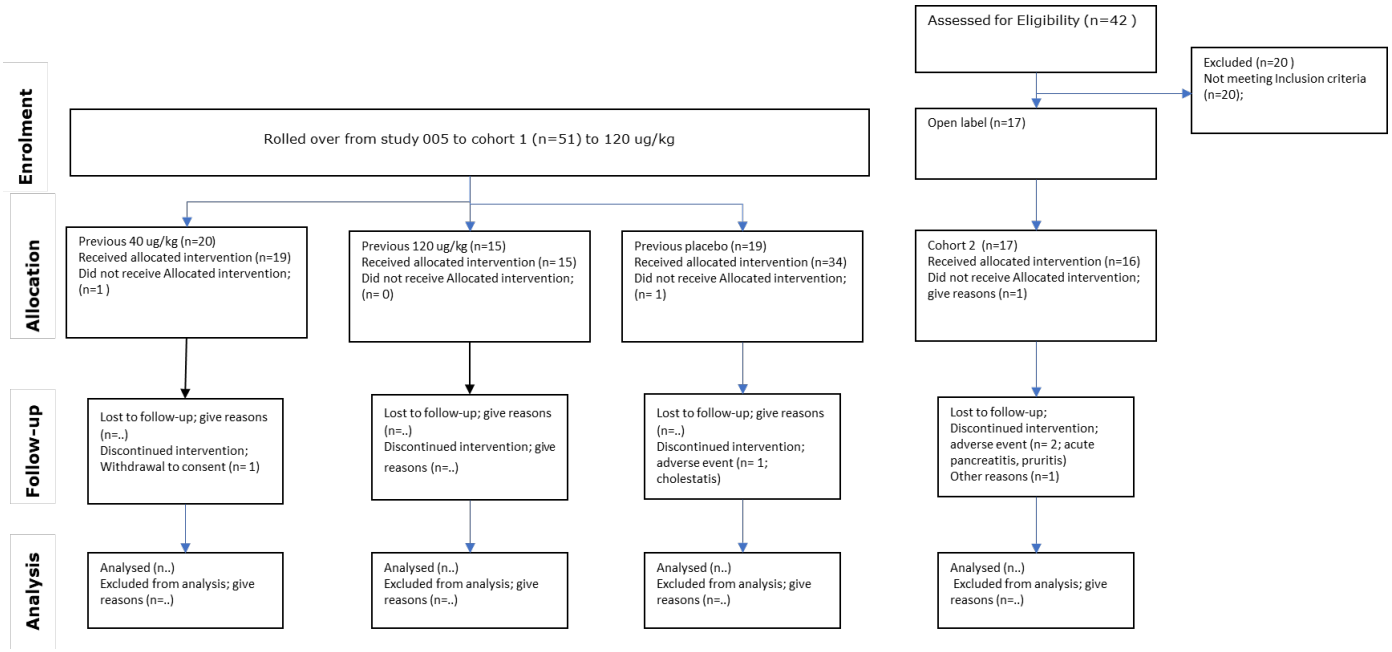
Study A4250-008

Study A4250-008 was 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).

Methods

Study participants

Figure 19: Participants flow in study A4250-008 (data cut-off 15 July 2020).



Note: Study 008 is ongoing; only interim data are available.

Inclusion and exclusion criteria

Cohort 1: Patients who completed the 24-week treatment period of study 005 or (prior to Amendment 6 of the A4250-005 protocol) withdrew due to patient/caregiver judgment of intolerable symptoms after completing at least 12 weeks of treatment were eligible for enrolment in Cohort 1.

Key exclusion criteria included patients with decompensated liver disease, those who were noncompliant with treatment in study 005, or any other conditions or abnormalities that could compromise the safety of the patient.

Cohort 2: treatment naïve patients of any age and a body weight ≥5 kg with a genetically confirmed diagnosis of PFIC who did not meet the eligibility criteria for study 005 or were eligible for enrolment after recruitment in study 005 was completed were included in Cohort 2. Patients were required to have an elevated serum bile acids concentration ≥100 µmol/L, taken as the average of 2 samples at least 7 days apart during screening; a history of significant pruritus; and a caregiver-reported average scratching score in the eDiary of ≥2 (on a 0 to 4 scale) in the 2 weeks prior to Visit 1.

Key exclusion criteria include patients with pathologic variations of the ABCB11 gene that predict complete absence of the bile salt export pump (BSEP) protein, prior liver transplant or planned transplant within 6 months, alanine aminotransferase (ALT) or total bilirubin >10 × upper limit of normal (ULN) at screening, decompensated liver disease, any uncontrolled, recalcitrant pruritic condition other than PFIC, or any other conditions or abnormalities that could compromise the safety of the patient or their ability to complete the study.

Treatment

Odevixibat is administered orally, once daily at a dose of 120 µg/kg/day; patients who are unable to tolerate the higher dose can reduce the dose to 40 µg/kg/day under specific conditions.

Outcomes/endpoints

Primary Efficacy Endpoints for the Interim Analysis

- Change from baseline in serum bile acid after 24 weeks of treatment in study 008.

Secondary Efficacy Endpoints for the Interim Analysis

• Change from baseline in serum bile acid at Weeks 4, 12, 22, 24, 36, 46, 48, 60, 70, 72, and 76.

• Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument from Weeks 0-4, 0-12, 0-22, 0-24, 0-36, 0-46, 0-48, 0-60, and 0-70, and the proportion of positive pruritus assessments at each 4-week interval between Visit 1/Screening and Week 24, then by each visit between Week 24 and Week 76.

• Proportion of individual AM and PM assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument from Weeks 0-4, 0-12, 0-22, 0-24, 0-36, 0-46, 0-48, 0-60, 0-70, and 0-72, and the proportion of positive pruritus assessments at each 4-week interval between Visit 1/Screening and Week 24, then by each visit between Week 24 and Week 76.

• Number of patients undergoing biliary diversion surgery or liver transplantation.

• Changes from baseline in APRI, FIB-4 and PELD/MELD scores; growth; and use of antipruritic medication.

Results

Baseline data

Demographics characteristics were generally similar across the study groups in Cohort 1 and Cohort 2 (Table 41).

Table 41: Summary of Patient Demographics (Full Analysis Set).

PARAMETER CATEGORY/ STATISTIC	ODEVIXIBAT 120 µg/kg, ONCE DAILY DOSING						
	COHORT 1a			ODEVIXIBAT ALL DOSES N=34	COHORT 2 N=16	COHORT 2 + PLACEBO[b] N=35	OVERALL N=69
	ODEVIXIBAT 40 µg/kg N=19	ODEVIXIBAT 120 µg/kg N=15	PLACEBO N=19				
Sex, n (%)							
Female	10 (52.6)	8 (53.3)	18 (52.9)	7 (36.8)	9 (56.3)	16 (45.7)	34 (49.3)
Male	9 (47.4)	7 (46.7)	16 (47.1)	12 (63.2)	7 (43.8)	19 (54.3)	35 (50.7)
Age (years)[c]							
n	19	15	34	19	16	35	69
Mean (SD)	3.82 (2.500)	5.50 (4.569)	4.56 (3.603)	4.34 (3.962)	7.89 (4.898)	5.96 (4.702)	5.27 (4.225)
Median	3.60	3.40	3.55	3.50	6.30	4.60	4.10
Min, max	1.2, 10.5	1.6, 13.9	1.2, 13.9	1.0, 15.6	1.3, 19.5	1.0, 19.5	1.0, 19.5
Age Category 1[c], n (%)							
< 6 months	0	0	0	0	0	0	0
6 months to 5 years	15 (78.9)	10 (66.7)	25 (73.5)	15 (78.9)	7 (43.8)	22 (62.9)	47 (68.1)
6 to 12 years	4 (21.1)	3 (20.0)	7 (20.6)	3 (15.8)	7 (43.8)	10 (28.6)	17 (24.6)
13 to 18 years	0	2 (13.3)	2 (5.9)	1 (5.3)	1 (6.3)	2 (5.7)	4 (5.8)
> 18 years	0	0	0	0	1 (6.3)	1 (2.9)	1 (1.4)

Age Category 2[c], n (%)							
<8 years	18 (94.7)	11 (73.3)	29 (85.3)	16 (84.2)	9 (56.3)	25 (71.4)	54 (78.3)
≥8 years	1 (5.3)	4 (26.7)	5 (14.7)	3 (15.8)	7 (43.8)	10 (28.6)	15 (21.7)
Race, n (%)							
Caucasian[d]	16 (84.2)	13 (86.7)	29 (85.3)	16 (84.2)	15 (93.8)	31 (88.6)	60 (87.0)
Black/African American	1 (5.3)	0	1 (2.9)	0	0	0	1 (1.4)
Asian	0	1 (6.7)	1 (2.9)	1 (5.3)	0	1 (2.9)	2 (2.9)
Other	2 (10.5)	1 (6.7)	3 (8.8)	2 (10.5)	1 (6.3)	3 (8.6)	6 (8.7)
Ethnicity, n (%)							
Hispanic or Latino	0	0	0	1 (5.3)	1 (6.3)	2 (5.7)	2 (2.9)
Not Hispanic or Latino	19 (100.0)	15 (100.0)	34 (100.0)	18 (94.7)	11 (68.8)	29 (82.9)	63 (91.3)
Unknown	0	0	0	0	4 (25.0)	4 (11.4)	4 (5.8)
Region, n (%)							
United States	0	3 (20.0)	3 (8.8)	3 (15.8)	3 (18.8)	6 (17.1)	9 (13.0)
Europe	12 (63.2)	9 (60.0)	21 (61.8)	12 (63.2)	7 (43.8)	19 (54.3)	40 (58.0)
Rest of World	7 (36.8)	3 (20.0)	10 (29.4)	4 (21.1)	6 (37.5)	10 (28.6)	20 (29.0)

CRF: case report form; max: maximum; min: minimum; SD: standard deviation.

a For patients in Cohort 1, dose indicated is dose administered during participation in Study A4250-005.

b Cohort 2 + Placebo = Patients enrolled in Cohort 2 and patients who were assigned to placebo during participation in Study A4250-005.

c For patients from France and Germany, only birth year (actual year) is collected on the CRF, and age is calculated based on collected age months and age years from the external file except for 2 patients in Cohort 2 from France. For these 2 patients in Cohort 2 from France, their ages may not be accurate since only the birth year is correctly collected and accurate age months and age years are not available.

d The study population from Middle Eastern countries is included under race category "Caucasian."

In the overall study population, the median height and weight were 92.5 cm and 15.0 kg, respectively.

Baseline Disease Characteristics

The baseline disease characteristics for Cohort 1 and Cohort 2 are presented in Table 42. All 69 patients had genetic confirmation of PFIC based on central reader review.

Baseline renal and hepatic functions were largely similar across the groups. **Table 42: Summary of Baseline Disease Characteristics (Full Analysis Set).**

PARAMETER CATEGORY/ STATISTIC	ODEVIXIBAT 120 µg/kg, ONCE DAILY DOSING						
	Cohort 1				COHORT 2 N=16	COHORT 2 + PLACEBOb N=35	OVERALL N=69
	40 µg/kg N=19	120 µg/kg N=15	ALL DOSES N=34	PLACEBO N=19			
Years since PFIC diagnosis, n	19	15	34	19	16	35	69
Mean (SD)	2.69 (2.529)	4.36 (3.784)	3.43 (3.205)	3.52 (3.690)	3.84 (3.096)	3.67 (3.386)	3.55 (3.276)
Median	1.80	3.00	2.10	1.90	3.00	3.00	2.60
Min, max	0.4, 9.6	0.9, 12.5	0.4, 12.5	0.5, 13.9	0.2, 11.3	0.2, 13.9	0.2, 13.9
Type of PFIC, n (%)							

Type 1	6 (31.6)	4 (26.7)	10 (29.4)	5 (26.3)	3 (18.8)	8 (22.9)	18 (26.1)
Type 2	13 (68.4)	11 (73.3)	24 (70.6)	14 (73.7)	7 (43.8)	21 (60.0)	45 (65.2)
Type 3	NA	NA	NA	NA	5 (31.3)	5 (14.3)	5 (7.2)
Other	NA	NA	NA	NA	1 (6.3)	1 (2.9)	1 (1.4)
Pathologic variants identified for:							
ABCB11	13 (68.4)	11 (73.3)	24 (70.6)	14 (73.7)	7 (43.8)	21 (60.0)	45 (65.2)
ATP8B1	6 (33.3)	4 (26.7)	10 (30.3)	5 (26.3)	3 (18.8)	8 (22.9)	18 (26.5)
ABCB4	NA	NA	NA	NA	5 (31.3)	NA	NA
MYO5B	NA	NA	NA	NA	1 (6.3)	NA	NA
BSEP subtype for PFIC2, n	13	11	24	14	7	21	45
Subtype 1	1 (7.7)	4 (36.4)	5 (20.8)	6 (42.9)	1 (14.3)	7 (33.3)	12 (26.7)
Subtype 2	12 (92.3)	7 (63.6)	19 (79.2)	8 (57.1)	4 (57.1)	12 (57.1)	31 (68.9)
Subtype 3	NA	NA	NA	NA	2 (28.6)	2 (9.5)	2 (4.4)
History of significant pruritus per Investigator, n (%)	19 (100.0)	15 (100.0)	34 (100.0)	18 (94.7)	15 (93.8)	33 (94.3)	67 (97.1)
Serum bile acids level > 100 µmol/L within 6 months before Screening, n (%)							
Yes	13 (68.4)	10 (66.7)	23 (67.6)	11 (57.9)	11 (68.8)	22 (62.9)	45 (65.2)
No	5 (26.3)	2 (13.3)	7 (20.6)	2 (10.5)	1 (6.3)	3 (8.6)	10 (14.5)
Not applicable	1 (5.3)	3 (20.0)	4 (11.8)	6 (31.6)	4 (25.0)	10 (28.6)	14 (20.3)
Baseline use of:							

UDCA	14 (73.7)	9 (60.0)	23 (67.6)	17 (89.5)	13 (81.3)	30 (85.7)	53 (76.8)
Rifampicin	8 (42.1)	7 (46.7)	15 (44.1)	17 (89.5)	7 (43.8)	24 (68.6)	39 (56.5)
UDCA and/or Rifampicin	16 (84.2)	11 (73.3)	27 (79.4)	18 (94.7)	13 (81.3)	31 (88.6)	58 (84.1)

BSEP: bile salt export pump; max: maximum; min: minimum; NA: not applicable; PFIC: progressive familial intrahepatic cholestasis; SD: standard deviation; UDCA: ursodeoxycholic acid.

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.

Medical and Surgical History

Overall, the conditions reported were typical of patients with PFIC; primarily pruritus, vitamin deficiencies, gastrointestinal morbidities, jaundice and other hepatobiliary disorders, and poor growth. The medical and surgical history of patients were similar across study groups in Cohort 1 and Cohort 2. Eight (12%) patients reported prior biliary tract surgeries (i.e. biliary diversion surgeries), including 1 (5%), 3 (20%), 2 (11%) Cohort 1 patients who had received 40 µg/kg/day odevixibat, 120 µg/kg/day odevixibat, and placebo, respectively in Study A4250-005 and 2 (13%) cohort 2 patients.

Prior Medications

Three of 16 patients (19%) in Cohort 2 reported using prior medications that were not PFIC-related. These included amoxicillin trihydrate; clavulanate potassium, clarithromycin, rifampicin, ibuprofen, lansoprazole, citric acid; sodium citrate; none were reported in >1 patient.

Use of prior PFIC-related medications was reported in 1 patient in Cohort 2 who received odevixibat in the Phase 2 study A4250-003.

Concomitant Medications

All 69 patients took at least one concomitant medication during the treatment period. Most patients received concomitant medications for the treatment of pruritus and vitamin supplementation. Generally, the types and use of these medications were similar across the study groups, with the exception that a higher percentage of treatment-naïve patients (89%) reported the use of bile acids and derivatives (UDCA) and other antibacterials (rifampicin) compared with patients who received odevixibat in Study A4250-005 (71%).

The most common concomitant medications among patients in Cohort 1 who had previously received odevixibat in Study A4250-005 included UDCA (24 patients, 71%), cholecalciferol (18 patients, 53%), rifampicin (16 patients, 47%), vitamin E NOS (12 patients, 35%), vitamin K NOS (11 patients, 32%), paracetamol (10 patients, 29%), and ibuprofen and phytomenadione (8 patients each, 24%).

In patients who were treatment-naïve, the most common concomitant medications were UDCA (31 patients, 89%), rifampicin (26 patients, 74%), vitamin K NOS (17 patients, 49%), vitamin D NOS (13 patients, 37%), vitamin E NOS (12 patients, 34%), cholecalciferol (10 patients, 29%), and phytomenadione (8 patients, 23%). Two patients initiated treatment with rifampicin during the treatment period.

Results

Change from Baseline to Week 24 in Serum Bile Acids Concentration

Table **43** presents the results of the primary efficacy endpoint, the summary of change in serum bile acids concentration from Study A4250-008 baseline to Week 22/24 (i.e. using the average of the values at Weeks 22 and 24).

Table 43: Summary of Change from Study A4250-008 Baseline in Serum Bile Acids (µmol/L) after 24 Weeks of Treatment (Full Analysis Set).

Parameter category/ statistic	ODEVIXIBAT 120 µg/kg, ONCE DAILY DOSING					
	Cohort 1				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[d] 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

Max: maximum; min: minimum; SE: standard error; SI: International System of Units

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 is calculated as the average of last 2 values before the first dose of study drug in Study A4250-008. d In cohort 1 study 008 patients previously in placebo in study 005 received odevixibat.

Change in serum bile acids concentration to Week 24 in Study A4250-008 was also analysed using Study A4250-005 baseline to assess the impact of long-term treatment in Cohort 1 patients who received odevixibat in Study A4250-005 (Table 44).

Table 44: Analysis of Change from Study A4250-005 Baseline in Fasting Serum Bile Acid Concentration (µmol/L) after 24 Weeks of Treatment in Study A4250-008 (Full Analysis Set, Cohort 1 Patients).

Visit statistic	Odevixibat 120 µg/kg, once daily dosing		
	COHORT 1[a]		
	40 µg/kg N=19	120 µg/kg N=15	ALL DOSES N=34
Baseline[b]			
n	19	15	34
Mean (SE)	251.1 (27.91)	252.7 (39.78)	251.8 (23.10)
Week 22/24			
n	12	9	21
Mean (SE)	79.1 (30.57)	93.1 (44.21)	85.1 (25.12)
Change from Baseline			
n	12	9	21
Mean (SE)	-193.2 (50.37)	-211.0 (62.45)	-200.8 (38.34)
p-value (t-test)	0.0028	0.0097	<0.0001
p-value (Wilcoxon signed rank)	0.0024	0.0078	<0.0001

SE: standard error.

a For patients in Cohort 1, dose indicated is dose administered during participation in Study A4250-005.

b Baseline was calculated as the average of last 2 values prior to the first dose in Study A4250-005.

Note: two-sided p-values are presented.

Pruritus Assessments

Proportion of Positive Pruritus Assessments at the Patient Level Over the 24-Week Treatment Period Based on ObsRO.

The results of the primary efficacy endpoint analysis, the proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on the combined AM and PM scores on the Albireo ObsRO instrument.

For patients in Cohort 1 who had received odevixibat in Study A4250-005, who entered the study with improved pruritus severity compared with treatment-naïve patients, a further reduction from Study A4250-008 baseline in pruritus severity was observed during longer-term treatment. The mean

proportion of positive pruritus assessments for this group of patients was 33% after 24 weeks of treatment at 120 µg/kg/day on Study A4250-008. The proportion of positive pruritus assessments was higher for patients who had received 40 µg/kg/day (37%) than for patients who had received 120 µg/kg/day (27%) during Study A4250-005.

Mean proportion of positive pruritus assessments over the 24-week treatment period in treatment-naïve patients was higher than that observed for patients in Cohort 1 who had previously received odevixibat in Study A4250-005. For patients in Cohort 1 who had received placebo in A4250-005, the proportion of positive pruritus assessments at the patient level was 56% over the 24-week treatment period. In Cohort 2, the proportion of positive pruritus assessments at the patient level was 62% over the 24-week treatment period, although limited data were available for this cohort through Week 24.

Growth

Improvement in growth was noted over time in all study groups in Cohort 1 and in Cohort 2.

Changes in Liver Pathology

PELD/MELD scores

Treatment with odevixibat over 24 weeks led to an improvement in PELD/MELD scores in all groups except the Cohort 2 group, which only had data available for 2 patients at Week 24. For PELD/MELD the mean (SE) changes from baseline to Week 24 were -0.09 (0.51) and -0.29 (0.31) in patients who had received 40 µg/kg/day or 120 µg/kg/day in study 005. For patients who had received placebo in study 005 this was -1.40 (1.21). For patients in Cohort 2 the mean (SE) changes from baseline to Week 24 was 1.74 (5.83).

Liver Fibrosis/Steatosis

Limited data were available for this analysis; changes from baseline to Week 24 for liver stiffness were tabulated for a total of 8 patients, including 6 patients in Cohort 1 (2 in the 40 µg/kg/day group, 1 in the 120 µg/kg/day group, and 3 in the placebo group), and for 2 patients in Cohort 2. Only 1 patient in Cohort 1 (the 120 µg/kg/day group) had data available for controlled attenuation at Week 24. Mean changes from baseline to Week 24 for liver stiffness were 1.50 kPa (mean change calculated for 1 patient in the 40 µg/kg/day group), 0.30 (1.701) kPa in the Cohort 1 placebo group, and 1.55 (0.6250) kPa in the 2 patients in Cohort 2, respectively.

Biliary Diversion Surgery or Liver Transplantation

Two patients in this study underwent surgical intervention due to lack of improvement in pruritus. Patient 19101-502, 1.4-year-old male with PFIC2/BSEP subtype 1, who received placebo in Study A4250-005, underwent biliary diversion surgery at Week 37 and Patient 24103-503, a 2.8-year-old male with PFIC2/ BSEP subtype 1, who also received placebo in Study A4250-005, underwent elective liver transplantation at Week 19. Patient 19101-502 did not experience a reduction in serum bile acids levels prior to surgery; a 25% reduction in serum bile acids was reported at Patient 24103-503's last assessment (Week 12) before the surgery.

Other additional secondary endpoints performed.

In line with the pivotal study, several other secondary and exploratory analysis on the FAS were performed that will not be discussed in this report. Additional results pertaining to reduction of SBAs, improvement of sleep parameters, reduced scratching all pointed in a similar positive direction and are consistent with the primary and secondary endpoint. Note that not all patients already had 24 weeks of treatment in study 008.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

General

A single pivotal study (A4250-005) was submitted to support the proposed indication. Given the rarity of PFIC only a limited number of patients could be enrolled; hence this is acceptable to the CHMP and not uncommon for orphan diseases. The pivotal study met the requirements as outlined in the guideline on "points to consider on application with 1. meta-analyses; 2. one pivotal study" (CPMP/EWP/2330/99). Further, the design of the clinical studies has previously been discussed with the EMA at various PRIME and SAWP procedures, and for the most part the studies followed the advices received. The studies have been conducted in accordance with the protocols; and it is considered that the reported protocol deviations had only minor and no consequence.

The indication applied for is the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months and older. To substantiate the indication, one randomised double-blinded placebo-controlled study (study 005) enrolling 62 paediatric patients, and one long term open-label follow-up study (study 008) are conducted. The proposed dose is supported by a dose-finding study 003.

Study 003

In the open-label dose-finding study 003, six dose cohorts were included. The study was originally designed to evaluate doses up to 300 µg/kg/day. However, two patients with Alagille syndrome in the 200 µg/kg/day cohort experienced elevations in LFTs >2 times baseline. Therefore, dosing up to 200 µg/kg/day was considered. Patients received a single dose of odevixibat and 2 weeks after the single-dose administration patients received multiple-dose treatment for 4 weeks. For efficacy evaluation serum bile acids, reduction of pruritis and sleep were measured. In addition, liver biochemical parameters were also evaluated as these may indicate reductions in hepatic damage, given that in patients with cholestatic disease, as in patients with PFIC, these endpoints are accepted by the CHMP. Safety evaluation is considered standard and is normally seen in clinical applications.

Study 005

Study 005 is a randomised placebo-controlled study in paediatric patients with PFIC type 1 and 2. The in- and exclusion criteria are appropriate to select the relevant paediatric patients with PFIC1 and PFIC2 with some functionality of the BSEP protein. The inclusion criterion for serum bile acids to be ≥100 µmol/L is determined based on the results from the Phase 2 study 003 and on information in the literature.

Two patients had baseline values ≤70 µmol\L and one patient had baseline value ≤ 100 µmol/L which is not in line with the inclusion criteria. The serum bile acid results were blinded during the Treatment Period (Visits 3-9) and the Follow-up Period (Visit 10). Serum bile acid results were kept unblinded during the Screening Period (Visits 1 and 2) to confirm study eligibility (Inclusion Criteria #3; Patient must have elevated sBA concentration, specifically measured to be ≥100 µmol/L, taken as the average of 2 samples at least 7 days apart [Visits 1 and 2] prior to randomisation). As the calculation of serum

bile acid eligibility and baseline serum bile acid used in analysis differ based on the visits in which the samples were obtained, some patients do in fact have a baseline serum bile acid that is less than the 100 µmol/L eligibility requirement.

Fifty-six patients were included in the per-protocol analysis (PP). The full analysis set (FAS) and PP populations only differ by 2 patients in each of the 3 arms. Six patients in the FAS were excluded from the PP analysis set as they had treatment compliance rates <80%, where the compliance rate was calculated based on actual duration of exposure for each patient. Patients who discontinued treatment early from the study due to the lack of efficacy or adverse events were not specifically excluded from the PP analysis set unless they met one of the criteria detailed above. Data from these were included as a conservative approach to the analysis of efficacy (i.e. included as treatment failures).

With regard to the reason for early treatment discontinuation of 'intolerable symptoms', this was to be reported for patients who elected to roll over early to the long-term extension Study A4250-008 and was specifically reported for patients who had a perceived lack of effect of treatment on pruritus symptoms (i.e. intolerable *pruritus* symptoms).

Three patients previously treated in study 003 were also enrolled (1 patient in each treatment arm) in study 005. These patients did not roll over directly from study 003 to study 005, but there was a "wash-out" period of at least 1.8 years.

Patients received either 40 µg/kg/day odevixibat (n=23), 120 µg/kg/day odevixibat (n=19) or placebo (n=20). After 24 weeks of treatment patients could enrol in the long-term follow study 008. A patient who had tolerability issues or lack of efficacy could also be rolled-over to study 008 if at least 12 weeks of treatment were completed. The doses administered in study 005 are in line with the dose recommendations in SmPC section 4.2. Dose reductions were not allowed in this study. Based on the proposed posology, some patients may be under- or overdosed depending on their bodyweight. The applicant elaborate that based on toxicology data, any odevixibat dose exceeding a total of >3 mg/kg (>3000 µg/kg) administered as a single dose or as a cumulative dose within 24 hours is defined as an overdose.

Patients were allowed to have UDCA and rifampicin as concomitant medication if they were on a stable dose 4 weeks prior to inclusion, and the dose was to be remained (no dose adjustments allowed) during the study. Two patients initiated treatment with rifampicin during the treatment period (1 patient in the placebo and 1 patient in the 120 µg/kg/day group). Protocol deviations were reported for both patients. Given that rifampicin alleviates pruritus this might impact the observed results; however, as one patient was in the placebo group this is not a considered an issue; the clinical effect of odevixibat on pruritus is larger than in the placebo group. The patient in the 120 µg/kg/day group was rolled-over to study 008, which is considered acceptable.

Primary Efficacy endpoint: In study 005, the primary efficacy endpoint was the proportion of patients experiencing at least a 70% reduction in serum bile acids (SBAs) concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment. This was discussed and agreed upon within SA.

Secondary Efficacy Endpoints: The important secondary endpoint was the proportion of positive pruritus assessments for AM and PM scores combined at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument. Further, the applicant was advised to submit an analysis of the number (%) of patients achieving a positive pruritus assessment (AM and PM Scores Combined) for more than 50% of the time during the 24-week treatment period.

Use of the Obsro and Pro for pruritus and sleep disturbance: The Obsro and Pro for pruritus and sleep disturbance have been validated, based on blinded interim data in study 005, against the Patient Global Impression of Change (PGIC), Patient Global Impression of Symptoms (PGIS), and Paediatric

Quality of Life Inventory (PedsQL). The equivalent for Global Impression of Change and Global Impression of Symptoms for the caregiver and clinician was also used. All measures were also individual endpoints in study 005. It was agreed by CHMP using interim data of study 005 in a blinded way to estimate a threshold for clinically meaningful change to use in the responder analysis of pruritus endpoints. This tool was discussed and agreed with during SA. As part of the efficacy analysis of the secondary endpoint, the applicant pre-specified a responder definition as a change in 1 point or greater of the PRO and ObsPRO from baseline. While the analysis did tend to support the applicant's definition of the degree of change in the pruritus PRO and ObsdPRO which would constitute a clinically meaningful difference, there are some aspects which limit the validity of this result. While the results of the analysis of the ObsPRO were positive, the small number of observations for the PRO meant that the outcome of that analysis cannot be relied upon. This is probably a function of age of the patient population, which was such as to make the ObsPEO more appropriate for the majority of those enrolled in the study. Nevertheless, it is premature to state that the results in themselves validate the definition of an MCID for all patients. In addition, the results used by the applicant only come from a single trial. The CHMP considered that the first analysis of the data generated in Study 005 using data should be confirmed from a separate study. In this regard, the applicant was recommended to consider using data from newly enrolled patients into Study 008 to verify the preliminary results. Given these limitations, it is premature to conclude that a change in 1 point in the pruritus PRO and ObsPRO constitutes an MCID. Consequently, it is not necessary to mention such an MCID in section 5.1 of the SmPC.

Study 008

Study 008 is an open-label long term follow-up study in which PFIC patients receive 120 µg/kg/day odevixibat up to 72 weeks. For long term follow-up patients previously treated, or those that receive placebo, in study 005 could enrol in cohort 1 of this study. Cohort 2 included treatment were not eligible for study 005. Further, as already mentioned above some patients were considered early rollover from study 005, these need some further clarification.

Choice of dose for study 005 and 008

Initially, the applicant chose the 120 µg/kg/day dose in study 008. The choice was made prior to the data of study 005 was unblinded. The choice was based on an animal-to-human conversion factor of 12.3, the ED_{50}, ED_{90}, and ED_{95} of odevixibat were 4.39, 39.5 and 83.4 µg/kg, respectively. Further, nonclinical findings were confirmed in the clinical Phase 1 dose-finding, PK and PD study, A4250-001, conducted in healthy adults. In evaluating the effect of multiple dosing of odevixibat for 7 days on systemic bile acids levels using a maximum effect model (Emax), it was found that odevixibat lowered serum bile acids levels in a dose-dependent manner with an ED50, ED90, and ED95, of 12.3, 111, and 234 µg/kg. Similarly, a dose-dependent increase in the AUC_{0-12} of C4, a biomarker for the rate of bile acids synthesis, was observed on Day 7. Again, using an Emax model, the estimated ED50, ED90, and ED95 were 18.1, 162, and 344 µg/kg, respectively.

In the 4-week Phase 2 study conducted in paediatric patients with cholestatic liver disease, Study 003, the dose range selected – from 10 to 200 µg/kg – provided adequate coverage relative to the ED_{50}, ED_{90}, and ED_{95} from the Phase 1 study. In this study, improvements in serum bile acids and pruritus were observed after treatment with odevixibat at doses ranging from 30 to 200 µg/kg/day. Patients with PFIC responded well across the dose range, including statistically significant reductions in bile acids levels and increases in C4; however, a clear dose relationship could not be established. Further, there were no significant differences in the safety profile of the dose groups up to 200 µg/kg/day.

The data from this Phase 2 study, taken together with the nonclinical data and the data from Study A4250-001, demonstrated a consistent PK/PD relationship for odevixibat. The lack of a dose-response in Study 003 may reflect the very sparse sample collection scheme used in the study. As efficacy was observed at both low and high doses in Study 003, and the safety profile appeared comparable, dose levels of 40 µg/kg/day (approximately 3× ED_{50}) and 120 µg/kg/day (approximately ED90) were selected for evaluation in the pivotal Phase 3 Study 005. This is agreed with; however, based on the study data from 005, it appears that the 40 µg/kg/day has a (numerically) better and sustained efficacy on the endpoints, the treatment effect is more pronounced at treatment initiation and a better overall safety profile. Post hoc analyses to compare the results for the primary analyses of pruritus and serum bile acids across the 40 and 120 µg/kg/day groups showed that there was no statistically significant difference between the 2 odevixibat dose groups for the proportion of positive pruritus assessments at the patient level over the 24-week treatment period (2-sided p-value = 0.5008) or in the proportion of serum bile acid responders (2-sided p-value = 0.1083).

However, as the choice for 120 µg/kg/day was made without further scientific discussion, the choice was not fully supported. The applicant was requested to compare the results from patients who started on 40 µg/kg/day in study 005 and switched to 120 µg/kg/day in study 008, and those who started on 120 µg/kg/day and remained on this dose. Although limited data is available it indicates that most patients who started on 40 µg/kg/day remained a responder. Nine of 20 patients that were not a responder on 40 µg/kg/day, an additional 4 became a responder when treated with 120 µg/kg/day. The applicant hence proposed the 40 µg/kg/day as the starting dose, which is agreed with.

Efficacy data and additional analyses

Given the debilitating intractable pruritus in PFIC patients and the progression to cirrhosis and ultimately liver failure requiring OLT, the reduction of pruritus and improvement of liver-related parameters are considered important for the B/R discussion.

Study 003

A reduction in the primary efficacy endpoint, total serum bile acid level, was observed at the end of the 4-week treatment period with odevixibat for all dose groups. In addition, for most PFIC patients, improvements in pruritus and sleep were observed in all dose cohorts.

As efficacy was observed at both low and high doses, the 40 µg/kg and 120 µg/kg/day were considered to be the optimal doses for evaluation in the pivotal study (005). The chosen doses are considered sufficiently justified.

Study 005

Baseline data: Study 005 included paediatric patients with PFIC 1 (n=12) or PFIC 2 (n=30). The median age was 3.2 years (min, max 0.5, 15.9 years). Among the PFIC 2 patients, 6 patients had the BSEP1 and 24 patients had the BSEP2 mutation. Although the number of enrolled patients is limited, given the rarity of the disease, this is considered acceptable.

As in the clinical practice, PFIC patients have intractable pruritis, which is difficult to suppress despite off label use of medications (e.g. UDCA or rifampicin) the only alternatives for these patients are SBD or liver transplantation. It is known that not in all patients who underwent SBD the disease symptoms will alleviate, requiring additional symptomatic treatment. Eight patients (13%) enrolled in the study had undergone SBD at least 6 months prior to enrolment in the study. This is in line with the in- and exclusion criteria and agreed with. This information is correctly included in SmPC section 5.1.

Based on the inclusion criteria patients were to have some functional protein; BSEP1 and BSEP2 are PFIC2 types that according to literature should have BSEP protein function left, according to literature BSEP3 is considered to have non-functional protein. In study 005 of the included patients with PFIC2, 12/45 had BSEP1 and 33/45 BSEP2. Based on the exclusion criteria patients with pathologic variations of the ABCB11 gene that predicted the complete absence of the BSEP protein were excluded. According to literature BSEP3 are considered the mutations that relates to none functional protein (Wessel et al., 2020). Hence, zero PFIC2 patients with BSEP3 were included; however, two patients with BSEP3 were included in study 008. See discussion further below. It is unknown whether patients with PFIC1 or PFIC3 are also patients with some protein functionality or absence of functionality. Although such information may help to potentially decide if a patient will benefit from odevixibat treatment, it is anticipated that this data is likely not available.

Serum bile acids: The primary endpoint (PE) the proportion of patients experiencing at least a 70% reduction in serum bile acids concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment was met.

In the FAS, after 24 weeks of odevixibat treatment, there were 33.3% responders [14/42 patients] in the overall group (43.5% [10/23 patients] and 21.1% [4/19 patients] in the odevixibat 40 µg/kg/day and odevixibat 120 µg/kg/day groups respectively), there were no responders [0/20 patients] in the placebo group. Similar results were observed in the PP population. Although only a limited number (n=14) of patients were considered a responder, this can be considered a benefit for the patient in this progressive disease for which there is an unmet medical need.

Based on literature references, it was demonstrated that after SBD PFIC2 patients showed a reduction of 75% in SBAs. Therefore, a post-hoc analysis "*Analysis of Number (%) of Patients Experiencing at Least a 75% Reduction in Fasting Serum Bile Acid Concentration from Baseline to Last Visit*" was conducted; these results are like the results regarding the primary endpoint.

The applicant performed a subgroup analysis in PFIC1 patients. Data showed that 2/12 PFIC1 patients met the criteria for a responder while in the placebo group none of the patients responded. When looking at the change from baseline to week 24 in SBAs, data shows that all 12 PFIC1 patients had reductions of SBAs; in contrast, SBAs increased in the placebo group. The data on PFIC1 patients suggests that odevixibat is somewhat less effective compared to PFIC2. In all subgroup analyses (e.g. by age category, hepatic impairment classification, Child-Pugh classification (A and B), BSEP type, use of UDCA and/or rifampicin) odevixibat treatment was superior over placebo. There were no patients included with severe hepatic impairment (Child-Pugh C), this is clearly stated in the SmPC.

The subgroup analysis per region shows that, in contrast to the other regions, in the US none of the 5 patients in the odevixibat groups where responders. Given the patient numbers is somewhat unexpected. This observation might be explained by the small sample size in this subgroup. It was shown that all 5 US patients experienced a reduction in serum bile acid levels and/or had a clinically meaningful reduction in pruritus symptoms during treatment with odevixibat. Fewer patients in the US were receiving rifampicin or UDCA and/or rifampicin at baseline.

Subgroup analysis for PFIC1 patients revealed that under continued odevixibat treatment some patients with PFIC1 showed beneficial results in the reduction of pruritis irrespective whether sBAs showed large reductions, e.g. some PFIC1 had SBAs level fluctuating around baseline levels.

It has been included in the SmPC section 4.4 that "*The mechanism of action of odevixibat requires some function in the enterohepatic circulation of bile acids; conditions or medications that impair either GI motility or enterohepatic circulation of bile acids have the potential to reduce the efficacy of odevixibat*". In addition, given that the efficacy of odevixibat may be reduced or that not all patients may respond satisfactorily to treatment, it is also stated that patients should be regularly monitored

and if the disease progresses, or efficacy is not considered optimal in terms of reducing pruritus after 6 months of continuous odevixibat treatment, other treatment options should be considered.

Pruritis: The reduction of pruritis was included as a secondary endpoint. It was defined as the proportion of positive pruritus assessments for AM and PM scores combined at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument. The data showed a statically significant, but moreover a clinically significant improvement, in the reduction of pruritus (AM night-time and PM daytime measures combined) after 24 weeks of odevixibat over placebo. Patients in the 40 µg/kg group have a slightly better improvement over the 120 µg/kg group; LS Mean Difference (SE) (odevixibat – placebo): 28.23 (9.182) and 21.71 (9.892) for the 40 µg/kg and 120 µg/kg respectively. No major differences were observed between the AM as the PM results separately. Additional requested mixed model-repeated measures (MMRM) analyses for the proportion of positive pruritus assessments over time (in 4-week intervals) showed that the results were consistent with the results from the ANCOVA analysis by each 4-week interval.

The proportion of patients achieving a positive pruritus assessment for >50% of the 24-week treatment period was 61.9% for the overall odevixibat group, including 73.9% and 47.4% of patients in the 40 and 120 µg/kg/day groups, respectively, compared with 20.0% in the placebo group.

In line with reducing serum bile acids, 6/12 PFIC1 patients showed a reduction of 1.0 point for pruritus score at Week 24, whereas in the placebo group, 1/5 patients showed a reduction. During the SAs the applicant was requested to discuss the clinical relevance of the 1-point reduction on the pruritus scale in the submission. As can be learned from the tools, 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. Therefore, the developed ObsRO instrument is fit to evaluate pruritus among paediatric patients with PFIC in study 005. Further data in study 005 on the reduction of pruritis showed that 10/12 patients showed a reduction in pruritus, although in the placebo group, some patients also showed reductions in pruritus though to a lesser extent. Although the patient numbers are limited it can be concluded that odevixibat is also effective in the treatment of pruritus in PFIC1 patients; data from study A4250-008 indeed confirms that PFIC1 patients also benefit from treatment with odevixibat. Two additional PFIC1 patients were enrolled (in cohort 2) the interim data shows that both patients also showed a reduction in pruritus.

It is noticed that for the tables pertaining to the analysis of the proportion of positive pruritus assessments (AM and PM Scores Combined, AM scores, and PM scores) at the patient level over the 24-week treatment period, the AM and PM baseline scores were rounded. This was due to the discrete nature of the pruritus scores (i.e. 5-point scale from 0 to 4), the rounded average baseline score for AM and the rounded average baseline score for PM from the 14 days prior to the first dose of study treatment were used in the derivation of a positive assessment, which was conducted at *each* of the daily post-baseline AM and PM assessments, and subsequently these values were used in the analysis of covariance (ANCOVA) model for the analysis of the proportion of positive pruritus assessments at the subject level over the 24-week treatment period. The applicant performed a post-hoc analysis based on the unrounded pruritis baseline values; results were consistent with the primary endpoint results which were based on rounded baseline pruritus scores, results based on the unrounded baseline pruritus score over the 24-week treatment period demonstrated statistically significant improvements in pruritus for odevixibat overall (one-sided p = 0.0018), 40 µg/kg/day (one-sided p = 0.0009), and 120 µg/kg/day (one-sided p = 0.0230) compared with placebo.

Liver pathology: Reductions in hepatic biochemical parameters (AST, ALT, total bilirubin and GGT) were observed with minimal changes observed in the placebo group. Although exploratory endpoints, the PELD/MELD, APRI, and FIB-4 scores are in line with the improvements with the hepatic biochemical

parameters. Data on liver fibrosis/steatosis, although limited, also indicated a delay of liver damage. Further, the applicant discussed the results of a patient listed for biliary diversion surgery being removed from the list due to the beneficial effect of odevixibat treatment. In addition, at data cut-off (4 December 2020) none of the patients was listed for transplant. In contrast, two patients who did not respond to treatment received a surgical intervention.

Growth: Data on height and weight (z-scores) suggest that compared to placebo, the patients treated with odevixibat had some marginal improvement in both parameters over 24 weeks of treatment over placebo. However, 24 weeks seem to be too short to make firm assumptions; patients were continued on odevixibat 120 µg/kg/day in study 008. See respective paragraph under study 008 for further discussion. The improvements in anthropometrics contribute to the overall benefit.

Other clinical efficacy endpoints: Several other secondary and exploratory parameters were measured, most pertained to the measurement of SBAs and pruritis (change from BL). All analyses pointed in the same positive direction, are consistent with the primary and important secondary endpoints and favour odevixibat treatment over placebo.

Study 008 and pooled results

Baseline data: Demographics characteristics were generally similar across the study groups in Cohort 1 and Cohort 2. At data cut-off (4 December 2020) a total of 79 PFIC patients enrolled in study A4250-008, although limited this is not uncommon for orphan diseases, and thus acceptable. The median age of the 79 patients at study entry was 3.8 years (4 months to 25 years). Only two patients aged 18 years and older were included. Consistent with patients with PFIC having impaired growth, median height-for-age and weight-for-age z-scores were -1.46 and -0.54, respectively, indicating the patients were below their age-matched peers for growth. In cohort 1, 17 patients with PFIC type 1 and 39 patients with PFIC type 2 were included. These patients previously were treated with odevixibat or placebo in study 005. Also, the patients that were considered early roll-overs are included in cohort 1.

Baseline disease characteristics of study 005 completers and early rollovers indicated that early rollover patients were PFIC2 (9/38, 24%) vs PFIC1 (2/16, 13%) and baseline pruritus score of ≥ 3 (7/27, 26%) vs score of <3 (4/27, 15%). No differences were observed in other baseline characteristics, including the use of UDCA and/or rifampicin, baseline hepatic biochemical parameters, and baseline serum bile acids levels. In cohort 2, five patients with PFIC type 1, twelve patients with PFIC type 2, five patients with PFIC type 3, and one patient with PFIC 6 (Myo5B) were included. This MyoB5 patient is the same patient as included in study 003.

For the twelve PFIC2 patients in cohort 2, one patient (27.3%) was considered BSEP type 1, four (54.5%) BSEP type 2 and two (18.2%) BSEP type 3. Both patients with BSEP3 had two truncated mutations and therefore were expected to have minimal (to no) residual protein functionality based on the central review of the genetic report. Neither of the patients experienced any clinically meaningful treatment effects following approximately 24 weeks of dosing with odevixibat 120 µg/kg/day as evidenced by unchanged serum bile acid levels and no improvement in pruritus severity scores. Hence, these patients should not be initiated on odevixibat, but should be offered alternative intervention(s). The applicant included a warning in the SmPC (section 4.4) mentioning that "*patients with PFIC2 who have a complete absence or lack of function of Bile Salt Export Pump (BSEP) protein will not respond to odevixibat"*. This is agreed with by the CHMP.

One patient (PFIC1; cohort 2) had baseline value <70 µmol/L which is not conform the in- and exclusion criteria, however given the explanation above (study 005) this is considered acceptable. The difference in baseline hepatic parameters (AST, ALT, bilirubin) is logical, as patients previously treated with odevixibat had improvements in these parameters, whereas patients previously on placebo and

those in cohort 2 did not receive treatment. Overall the hepatic parameters in all patients are indicative of hepatic damage.

The medical and surgical history of patients were similar across study groups in Cohort 1 and Cohort 2, are typical for PFIC patients. In cohort 2 two patients had a history of biliary diversion, whereas in cohort 1 six patients had a history of biliary diversion. The latter patients had their surgery conform to the protocol of study 005 performed at least 6 months prior to enrolment in study 005.

Generally, the types and use of concomitant medications were similar across the study groups, with the exception that a higher percentage of treatment-naïve patients (89%) reported the use of bile acids and derivatives (UDCA) and other antibacterials (rifampicin) compared with patients who received odevixibat in study 005 (71%).

Serum bile acids: Fourteen patients in Cohort 2 had data available at Week 22/24 at the time of the data cut-off (4 December 2020). The mean (SE) change from baseline study 008 to week 24 was 65.3 (28.4) %. The patients previously treated with odevixibat in study 005 showed further improvement in reducing SBAs under continued treatment (change from BL after 24 weeks in study 008 40 µg/kg/day: -5.8%; 120 µg/kg/day: -14.8%). For the patients who previously received placebo a similar rapid reduction of SBAs as was observed in the treatment groups in the pivotal study, confirming the pharmacodynamic properties of odevixibat.

Data on the change from baseline to week 24 in study A4250-008 for patients treated with odevixibat in study A4250-005 show that under continued odevixibat treatment patients had further improvement in most subgroup analyses. Data on six patients with a normal hepatic function conform the National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) at study 008 entry. This was due to treatment in the preceding study 005. At study 005 baseline these 6 patients all had *mild to moderate* hepatic impairment based on the NCI ODWG and the Child-Pugh classification. The 6 patients included 4 males and 2 females and ranged in age from 0.9 to 9.2 years; all 6 had PFIC2. It was shown that these 6 patients all achieved substantial improvements in serum bile acids concentrations prior to entry into study 008 with baseline serum bile acids ranging from 2.5 to 103.5 µmol/L. The patients then maintained or showed additional improvements over the course of treatment in study 008. At Week 24 in Study 008, 5 of the 6 patients had reductions in serum bile acids from Study 005 baseline of >85% and for 1, the reduction was 57%.

Pruritus: For patients in Cohort 1 - who had received odevixibat (40 or 120 µg/kg/day) in study 005 -, who entered the study with improved pruritus severity compared with treatment-naïve patients, a further reduction from Study 008 baseline in pruritus severity was observed during longer-term treatment with 120 µg/kg/day. The mean proportion of positive pruritus assessments for this group of patients was 34.3 % after 24 weeks of treatment at 120 µg/kg/day in study 008. The proportion of positive pruritus assessments was higher for patients who had received 40 µg/kg/day (39.6 %) than those who had received 120 µg/kg/day (27.4 %) during Study 005. For the patients (n=19) previously on placebo in study A4250-005, 59.3% showed a response. This confirms the efficacy of continued odevixibat treatment in PFIC patients. The pooled data of both studies are in line with these results, showing that under continued odevixibat treatment the proportion of positive pruritus assessments at the patient level is increasing up to week 48. For the naïve patients enrolled in cohort 2 this proportion was 78.4%.

Changes in Liver Pathology: Data on the change from baseline to week 48 for ALT, GGT, and total bilirubin showed that for the patients previously treated with odevixibat continued treatment further improved the parameters. Notably, patients who were treatment naïve (previous placebo group and cohort 2) also showed improvements except for ALT. Some variability in mean changes over time was observed for both ALT and total bilirubin across the cohorts; these are related to individual patients with transient elevations in these parameters, typically related to intercurrent illness – most of whom

have recovery of the elevations within 1 or 2 visits. Baseline study 008 values indicate that most patients were likely to have minimal fibrosis (e.g. APRI score about 0.64, APRI <0.5 is indicative for not having fibrosis, whilst APRI >1.5 is indicative for likelihood to have fibrosis). Notably the patients in cohort 1 already received odevixibat treatment and PELD/MELD scores marginally improved during treatment in study 005. Continued treatment with odevixibat 120 µg/kg/day over 48 weeks in study 008 led to a further improvement in PELD/MELD scores for the patients previously treated with odevixibat in study 005. For the patients (n=19) previously enrolled in study 005 24 weeks of treatment in study 008 PELD/MELD score improved; mean (SE) -2.86 (1.9). Longer term data up to 60 weeks (available for cohort 1 patients) in study 008 indicates some further improvement/stabilisation.

It is therefore concluded that currently only short-term data is available for odevixibat which indicate an improvement in the biochemical markers of cholestasis and an improvement or at least a stabilisation of the PELD/MELD scores for over one year.

Only limited data on fibrosis is available. For both APRI and FIB-4 scores, differences were limited. The observed short-term improvements in APRI scores and the stabilisation of FIB-4 scores in patients treated with odevixibat are indicative of stabilisation of disease progression or improvement in fibrosis staging. It remains to be demonstrated whether these early observations will be maintained over a longer time and will result in delay of SBD and/or OLT.

Growth: Data on height (z-scores) show that patients previously treated with odevixibat in study 005 (Cohort 1) showed further improvement from BL to week 60 in study 008 under continued odevixibat 120 µg/kg/day treatment. Patients previously on placebo also showed improvement in gaining length, this is in line with the results in the pivotal study. Data up to week 60 in cohort 1 suggests that patients will still catch up growth. This is confirmed by the pooled analysis in growth; treatment with odevixibat (40 µg/kg/day or 120 µg/kg/day) led to clinically relevant improvement in growth over time, indicating catch-up growth. Mean height z-scores improved to -0.78 at Week 48, representing a mean (SE) change of 0.52 (0.134). Mean weight z-scores increased to -0.02 at Week 48, representing a mean (SE) change of 0.51 (0.144). Similar results were observed for patients who had received 120 µg/kg/day throughout their treatment course with mean (SE) changes from baseline to Week 48 of 0.66 (0.177) and 0.39 (0.233) in height and weight z-scores, respectively. Notably, the patients included in cohort 2 also showed improvement up to week 24 in study 008. Although the data is limited beyond week 24 the results are consistent with the results observed in patients previously treated in study 005. The observed growth improvement is comparable to the effects observed following surgical intervention (i.e. 1-year data post biliary diversion surgery or liver transplantation).

Other clinical efficacy endpoints: Several other secondary and exploratory parameters were measured, most pertained to the measurement of SBAs and pruritis (change from BL). The data showed that patients previously receiving odevixibat in study 005 continued to improve in these endpoints, confirming the beneficial effects of odevixibat. The observed changes are consistent with the primary and important secondary endpoint. For the patients previously on placebo similar changes from BL to 24 weeks of treatment in study 008 were observed, as in study 005. Data on the QoL are also consistent with the results on the reduction of pruritus.

Additional efficacy data needed in the context of an MA under exceptional circumstances

It is considered that odevixibat demonstrated a clear clinically relevant effect on the main symptoms of PFIC e.g. reduction of pruritus. In addition, clinically relevant reductions in sBAs were observed. From the literature, it is known that the reduction of serum bile acid levels, ASAT, total bilirubin or improvement of PELD or MELD is associated with prolonged native liver survival in PFIC1 and PFIC2

patients. However, it was also indicated that the predictive value of SBAs in PFIC1 and PFIC2 does not qualify the SBAs as a surrogate parameter for liver survival. In the clinical studies conducted, the current data does not allow to convincingly conclude whether odevixibat effectively delays surgery (SBD) and/or OLT despite the improvements in hepatic parameters and liver histopathology parameters. In order to provide further solid information on this fact, a long-term follow-up study would be required.

The applicant applied for an MA under exceptional circumstances with the main reason that *indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence* (see EMEA/357981/2005). It should be noted that the orphan drug designation in the treatment of progressive familial intrahepatic cholestasis was granted on the basis of the rarity of the disease; the prevalence of PFIC in Europe was estimated at 0.07/10,000 persons. The life expectancy is short, depending on the type of PFIC and due to severe hepatic damage, the condition ultimately leads to portal hypertension, liver failure, cirrhosis, and hepatocellular carcinoma. Liver transplantation is often necessary. Given the orphan designation of odevixibat in the EU, the size of the target population and the clinical studies already conducted, CHMP considered that it is unlikely that the applicant will be in a position to generate comprehensive data on efficacy.

In order to investigate further a possible effect of odevixibat on surgery and / or liver transplantation the Applicant has proposed to set up a registry to record registry information on liver survival, SBD and death. As a Specific Obligation in the context of a marketing authorisation under exceptional circumstances, the Applicant agreed to conduct a post-authorisation registry-based efficacy study to investigate whether odevixibat treatment delays SBD and/or liver transplantation, with matched comparison against untreated PFIC patients.

2.5.4. Conclusions on the clinical efficacy

Based on the results of the submitted clinical development programme, odevixibat was proven to be effective in the reduction of SBAs and reduction of pruritis in patients with PFIC1, PFIC2, PFIC 3 and PFIC6. The applicant has thoroughly substantiated that the data collected in mainly in the PFIC1, PFIC2 and to a lesser extent in PFIC3 and PFIC6 patients can be extrapolated to the broader PFIC patient population as claimed indication *"treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older".* Extrapolation is based on the fact, that all PFIC patients share the same disease pathophysiology pathway, i.e. odevixibat acts upon the IBAT receptor which is similar to all PFIC patients. Other PFIC types (i.e. PFIC4 and 5) are encountered so rarely that it is considered unfeasible to study these PFIC types separately.

The clinical relevance of reducing 70% in SBAs (change from BL) and reduction of pruritus (change from BL) has been sufficiently substantiated. In the pivotal study, two doses were investigated, i.e. 40 and 120 µg/kg/day; post-hoc analyses showed that both doses are equally effective in reducing SBAs and reducing pruritus (e.g. no statistically significant difference). However, based on the additional requested analysis a starting dose of 40 µg/kg/day is considered most appropriate and agreed with by the CHMP. Based on the study results it appears that at least numerically the 40 µg/kg/day is somewhat more effective. In addition, safety suggests a similar observation; patients in the 40 µg/kg/day groups have numerically less diarrhoea. It is now mentioned in the SmPC that if after 3 months of 40 µg/kg/day odevixibat treatment no satisfactorily response is noted, the dose may be increased to 120 µg/kg/day.

In the conducted studies, it has also been observed, that not all PFIC1 and PFIC2 patients had a similar efficacy response. This may be attributed to the residual protein functionality of the specific membrane

protein (e.g. BSEP1, BSEP2 and BSEP3). Two patients in study 008 received SBD due to disease progression despite odevixibat treatment. Therefore, a warning is included in the SmPC that patients should be monitored and if the disease progresses or efficacy is not optimal after 6 months of continued odevixibat treatment, other approaches should be considered. It is also stated that some conditions or medications that impair either GI motility or enterohepatic circulation of bile acids have the potential to reduce the efficacy of odevixibat.

The observed reductions in pruritus are considered clinically relevant to the patients, as this is the most important debilitating symptom of the disease, and an important reason for SBD or OLT. Furthermore, the CHMP considers that sufficient evidence is available to demonstrate that under continued odevixibat treatment, patients start to catch-up on growth towards normal healthy peer values, which is considered beneficial and contributes to the benefit of treatment. Similar results are also observed after SBD or OLT in clinical practice. Liver histopathology and hepatic biochemistry were considered exploratory endpoints in the studies. The data suggest that under continued treatment with odevixibat hepatic damage is stabilised (or at least delayed) where untreated PFIC patients progress to liver fibrosis and ultimately, liver failure requiring liver transplantation.

Based on literature data, reduction of serum bile acid levels, ASAT, total bilirubin or improvement of PELD or MELD is associated with significantly prolonged native liver survival in PFIC1 and PFIC2 patients. However, it was also indicated that the predictive value of SBAs in PFIC1 and PFIC2 does not qualify SBA's as a surrogate parameter for liver survival. In the clinical studies conducted, the current data does not allow to convincingly conclude whether the improvements/stabilisation in liver related parameters observed with odevixibat treatment would translate into a delay of surgery (SBD) /OLT. In order to provide further solid information on this fact,

The CHMP considers the following Specific obligation necessary to generate long-term follow up efficacy data in the context of an MA under exceptional circumstances:

- Post-authorisation registry-based efficacy study: In order to investigate whether odevixibat treatment delays surgical biliary diversion (SBD) and/or liver transplantation (OLT), with matched comparison against untreated PFIC patients, the MAH should conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) according to an agreed protocol.

Annual reports are to be submitted as part of the annual reassessment. Feasibility assessment for this study are to be submitted within 3 months of EC decision.

2.6. Clinical safety

Patient exposure

The duration of study treatment for the Phase 2 and 3 studies and treatment compliance (Phase 3 studies only) are provided for the Safety Analysis Set in Table 45 and Table 46, respectively.

As detailed previously, Study A4250-005 was a 24-week study; eligible patients from this study could rollover to the 72-week extension Study A4250-008. For Study A4250-005, the median duration of exposure was approximately 24 weeks in all treatment groups, and median treatment compliance was high (>90% in all groups).

Across all patients treated with odevixibat in the Pooled Phase 3 group, the median duration of exposure as of the 15 July 2020 cut-off was 37.4 weeks and ranged from 1 to 107.9 weeks. Overall, 29 (38%) of the 77 patients received ≥52 weeks of treatment with odevixibat as of the cut-off date.

In the 4-week dose-finding study A4250-003, the median duration of exposure was 6.1 weeks and ranged from 6 to 13.4 weeks; the exposure durations of >4 weeks are due to 4 patients who received a second 4-week treatment course as allowed by the protocol; total exposure duration for these patients across both treatment courses are included. Treatment compliance in this study was 96%.

Table 45: Duration of Study Treatment (Safety Analysis Set).

CATEGORY STATISTIC	STUDY A4250-003[a] (ALL DOSES COMBINED)		STUDY A4250-005 (BY TREATMENT)			STUDIES A4250-005/ A4250-008 POOLED
	PFIC PATIENTS (N=10) N (%)	ALL OTHER PATIENTS (N=10) N (%)	PLACEBO (N=20) N (%)	40 µg/KG/DAY (N=23) N (%)	120 µg/Kg/DAY (N=19) N (%)	ODEVIXIBATALL DOSES[b] (N=77) N (%)
Duration of exposure (weeks)						
n	10	10	20	23	19	77
Mean (standard deviation)	8.1 (3.20)	6.8 (1.78)	21.6 (4.57)	21.7 (4.95)	21.7 (5.83)	44.0 (27.37)
Median	6.1	6.1	23.7	23.9	23.9	37.4
Minimum, maximum	6, 13.4	6, 11.9	11.7, 29.1	10.7, 25.9	4, 27.6	1, 107.9
Duration category, n (%)						
< 4 weeks	0	0	0	0	0	2 (2.6)
≥ 4 - < 8 weeks	7 (70.0)	9 (90.0)	0	0	1 (5.3)	2 (2.6)
≥ 8 - < 12 weeks	0	1 (10.0)	1 (5.0)	3 (13.0)	1 (5.3)	3 (3.9)
≥ 12 - < 16 weeks	3 (30.0)	0	2 (10.0)	1 (4.3)	1 (5.3)	5 (6.5)
≥ 16 - < 20 weeks	N/A	N/A	2 (10.0)	1 (4.3)	0	6 (7.8)
≥ 20 - < 24 weeks	N/A	N/A	11 (55.0)	12 (52.2)	10 (52.6)	6 (7.8)
≥ 24 - < 28 weeks	N/A	N/A	3 (15.0)	6 (26.1)	6 (31.6)	4 (5.2)

≥ 28 - < 32 weeks	N/A	N/A	1 (5.0)	0	0	2 (2.6)
≥ 32 - < 36 weeks	N/A	N/A	0	0	0	6 (7.8)
≥ 36 - < 40 weeks	N/A	N/A	0	0	0	6 (7.8)
≥ 40 - < 44 weeks	N/A	N/A	0	0	0	3 (3.9)
≥ 44 - < 48 weeks	N/A	N/A	0	0	0	1 (1.3)
≥ 48 – 52 weeks	N/A	N/A	0	0	0	2 (2.6)
≥ 52 weeks	N/A	N/A	0	0	0	29 (37.7)

N/A: not applicable; PFIC: progressive familial intrahepatic cholestasis.

a Study A4250-003 evaluated doses of 10, 30, 60, 100, and 200 µg/kg/day administered for 4 weeks. A total of 24 patient treatment courses were administered in 20 unique patients across the 5 dose cohorts. Four patients who completed their initial cohort were re-enrolled in a second cohort, as permitted by the protocol. Of those 4 patients, 3 had an underlying diagnosis of PFIC and 1 had intrahepatic cholestasis associated with microvillous atrophy.

b Includes patients who received odevixibat only on Study A4250-005 without going on Study A4250-008, patients who received placebo or odevixibat on Study A4250-005 who went on to receive odevixibat 120 µg/kg/day in Study A4250-008, and patients in Cohort 2 of Study A4250-008.

Note: For the pooled Phase 3 presentation, exposure is based on the time from the first to the last dose of odevixibat, including exposure during Study A4250-005 and Study A4250-008.

Table 46: Treatment Compliance Based on Data Entered in the eDiary (Safety Analysis Set).

CATEGORY STATISTIC	STUDY A4250-005 (BY TREATMENT)			STUDIES A4250-005/A4250-008 POOLED
	PLACEBO (N=20) N (%)	40 µG/KG/DAY (N=23) N (%)	120 µG/KG/DAY (N=19) N (%)	ODEVIXIBAT ALL DOSES[a] (N=77) N (%)
Compliance rate (%)				
n	20	23	19	77
Mean (standard deviation)	95.17 (8.549)	91.30 (8.806)	90.53 (8.243)	91.47 (9.346)
Median	98.63	94.01	91.52	94.72
Minimum, maximum	64.9, 100	72.6, 100	64.3, 100	62.9, 100
Compliance rate category, n (%)				
< 80%	1 (5.0)	4 (17.4)	1 (5.3)	10 (13.0)
80% - 120%	19 (95.0)	19 (82.6)	18 (94.7)	67 (87.0)
> 120%	0	0	0	0

eDiary: electronic diary.

a Includes patients who received odevixibat only on Study A4250-005 without going on Study A4250-008, patients who received placebo or odevixibat on Study A4250-005 who went on to receive odevixibat 120 µg/kg/day in Study A4250-008, and patients in Cohort 2 of Study A4250-008.

Note: For the pooled Phase 3 presentation, exposure is based on the time from the first to the last dose of odevixibat, including exposure during Study A4250-005 and Study A4250-008.

Adverse events

An overview of TEAE incidence is presented for the Safety Analysis Set in Table 47 (see further below).

In the Pooled Phase 3 group, 61 (79%) of 77 patients experienced at least 1 TEAE. In Study A4250-005, the overall incidence of TEAEs was similar in the 40 and 120 µg/kg/day groups (84% and 83%, respectively) and in the placebo group (85%). The overall incidence of TEAEs for patients with PFIC in Study A4250-003, a 4-week uncontrolled Phase 2 study, was 70%.

Treatment-emergent AEs leading to interruption of study treatment were reported in 17 patients (22%) in the Pooled Phase 3 group, mostly related to patients meeting the protocol criteria for interruption of study drug. In Study A4250-005, treatment interruptions due to TEAEs were more commonly reported among patients who received 120 µg/kg/day (32%) compared with patients who received 40 µg/kg/day (13%) or placebo (5%). No treatment interruptions due to TEAEs were reported in Study A4250-003.

Discontinuation of treatment was reported in 4 patients (5%) in the Pooled Phase 3 group; this included 1 patient in the 120 µg/kg/day group during Study A4250-005 and 3 patients during Study A4250-008. The TEAE leading to treatment discontinuation in Study A4250-005 (diarrhoea) was assessed as drug-related; all other TEAEs leading to discontinuation were reported as unrelated to odevixibat.

Treatment-emergent AEs reported in ≥ 5% of patients in the Pooled Phase 3 group are presented in Table **48**47. Drug-related TEAEs reported in ≥ 5% of patients in the Pooled Phase 3 group are presented in Table **49**48.

Table 47: Overall Summary of Treatment-emergent Adverse Events (Safety Analysis Set).

Patients with any:	**Study A4250-003[a] (all doses combined)**		**Study A4250-005 (by treatment)**			**Studies A4250-005/ A4250-008 pooled**
	PFIC PATIENTS (N=10) **N (%)**	**ALL OTHER PATIENTS (N=10)** **N (%)**	**PLACEBO (N=20)** **N (%)**	**40 µG/KG/DAY (N=23)** **N (%)**	**120 µG/KG/DAY** **(N=19)** **N (%)**	**ODEVIXIBAT ALL DOSES[b]** **(N=77)** **N (%)**
TEAEs	7 (70.0)	8 (80.0)	17 (85.0)	19 (82.6)	16 (84.2)	61 (79.2)
Drug-Related TEAEs	0	1 (10.0)	3 (15.0)	7 (30.4)	7 (36.8)	32 (41.6)
Severe TEAEs	1 (10.0)	0	2 (10.0)	1 (4.3)	2 (10.5)	8 (10.4)
Serious TEAEs	2 (20.0)	0	5 (25.0)	0	3 (15.8)	7 (9.1)
Drug-Related Serious TEAEs	0	0	0	0	0	0
TEAEs Leading to Study Treatment Interruption	0	0	1 (5.0)	3 (13.0)	6 (31.6)	17 (22.1)
TEAEs Leading to Study Treatment Discontinuation	0	0	0	0	1 (5.3)	4 (5.2)
Drug-Related TEAEs Leading to Study Treatment Discontinuation	0	0	0	0	1 (5.3)	1 (1.3)

TEAEs Leading to Death	0	0	0	0	0	0
Liver-Related TEAEs[c]	N/A	N/A	4 (20.0)	5 (21.7)	6 (31.6)	25 (32.5)
Liver Decompensation TEAEs[c]	N/A	N/A	0	0	0	1 (1.3)
All-Cause Mortality[d]	0	0	0	0	0	0

AE: adverse event; n: number of patients with events; PFIC: progressive familial intrahepatic cholestasis; TEAE: treatment-emergent adverse event.

a Study A4250-003 evaluated doses of 10, 30, 60, 100, and 200 µg/kg/day administered for 4 weeks. A total of 24 patient treatment courses were administered in 20 unique patients across the 5 dose cohorts. Four patients who completed their initial cohort were re-enrolled in a second cohort, as permitted by the protocol. Of those 4 patients, 3 had an underlying diagnosis of PFIC and 1 had intrahepatic cholestasis associated with microvillous atrophy.

b Includes patients who received odevixibat only on Study A4250-005 without going on Study A4250-008, patients who received placebo or odevixibat on Study A4250-005 who went on to receive odevixibat 120 µg/kg/day in Study A4250-008, and patients in Cohort 2 of Study A4250-008.

c Liver-related TEAEs and liver decompensation TEAEs were collected and indicated on the AE CRFs.

d All deaths are reported whether caused by TEAEs or not (i.e. includes deaths that occurred during screening).

Table 48: Treatment-emergent Adverse Events (≥ 5% of Patients in the Pooled Population for Studies A4250-005 and A4250-008) by System Organ Class and Preferred Term (Safety Analysis Set).

SYSTEM ORGAN CLASS PREFERRED TERM	STUDY A4250-003[a] (ALL DOSES COMBINED)		STUDY A4250-005 (BY TREATMENT)			STUDIES A4250-005/ A4250-008 POOLED
	PFIC PATIENTS (N=10) N (%)	ALL OTHER PATIENTS (N=10) N (%)	PLACEBO (N=20) N (%)	40 µG/KG/DAY (N=23) N (%)	120 µG/KG/DAY (N=19) N (%)	ODEVIXIBAT ALL DOSES[b] (N=77) N (%)
Patients with any TEAEs	***7 (70.0)***	***8 (80.0)***	***17 (85.0)***	***19 (82.6)***	***16 (84.2)***	***61 (79.2)***
Gastrointestinal disorders	**2 (20.0)**	**4 (40.0)**	**6 (30.0)**	**14 (60.9)**	**8 (42.1)**	**36 (46.8)**
Diarrhoea	0	1 (10.0)	1 (5.0)	9 (39.1)	4 (21.1)	15 (19.5)
Vomiting	1 (10.0)	0	0	4 (17.4)	3 (15.8)	11 (14.3)
Abdominal pain	0	0	0	2 (8.7)	1 (5.3)	6 (7.8)
Constipation	0	1 (10.0)	4 (20.0)	0	0	6 (7.8)
Infections and infestations	**5 (50.0)**	**3 (30.0)**	**12 (60.0)**	**11 (47.8)**	**11 (57.9)**	**36 (46.8)**
Upper respiratory tract infection	0	0	3 (15.0)	3 (13.0)	5 (26.3)	19 (24.7)
Nasopharyngitis	1 (10.0)	0	1 (5.0)	1 (4.3)	2 (10.5)	6 (7.8)
Otitis media	0	0	0	0	2 (10.5)	5 (6.5)

Influenza	1 (10.0)	0	2 (10.0)	0	1 (5.3)	4 (5.2)
Rhinitis	1 (10.0)	1 (10.0)	0	2 (8.7)	0	4 (5.2)
Investigations	**1 (10.0)**	**1 (10.0)**	**4 (20.0)**	**7 (30.4)**	**8 (42.1)**	**31 (40.3)**
Blood bilirubin increased	0	0	2 (10.0)	3 (13.0)	2 (10.5)	12 (15.6)
Alanine aminotransferase increased	1 (10.0)	0	1 (5.0)	3 (13.0)	3 (15.8)	10 (13.0)
International normalised ratio increased	0	0	1 (5.0)	1 (4.3)	0	7 (9.1)
Aspartate aminotransferase increased	0	0	1 (5.0)	2 (8.7)	1 (5.3)	5 (6.5)
Vitamin D decreased	0	0	0	0	1 (5.3)	4 (5.2)
General disorders and administration site conditions	**2 (20.0)**	**2 (20.0)**	**5 (25.0)**	**9 (39.1)**	**5 (26.3)**	**22 (28.6)**
Pyrexia	1 (10.0)	2 (20.0)	5 (25.0)	7 (30.4)	5 (26.3)	20 (26.0)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**4 (20.0)**	**3 (13.0)**	**4 (21.1)**	**21 (27.3)**
Cough	0	0	3 (15.0)	0	2 (10.5)	12 (15.6)

Epistaxis	0	0	1 (5.0)	1 (4.3)	1 (5.3)	5 (6.5)
Skin and subcutaneous tissue disorders	**0**	**1 (10.0)**	**6 (30.0)**	**3 (13.0)**	**2 (10.5)**	**17 (22.1)**
Pruritus	0	0	1 (5.0)	2 (8.7)	1 (5.3)	9 (11.7)
Metabolism and nutrition disorders	**0**	**1 (10.0)**	**3 (15.0)**	**0**	**3 (15.8)**	**12 (15.6)**
Vitamin D deficiency	0	0	1 (5.0)	0	2 (10.5)	4 (5.2)
Blood and lymphatic system disorders	**1 (10.0)**	**0**	**1 (5.0)**	**0**	**2 (10.5)**	**10 (13.0)**
Splenomegaly	0	0	0	0	2 (10.5)	7 (9.1)
Hepatobiliary disorders	**0**	**0**	**0**	**1 (4.3)**	**1 (5.3)**	**10 (13.0)**
Jaundice	0	0	0	1 (4.3)	0	4 (5.2)

AE: adverse event; n: number of patients with events; PFIC: progressive familial intrahepatic cholestasis; TEAE: treatment-emergent adverse event.

a Study A4250-003 evaluated doses of 10, 30, 60, 100, and 200 µg/kg/day administered for 4 weeks. A total of 24 patient treatment courses were administered in 20 unique patients across the 5 dose cohorts. Four patients who completed their initial cohort were re-enrolled in a second cohort, as permitted by the protocol. Of those 4 patients, 3 had an underlying diagnosis of PFIC and 1 had intrahepatic cholestasis associated with microvillous atrophy.

b Includes patients who received odevixibat only on Study A4250-005 without going on Study A4250-008, patients who received placebo or odevixibat on Study A4250-005 who went on to receive odevixibat 120 µg/kg/day in Study A4250-008, and patients in Cohort 2 of Study A4250-008.

Table 49: Treatment-related Treatment-emergent Adverse Events (≥ 5% of Patients in the Pooled Population for Studies A4250-005 and A4250-008) by System Organ Class and Preferred Term (Safety Analysis Set).

SYSTEM ORGAN CLASS PREFERRED TERM	STUDY A4250-003[a] (ALL DOSES COMBINED)		STUDY A4250-005 (BY TREATMENT)			STUDIES A4250-005/ A4250-008 POOLED
	PFIC PATIENTS (N=10) N (%)	ALL OTHER PATIENTS (N=10) N (%)	PLACEBO (N=20) N (%)	40 µg/kg/day (N=23) N (%)	120 µg/kg/day (N=19) N (%)	ODEVIXIBAT ALL DOSES[b] (N=77) N (%)
Patients with any treatment related TEAEs	***0***	***1 (10.0)***	***3 (15.0)***	***7 (30.4)***	***7 (36.8)***	***32 (41.6)***
Investigations	**0**	**0**	**1 (5.0)**	**3 (13.0)**	**4 (21.1)**	**18 (23.4)**
Blood bilirubin increased	0	0	1 (5.0)	2 (8.7)	2 (10.5)	10 (13.0)
Alanine aminotransferase increased	0	0	1 (5.0)	2 (8.7)	2 (10.5)	8 (10.4)
Aspartate aminotransferase increased	0	0	1 (5.0)	2 (8.7)	1 (5.3)	5 (6.5)
Gastrointestinal disorders	**0**	**1 (10.0)**	**2 (10.0)**	**2 (8.7)**	**3 (15.8)**	**10 (13.0)**
Diarrhoea	0	1 (10.0)	0	2 (8.7)	2 (10.5)	5 (6.5)

AE: adverse event; n: number of patients with events; PFIC: progressive familial intrahepatic cholestasis; TEAE: treatment-emergent adverse event.

a Study A4250-003 evaluated doses of 10, 30, 60, 100, and 200 µg/kg/day administered for 4 weeks. A total of 24 patient treatment courses were administered in 20 unique patients across the 5 dose cohorts. Four patients who completed their initial cohort were re-enrolled in a second cohort, as permitted by the protocol. Of those 4 patients, 3 had an underlying diagnosis of PFIC and 1 had intrahepatic cholestasis associated with microvillous atrophy.

b Includes patients who received odevixibat only on Study A4250-005 without going on Study A4250-008, patients who received placebo or odevixibat on Study A4250-005 who went on to receive odevixibat 120 µg/kg/day in Study A4250-008, and patients in Cohort 2 of Study A4250-008.

Note: Patients reporting more than 1 event were counted only once at the highest relationship to study drug. AEs with missing relationship were classified as related.

Treatment-emergent Adverse Events of Interest

Diarrhoea Events, including Clinically Significant Diarrhoea

An overview of the overall incidence of TEAE reports of diarrhoea, including relationship, intensity, seriousness, and action taken with study drug is provided in Table 50.

Table 50: Overall Summary of Treatment-emergent Diarrhoea Adverse Events (Safety Analysis Set).

TREATMENT	ANY AE n (%)	RELATED AE n (%)	SEVERE AE N (%)	SERIOUS AE N (%)	DC DUE TO AE N (%)
Studies A4250-005/A4250-008 Pooled					
Odevixibat All Doses[a] (N=77)	18 (23.3)	7 (9.1)	0	0	1 (1.3)
STUDY A-4250-003					
PFIC Patients (N=10)	0	0	0	0	0
All Other Patients (N=10)	1 (10.0)	1 (10.0)	0	0	0
STUDY A-4250-005					
Placebo (N=20)	1 (5.0)	0	0	0	0
Odevixibat 40 µg/kg/day (N=23)	9 (39.1)	2 (8.7)	0	0	0
Odevixibat 120 µg/kg/day (N=19)	4 (21.1)	2 (10.5)	0	0	1 (5.3)

AE: adverse event; DC: discontinued; n: number of patients with events.
a Includes patients who received odevixibat only on Study A4250-005 without going on Study A4250-008, patients who received placebo or odevixibat on Study A4250-005 who went on to receive odevixibat 120 µg/kg/day in Study A4250-008, and patients in Cohort 2 of Study A4250-008.
Note: diarrhoea AEs include preferred terms of diarrhoea, diarrhoea haemorrhagic, frequent bowel movements, and faeces soft.

Serious adverse event/deaths/other significant events

There were no deaths in the Phase 2 or Phase 3 studies. Treatment-emergent SAEs were reported in 7 (9%) of the 77 patients in the Pooled Phase 3 group. In Study A4250-005, there were no SAEs reported in patients who received 40 µg/kg/day; 3 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.

Laboratory findings

No consistent effect was seen on the haematological, coagulation parameters or clinical chemistry. None of the observations were clinically significant, no clinically meaningful differences were noted for changes from baseline to the last assessment for urine analysis. Analysis of the vital signs and physical examination did not reveal clinically relevant changes. ECG were obtained from healthy volunteers (N= 150), no clinically significant findings were reported, and all QT intervals were ≤ 500 ms. No ECGs were collected in the Phase 2 or 3 studies. No patients reported Torsade de pointes or QT prolongation as an AE in the phase 2 or 3 studies.

Safety in special populations

Age

In general, age did not appear to affect the overall observed safety and tolerability profile. Due to the imbalance with the number of patients aged 6 to 12 years (N=19) and ≥ 13 years of age (N=5) compared to 53 patients ≤ 5 years of age, the subgroup analyses should be interpreted with caution.

The incidence of TEAEs by age in the Pooled Phase 3 group was highest among patients ≤ 5 years of age compared with the 6 to 12 years of age and ≥ 13 years of age categories (85% versus 63% and 80%, respectively). In the age category ≤ 5 years of age, the difference in the incidence of TEAEs was primarily observed with a higher incidence in events of vomiting in the GI disorders SOC and in the Infections and infestations SOC with a higher incidence of events of upper respiratory tract infection, nasopharyngitis, and influenza. Based on medical review, in a number of these patients, the timing of the events of vomiting and infections was simultaneous or overlapping and often in conjunction with an event of pyrexia.

Four patients in the age category ≤ 5 years of age experienced a TEAE of jaundice; 2 of the 4 patients had an ongoing medical history of jaundice. In general, a higher proportion of patients in age group ≤ 5 years of age had an ongoing medical history of jaundice compared with patients in the 6 to 12 years of age category (26% versus 11%).

Sex

The incidence of TEAEs in the Pooled Phase 3 group was slightly higher among male versus female patients (84% versus 74%). However, this was not the case for TEAE's in the GI disorders SOC, where the incidence of TEAEs was slightly lower in male patients compared with female patients.

The incidence of TEAEs in the Infections and infestations SOC was comparable between male and female patients (47% and 46%, respectively).

In the Investigations SOC, TEAEs were most commonly increased hepatic biochemical parameters; the following observations are important. Moderate hepatic impairment (Child-Pugh classification) was more prominent in male patients compared with female patients, who mainly had mild hepatic impairment by Child-Pugh classification. In evaluating the incidence of investigations and hepatic TEAEs, it should be noted that male patients had higher baseline ALT and total bilirubin levels compared with female patients. More female patients presented with lower baseline ALT and total bilirubin levels.

In male and female patients, the incidence of TEAEs of bilirubin increased was 21% and 10%, respectively; ALT increased was 18% and 8%, respectively; and AST increased was 11% and 3%, respectively. Treatment-emergent AEs of vitamin D decreased were reported in 8% and 3%, of male and female patients, respectively.

Race

The incidence of TEAEs in the Pooled Phase 3 group was higher among non-Caucasian patients than Caucasian patients (91% versus 77%). However, fewer patients were non- Caucasian than Caucasian (N=11 and N=66, respectively), which should be considered when reviewing the observed incidences of TEAEs by SOC.

Ethnicity

In the Pooled Phase 3 group, 2 patients were Hispanic or Latino in ethnicity.

Region

In the Pooled Phase 3 group, most patients (N=42) were enrolled at sites in Europe, followed by the RoW (N=24) and the US (N=11). Patients enrolled in the US generally had comparable baseline

disease characteristics to those enrolled in Europe and RoW. It was noted that fewer patients in the US were treated with UDCA, rifampicin, or UDCA and/or rifampicin.

The incidence of TEAEs in Europe (76%) and RoW (88%) was generally similar. In addition, the incidence of TEAEs was similar between the European and RoW in the SOCs where events were most commonly reported: GI disorders (48% and 46%, respectively), Investigations (43% and 38%, respectively), and Infections and infestations (48% and 54%, respectively). The low number of patients precludes meaningful subgroup comparisons at the preferred term level between treatment groups in Study A4250-005, and by SAEs in Study A4250-005 and in the Pooled Phase 3 group.

PFIC Type

In the Pooled Phase 3 group, 20 patients had PFIC1, and 51 patients had PFIC2. The incidence of TEAEs by the diagnosis of PFIC1 versus PFIC2 was similar (80% in each). Patients with PFIC1 compared with PFIC2 had a higher incidence of TEAEs in the most common SOCs of GI disorders (60% versus 47%), Infections and infestations (65% versus 45%), and Investigations (50% versus 35%). It is notable that all 4 of the patients in the Pooled Phase 3 group with TEAEs of jaundice in the Hepatobiliary SOC had PFIC2. In general, the low number of patients with PFIC1 precludes meaningful subgroup comparisons by PFIC type at the preferred term level, between treatment groups in Study A4250-005, and by SAEs in Study A4250-005 and in the Pooled Phase 3 group.

Five patients with PFIC3 enrolled in Cohort 2 of Study A4250-008. The medical review revealed no clinically meaningful differences in clinical safety laboratory data or reported TEAEs compared with PFIC1 or PFIC 2 patients. Three of the 5 patients did trigger criteria for adjudication (hepatic biochemical parameters and/or INR increased); all events were adjudicated as related to underlying disease.

Hepatic function

The incidence of TEAEs by Child-Pugh classification was similar among patients with mild and moderate impairment (78% and 82%, respectively). In the most common SOC of GI disorders, the incidence of TEAEs was similar among patients with mild and moderate impairment (46% and 48%, respectively). However, the incidence of TEAEs was lower among patients with mild versus moderate impairment in the SOCs of Infections and infestations (42% versus 56%, respectively) and Investigations (36% and 48%, respectively).

A review of preferred terms in the GI disorders SOC for patients in the Pooled Phase 3 group revealed diarrhoea was reported in 26% and 7% of patients with mild and moderate hepatic impairment, respectively. Vomiting was reported in 14% and 15% of patients with mild and moderate hepatic impairment, respectively.

Immunological events

No evaluation and/or studies considering antibody formation were performed. This is considered acceptable by the CHMP, as the systemic exposition of odevixibat is very limit an immunologic response is not to be expected.

Safety related to drug-drug interactions and other interactions

No human drug-drug interaction studies were submitted. This is considered acceptable by the CHMP, as the systemic exposition of odevixibat is very limit and systemic drug-drug reaction are not expected.

Discontinuation due to adverse events

A by-patient listing of TEAEs leading to study drug discontinuation is provided in Table 51.

In the Pooled Phase 3 group, 4 (5%) of 77 patients experienced a TEAE leading to study drug discontinuation, including 1 patient in the 120 µg/kg/day group in Study A4250-005 and 3 patients in Study A4250-008. No patients in the 40 µg/kg/day and placebo groups experienced a TEAE leading to study drug discontinuation during Study A4250-005. Two events leading to discontinuation, cholestasis in one Patient and acute (on chronic) pancreatitis in another Patient, were severe in intensity, and both were reported as SAEs. One patient had an interruption in study drug due to the event of acute pancreatitis and subsequently withdrew consent to participate. The only TEAE leading to study drug discontinuation that was assessed by the investigator as study drug-related was diarrhoea in one patient. Mild to moderate TEAEs of splenomegaly, jaundice, hypophagia, and weight decreased were reported in one patient. Except the TEAE of splenomegaly, all TEAEs leading to study drug discontinuation were resolved at the time of the data cut-off. No patients discontinued study drug due to TEAEs during Study A4250-003.

Table 51: Listing of Patients with Treatment-Emergent Adverse Events Leading to Treatment Discontinuation (Safety Analysis Set).

PATIENT ID	AGE/SEX/PFIC TYPE	TEAE LEADING TO DISCONTINUATION	START/ STOP DAY	RELATIONSHIP PER INVESTIGATOR	INTENSITY	SAE?	OUTCOME
STUDY A4250-005							
120 µG/KG/DAY GROUP							
XXXX	5.5 YRS/FEMALE/PFIC2	DIARRHOEA	D28-28	RELATED	MILD	NO	RESOLVED
Study A4250-008							
Cohort 1: Placebo to 120 µg/kg/day Group							
xxx	1.0 yrs/Male/PFIC2	Cholestasis	D253-264	Unrelated	Severe	Yes	Resolved
Cohort 2							
xxx	19.5 yrs/Female/ PFIC2	Acute pancreatitis	D139-151	Unrelated	Severe	Yes	Resolved
xxx	1.3 yrs/Male/PFIC2	Splenomegaly	D102-ongoing	Unrelated	Mild	No	Not resolved
		Jaundice	D105-ongoing	Unrelated	Mild	No	Not resolved
		Hypophagia	D102-105	Unrelated	Moderate	No	Resolved

		Weight decreased	D102-105	Unrelated	Moderate	No	Resolved

D: study day; EOT: end-of-treatment; ID: identification; PFIC: progressive familial intrahepatic cholestasis; SAE = serious adverse event; TEAE: treatment-emergent adverse event

[a] *One Patient in Cohort 2 withdrew consent to participate in the study and the reason for discontinuation in the EOT form was consent withdrawal.*

[b] *One Patient in Cohort 2 discontinued treatment due to TEAEs of splenomegaly, hypophagia, and weight decrease; however, the EOT form was not completed at the interim cut and therefore this patient was considered as ongoing. A query was issued to the site to complete the EOT form.*

Post marketing experience

Not applicable, at time of submission the product was not marketed in any country.

2.6.1. Discussion on clinical safety

The primary evaluation of the safety and tolerability of odevixibat in the proposed indication is based on the two Phase 3 studies A4250-005 and A4250-008 (Pooled Phase 3 Group) including a total of 84 patients with PFIC who received at least 1 dose of odevixibat. Supportive data are provided by the Phase 2 study A4250-003 conducted in 20 patients, including 10 patients with PFIC. Given the limited number of patients, no robust conclusions on safety can be drawn. Given the limited number of patients at the time of authorisation, safety would need to be supported by long-term data. For this reason, the final safety report generated by the applicant-initiated extension study (008) is of interest and the applicant committed to provide the results by July 2023. The applicant has committed to do so and the clinical study is included in the RMP.

From the 84 patients included in the Pooled Phase 3 Group, 44 (52%) patients received ≥52 weeks and 26 (31%) received ≥76 weeks of treatment with odevixibat as of the cut-off date.

All TEAEs in Study A4250-003 were mild to moderate in severity except for one report of gastroenteritis which was severe and reported as an SAE; one other serious event, mild influenza, was reported in this study. Both SAEs were assessed as unrelated to study treatment. In the Pooled Phase 3 group, 71 (84.5%) of 84 patients experienced at least 1 TEAE. In Study A4250-005, the overall incidence of TEAEs was similar in the 40 and 120 µg/kg/day groups (84% and 83%, respectively) and in the placebo group (85%).

The most commonly reported TEAEs (≥ 10%) among patients in the Pooled Phase 3 group were pyrexia (23 patients, 27.4%), upper respiratory tract infection (20 patients, 23.8%), diarrhoea (17 patients, 20.2%), blood bilirubin increased (15 patients each, 17.9%), cough (13 patients, 15.5%) vomiting (11 patients, 13.1%), ALT increased (13 patients, 15.5%), and pruritus (9 patients, 10.7%). Most TEAEs were mild to moderate in intensity and were assessed as unrelated to study treatment. Severe TEAEs were reported in 8 (9.5%) of the 84 patients in the Pooled Phase 3 group.

In the Pooled Phase 3 group, 35 (41.7%) patients experienced a drug related TEAE. The incidence of drug-related TEAEs in Study A4250-005 in the 40 and 120 µg/kg/day groups (30% and 37%, respectively) was like the Pooled Phase 3 group but was higher among odevixibat-treated patients compared with the placebo group in that study (15%). Most drug related TEAEs were mild to moderate in intensity. The most common drug related TEAEs in the Pooled Phase 3 group were blood bilirubin

increased (14.3%), ALT increased (10.7%), and AST increased (6.0%). It is however difficult to separate whether adverse events are disease-related or drug-related, cholestasis and elevated hepatic biochemical parameters, most excursions in ALT, AST, and total bilirubin values were considered related to the underlying disease and therefore not included in the SmPC. Additional information of the liver function tests in relation to treatment efficacy will be generated via a registry-based safety study in order to collect safety data on hepatotoxicity, diarrhoea, fat-soluble vitamins and fat-soluble nutrients in patients treated with odevixibat, to which the applicant agreed.

Furthermore, in toxicology studies in juvenile rats, dose-limiting focal hepatic toxicities (hepatocyte necrosis/apoptosis) were observed; This, however, was seen at an exposition 1200 times the exposition reported in humans only. As at the lower exposition levels no hepato-toxicity is reported this observation is considered not clinically relevant.

Initially, the applicant proposed to include in the SmPC section 4.8, every adverse event considered related by investigators. This approach was not supported. As the cholestasis and elevated hepatic biochemical parameters, most excursions in ALT, AST, and total bilirubin values were considered related to the underlying disease and these are not included in the SmPC. However, more information of the liver function tests in relation to treatment will be generated in the above mentioned registry.

Special attention is given for some adverse events that are to be expected based on the pharmacodynamic effects of the product.

Diarrhoea, (including diarrhoea, diarrhoea haemorrhagic, frequent bowel movements) were one of the most common TEAEs in patients treated with odevixibat, occurring in 18 (23%) of 77 patients in the Pooled Phase 3 group. In Study A4250-005, these diarrhoea events occurred in 39% and 21% of patients in the 40 and 120 µg/kg/day groups, respectively, and in 5% of patients in the placebo group. Given the limited safety database and the seriousness of the diarrhoea (some intervention appears to be necessary), further information on this adverse event will be generated in post-marketing setting, as stated earlier. Furthermore, about 13% of the patients in the Pooled Phase 3 group had TEAEs of fat-soluble vitamin deficiency, including 3 (16%) patients in the 120 µg/kg/day group during Study A4250-005. No patients in the Study A4250-005 40 µg/kg/day group had a TEAE of fat-soluble vitamin deficiency. In the majority of these patients, the deficiencies were transient or not considered clinically relevant by the investigators. Most of the patients were receiving vitamin therapy at study entry, either as a treatment for vitamin deficiency or supplements. Most deficiencies resolved without further intervention. Although the occurrence of deficiencies in fat-soluble vitamins (e.g. vitamins A, D, E, K) might be related to both the treatment as the underlying disease, this is not considered an important issue, as in clinical practice these patients are regularly evaluated and if necessary supplemented. Possible interactions with fat-soluble drugs were identified as a concern. As absorption of fat-soluble drugs might be changed and might change over time (modulation of receptors and/or intracellular pathway, changes in disease activity due to the drug) more information on the long-term interaction with lipophile drugs is considered necessary and will therefore also be collected in the above mentioned registry based safety study.

In order to conduct the above mentioned registry based safety study, the applicant agreed to set up a disease registry in order to gather data on the natural history of the disease, treatment efficacy, safety, including long-term outcomes, pregnancy, breastfeeding and new-borns in patients with PFIC. In particular, there is currently no data on the use of odevixibat in pregnancy. As animal studies have indicated possible reproductive toxicity, the embryofoetal toxity risk to newborns/infants cannot be excluded. Hence, data on pregnancy, breastfeading and new-borns is to be collected. These will be reviewed on an on-going basis as a part of signal detection and reported within PSURs.

Treatment-emergent SAEs were reported in nine (10.7%) of the patients in the Pooled Phase 3 group. 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 five (25%) in the placebo group experienced SAEs. Two (20%) of the patients with PFIC in Study A4350-003 experienced SAEs. None of the treatment-emergent SAEs was assessed by the investigator as related to study drug.

The dose finding study A4250-005 suggests that there are slightly more adverse events in the higher dose group compared to the 40 µg/kg/day. These differences are not unexpected (more adverse events in the higher dose) and not considered clinically relevant.

There were no deaths in the Phase 2 or Phase 3 studies. No clear and consistent effect was seen on the haematological, coagulation parameters or clinical chemistry. None of the observation was clinically significant. No clinically meaningful differences were noted for changes from baseline to the last assessment for urine analysis. Analysis of the vital signs and physical examination did not reveal clinically relevant changes. ECGs were obtained from healthy volunteers (N= 150) no clinically significant findings were reports and all QT intervals were ≤ 500 ms. No ECGs were collected in the Phase 2 or 3 studies. Furthermore, no patients reported Torsade de pointes or QT prolongation as an AE in the phase 2 or 3 studies. No clear and consistent difference in the safety profile between the 40 and 120 µg/kg/day could be identified, although it should be taken in mind that this is based on 23 and 19 patients, respectively. Age or gender did not appear to affect the overall observed safety and tolerability profile. The analysis of race and ethnicity were hampered by the low number of non-Caucasian patients. Patients with PFIC1 compared with PFIC2 had a higher incidence of TEAEs in the most common SOCs of GI disorders (55% versus 46%), Infections and infestations (59% versus 48%), and Investigations (59% versus 38%). Treatment-emergent AEs leading to interruption of study treatment were reported in 21 patients (25%) in the Pooled Phase 3 group, mostly related to patients meeting the protocol criteria for interruption of study drug. Discontinuation of treatment was reported in five patients (6%) in the Pooled Phase 3 group, this included one patient in the 120 µg/kg/day group and four patients during the extension phase (120 µg/kg/day). The TEAE leading to treatment discontinuation (diarrhoea) was assessed as drug-related; all other TEAEs leading to discontinuation were reported as unrelated to odevixibat.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

As expected in a rare disease setting, the safety database is limited and does not allow for robust conclusions. Therefore, safety would need to be supported by long-term data. The final safety report of the ongoing Study A4250-008 should be submitted upon completion and this commitment is also reflected in the RMP. Furthermore, additional information of the adverse events will be collected via a registry based safety study; special attention should be paid to the uptake of fat-soluble food components (among others Vit A, D, E, K) and interactions with fat-soluble medicinal products, hepatotoxicity, and diarrhoea, in patients treated with odevixibat

The safety profile from the limited data available is considered acceptable. Although the safety database is considered limited at the time of approval, additional safety data will be collected in the post-authorisation phase.

The CHMP considers the following measures necessary to address the missing safety data:

- The final safety report generated by the ongoing extension study A4250-008 should be submitted upon completion in 2023.

- Registry based safety study in order to collect safety data on hepatotoxicity, diarrhoea, fat-soluble vitamins and fat-soluble nutrients in patients treated with odevixibat.
- Disease registry: Utilization of a Disease Registry to document the natural history of the disease, treatment efficacy, safety, including long-term outcomes, pregnancy, breastfeeding and new-borns in patients with PFIC. Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance
Important potential risks	• Hepatotoxicity • Embryofoetal toxicity • Interactions with fat-soluble drugs
Missing information	• Long-term use • Use during pregnancy and use in breastfeeding women

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Disease Registry: Utilization of a Disease Registry to Document the Natural History of the Disease, Treatment Efficacy, Safety, including Long-term Outcomes,	To collect more specific data on efficacy and safety including: a.Information on long-term	• Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance • Hepatotoxicity	Protocol submission	Within 6 months of EC decision* *(*An update*

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Pregnancy, Breastfeeding and Newborns in Patients with PFIC. Proposed	efficacy to evaluate the impact of odevixibat on the incidence and time to biliary diversion surgery, liver transplantation and death b.Information on AEs, SAEs and hospitalizations with special attention to the following events: i. the frequency, seriousness, and best treatment options of the observed diarrhoea (including diarrhoea, diarrhoea haemorrhagic, frequent bowel movements and faeces soft) ii. information on hepatotoxicity in humans (among others hepatic function tests, bilirubin, serum cholic acids). Analysis exploring this information related to treatment failure to be provided. iii. Long-term safety with	• Embryofoetal toxicity • Interactions with fat-soluble drugs • Long-term use • Use during pregnancy and use in breastfeeding woman	Regular updates	*to be provided within 3 months after EC decision)* Data gathered in this registry to be reviewed on an ongoing basis as a part of signal detection and reported within PSURs

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	special attention to the effects on fat soluble nutrients and drugs. c.Use during pregnancy and in breastfeeding women.			
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 (PEDFIC 2) Ongoing	Primary Objective (Cohort 1) • To demonstrate a sustained effect of A4250 on s-BAs and pruritus in children with PFIC Types 1 and 2. Primary Objective (Cohort 2) • To evaluate the effect of A4250 on s-BAs and pruritus in patients with PFIC who either (1) do not meet eligibility criteria for Study A4250-005 (PEDFIC 1) or (2) patients who do meet the eligibility criteria for Study A4250-005 after recruitment of Study A4250-005 has been completed. Secondary Objectives (Cohorts 1 and 2) • To evaluate the long-term safety and tolerability of repeated daily doses of A4250 • To evaluate the effect of A4250 on growth • To evaluate the effect of A4250 on	• Long-term use • Interactions with fat-soluble drugs • Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance • Hepatotoxicity	Final study report	31-Jul-2023

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	biliary diversion and/or liver transplantation • To evaluate the effect of A4250 on biochemical markers of cholestasis and liver disease			
Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC Proposed	•Collect safety data on adverse events including, but not limited to: -Episodes of diarrhoea lasting more than 3 days, bloody diarrhoea or diarrhoea leading to dehydration or electrolyte imbalance and any treatment -Episodes of fat-soluble vitamin deficiencies, including symptoms and treatment -Hospitalisations including diagnoses and treatments • Collect available specified laboratory data -ALT, AST, bilirubin, INR, and fat-soluble vitamin levels • Collect data on growth (height and weight z-scores)	• Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance • Hepatotoxicity • Long-term use • Interactions with fat-soluble drugs	Protocol Submission Final study report	Within 6 months of EC decision 31-Dec-2026
DDI study with oral contraceptives Proposed	To evaluate the effects of odevixibat on the fat-soluble drugs and those with a	• Interactions with fat-soluble drugs	Final study report	31-Dec-2022

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	known entero-hepatic cycle			

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	Routine risk minimisation measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 • Recommendation regarding monitoring for events of diarrhea and regular monitoring to ensure adequate hydration during episodes of diarrhoea in SmPC section 4.4. • Instruction for patients to notify their doctor if they develop diarrhoea while taking Bylvay and recommendation for drinking sufficient liquid in patients with diarrhea in PL section 2 • Legal status: Prescription only medicine. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • 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 (PEDFIC 2). Final study report: 31-Jul-2023 • Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC Final study report: 31-Dec-2026 • Proposed Disease Registry: Utilization of a Disease Registry to Document the Natural History of the Disease, Treatment Efficacy,

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Safety, including Long-Term Outcomes, Pregnancy, Breastfeeding and Newborns in Patients with PFIC. Regular update: ongoing basis as a part of signal detection and reported within PSURs
Hepatotoxicity	Routine risk minimisation measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 • Warning in section 4.4 of the SmPC that 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. • Guidance on assessment of liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and total bilirubin) for all patients prior to initiating Bylvay, with monitoring per standard clinical practice in SmPC sections 4.4 and PL section 2. • Recommendations for more frequent monitoring for patients with liver function test elevations in SmPC section 4.4 and PL section 2. • Instruction for patients to notify their doctor or pharmacist before taking Bylvay if they have been diagnosed with a complete absence or lack of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • 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 (PEDFIC 2). Final study report: 31-Jul-2023 • Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC Final study report: 31-Dec-2026 • Proposed Disease Registry: Utilization of a Disease Registry to Document the Natural

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	function of bile salt export pump protein and if they have severely reduced liver function in PL section 2. • Legal status: Prescription only medicine. Additional risk minimisation measures: • None	History of the Disease, Treatment Efficacy, Safety, including Long-Term Outcomes, Pregnancy, Breastfeeding and Newborns in Patients with PFIC. Regular update: ongoing basis as part of signal detection and reported within PSURs
Embryofoetal toxicity	Routine risk minimisation measures: • SmPC section 4.6 and 5.3 • PL section 2 • SmPC section 4.6 and PL section 2 notes that Bylvay is not recommended for use during pregnancy and in women of childbearing potential not using contraception. Use of a barrier contraceptive method is recommended. • Legal status: Prescription only medicine. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Proposed Disease Registry: Utilization of a Disease Registry to Document the Natural History of the Disease, Treatment Efficacy, Safety, including Long-Term Outcomes, Pregnancy, Breastfeeding and Newborns in Patients with PFIC. Regular update: ongoing basis as a part of signal detection and reported within PSURs
Interactions with fat-soluble drugs	Routine risk minimisation measures: • SmPC section 4.4, 4.5 and 4.8 • PL section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC section 4.5 notes that no interaction studies have been conducted with oral hormonal contraceptives or other lipophilic medicinal products. It cannot be excluded that the absorption of oral contraceptives is affected by concomitant use of odevixibat. • Recommendation for monitoring of levels of fat-soluble vitamins in SmPC section 4.5. • Guidance on assessment of fat-soluble vitamin levels (Vitamins A, D. E) and INR for all patients prior to initiating Bylvay, with monitoring per standard clinical practice in SmPC section 4.4. • Warning in section 4.4 of the SmPC that treatment with odevixibat may impact the absorption of fat-soluble medicinal products, including lipophilic oral contraceptives. • Instruction for patients in PL section 2 to notify their doctor or pharmacist if they are using, have recently used or might use any other medicines. Treatment with odevixibat may impact the absorption of fat-soluble vitamins such as Vitamin A, D and E, and some medicines, including oral contraceptives. • Legal status: Prescription only medicine. Additional risk minimisation measures: • None	• None Additional pharmacovigilance activities: • 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 (PEDFIC 2). Final study report: 31-Jul-2023 • DDI study with oral contraceptives Final study report: 31-Dec-2022 • Proposed Disease Registry: Utilization of a Disease Registry to Document the Natural History of the Disease, Treatment Efficacy, Safety, including Long-Term Outcomes, Pregnancy, Breastfeeding and Newborns in Patients with PFIC. Regular update: ongoing basis as a part of signal detection and reported within PSURs • Prospective Registry-based Study of the Long-

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		term Safety of Odevixibat in Patients with PFIC Final study report: 31-Dec-2026
Long-term use	Routine risk minimisation measures: • Legal status: Prescription only medicine. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • 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 (PEDFIC 2). Final study report: 31-Jul-2023 • Proposed Disease Registry: Utilization of a Disease Registry to Document the Natural History of the Disease, Treatment Efficacy, Safety, including Long-Term Outcomes, Pregnancy, Breastfeeding and

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Newborns in Patients with PFIC. Regular update: ongoing basis as a part of signal detection and reported within PSURs • Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC Final study report: 31-Dec-2026
Use during pregnancy and use in breastfeeding women	Routine risk minimisation measures: • SmPC section 4.6 and 5.3 • PL section 2 • SmPC section 4.6 and PL section 2 notes that Bylvay is not recommended for use during pregnancy and in women of childbearing potential not using contraception. Use of a barrier contraceptive method is recommended • SmPC section 4.6 mentions that patients are advised that the doctor will help to decide whether to discontinue breastfeeding or to discontinue/abstain from odevixibat therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother. • Guidance in section 2 of the PL advising patient that the doctor will help the patient to decide whether to stop breastfeeding or to avoid Bylvay treatment considering the benefit of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Proposed Disease Registry: Utilization of a Disease Registry to Document the Natural History of the Disease, Treatment Efficacy, Safety, including Long-Term Outcomes, Pregnancy, Breastfeeding and Newborns in Patients with PFIC. Regular update: ongoing basis as a part of signal

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	breastfeeding to the baby and Bylvay to the mother. • Legal status: Prescription only medicine. Additional risk minimisation measures: • None	detection and reported within PSURs

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Bylvay is a new active substance and the CHMP is of the opinion that a separate entry in the EURD list for Bylvay is needed. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of odevixibat with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers odevixibat to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

Not applicable.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Bylvay (odevixibat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Odevixibat is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. Odevixibat is orally administered and acts locally in the gut where it binds reversibly to IBAT to decrease the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acids. 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. PFIC is a rare disease estimated to affect one in every 50,000 to 100,000 children born worldwide. PFIC is generally categorised into 3 main subtypes, PFIC1, PFIC2, and PFIC3, although at least 3 other subtypes have been described in the literature. Each PFIC type is based on a different mutation, leading to disruption of specific membrane transporter proteins in the hepatocyte to enterocyte involved in shuttling bile acids (BAs) from the hepatocyte to the ileum. Due to accumulation of BAs hepatoxic concentrations are reached, leading to severe pruritus, growth retardation and ultimately cirrhosis. PFIC2 is considered the most severe form of the disease with rapid progression in early childhood (neonatal onset). The prognosis is poor; many PFIC patients progress to end-stage liver disease and require liver transplantation. Performing orthotopic liver transplantation (OLT) or biliary diversion surgery (SBD) is also one of the major reasons to cope with the burden of intractable pruritus in these patients. Survival in patients with PFIC not undergoing surgical biliary diversion or liver transplant is 50% at 10 years of age and <10% at 20 years of age.

3.1.2. Available therapies and unmet medical need

There is currently no medicinal product approved for use in treatment of PFIC1 and PFIC2. The therapeutic choices are restricted to non-specific therapy of the clinical symptoms and signs of the

disease such as nutritional support, prevention of vitamin deficiencies, and symptomatic treatment of extrahepatic features, including pruritus. Medical treatment options include off-label use of ursodeoxycholic acid (UDCA), rifampicin, hydroxyzine, antihistamines, and naltrexone, but none of these therapies have proven benefits for the long-term prognosis of patients with PFIC. For PFIC3 UDCA is registered in France only. As symptomatic medical treatment is rarely effective, surgical options are considered, including biliary diversion (such as partial external biliary diversion [PEBD] or ileal exclusion) and liver transplantation. Treatment-resistant pruritus is the leading indication for surgical biliary diversion, particularly in patients with PFIC2 where it is listed as an indication for surgery in 89% of patients. Continued elevated serum bile acids and pruritus are also seen in some patients after biliary diversion surgery. While biliary diversion surgery may postpone or eliminate the need for liver transplantation and improve pruritus associated with PFIC in some patients, it is an invasive procedure. Although liver transplantation may resolve cholestasis in patients with PFIC1 and PFIC2, the overall outcome remains unsatisfactory in many patients with PFIC1; this is mainly due to extrahepatic manifestations, organ rejection, and the complications and the risks associated with chronic immune-suppressant therapy. Therefore, there is a clear unmet medical need, in which odevixibat might prove to be a suitable option.

3.1.3. Main clinical studies

The applicant submitted the pivotal double-blind, randomized, placebo-controlled, phase 3 study (study 005), in addition to the open-label extension study (study 008) to evaluate long term efficacy and safety of odevixibat in children with progressive familial intrahepatic cholestasis types 1 and 2 (study 005) and PFIC types 1 to 3 and PFIC 6 (or MyoB5) (study 008).

Study 005 included 62 paediatric patients with PFIC 1 (n=17) or PFIC 2 (n=45). The median age was 3.2 years (min, max 0.5, 15.9 years). Among the PFIC 2 patients, 12 patients were BSEP1 and 33 patients were BSEP2. Patients were randomised to odevixibat 40 µg/kg/day (n=23), 120 µg/kg/day (n=19) or placebo (n=20). Treatment was 24 weeks after which patients could enrol in the open-label follow-up study 008. If in study 005 patients had tolerability issues or lack of efficacy after a minimal treatment period of 12 weeks, they could be switched over to study 008 (e.g. "the early roll over" patients) were they were treated with odevixibat 120 µg/kg/day. Three of 62 patients in study 005 were previously treated in the dose finding study 003; the patients were randomised to each study arm.

The dosages used in the pivotal study were based on the dose-finding study 003. The in- and exclusion criteria are appropriate to select the relevant paediatric patients with PFIC1 and PFIC2 with some functionality of the BSEP protein.

The primary efficacy endpoint was the proportion of patients experiencing at least a 70% reduction in fasting serum bile acids (SBAs) concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment. The important secondary endpoint was the proportion of positive pruritus assessments for AM and PM scores combined at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument. Further, the applicant was advised to submit an analysis of the number (%) of patients achieving a positive pruritus assessment (AM and PM Scores Combined) for more than 50% of the time during the 24-week treatment period. In addition, liver-related parameters (e.g. MELD/PELD, APRI, FIB-4 score, Fibroscan) were measured that may support a delay in fibrosis development and delaying SBD or OLT.

In the ongoing study 008, as of the data cut-off of 4 December 2020, all patients received odevixibat 120 µg/kg/day, which was decided based on (pre)clinical data prior to unblinding study 005. Dose lowering to 40 µg/kg/day was allowed in case of tolerability issues. The study consists of two cohorts.

Cohort 1 includes all patients previously treated in study 005 (40 µg/kg/day (n=21); 120 µg/kg/day (n= 16) and placebo (n= 19)), and cohort 2 includes treatment naïve patients (n=23). Cohort 2 includes 5 patients with PFIC1, 12 with PFIC2, 5 with PFIC3 and 1 patient with PFIC6. The endpoints in study 008 are similar to study 005.

3.2. Favourable effects

Study 005

Reduction of serum bile acids: The primary efficacy endpoint, the proportion of patients experiencing at least a 70% reduction in serum bile acids concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment, was met. In the FAS, 10/23 patients (43.5%) and 4/19 patients (21.1%) in the odevixibat 40 µg/kg/day and odevixibat 120 µg/kg/day respectively responded to treatment. There were no responders (0/20 patients) in the placebo group.

Reduction of pruritus: The proportion of positive pruritus assessments (night-time (AM) and day-time (PM) values combined) at the patient level over the 24-week treatment was as follows: LS Mean Difference (SE) (odevixibat – placebo): 28.23 (9.182) and 21.71 (9.892) for the 40 µg/kg and 120 µg/kg respectively. No major differences were observed between the AM as the PM results separately.

The CHMP also requested to demonstrate the proportion of patients achieving a positive pruritus assessment for >50% of the 24-week treatment period. The proportion was 61.9% for the overall odevixibat group, including 73.9% and 47.4% of patients in the 40 and 120 µg/kg/day groups, respectively, compared with 20.0% for the placebo group.

Changes in liver pathology and liver biochemistry: The mean changes from baseline to week 24 in PELD/MELD scores were -2.43 and -1.10 in the odevixibat 40 and 120 µg/kg/day groups, respectively, compared with -0.66 in the placebo group. In line with the PELD/MELD score, the APRI and FIB-4 score also showed marginal improvements in changes from baseline to week 24.

Growth: The mean (SE) change from baseline to Week 24 in height z-score were -0.16 (0.104), 0.05 (0.105) and 0.00 (0.163) for placebo, 40 µg/kg/day and 120 µg/kg/day, respectively.

Study 008

Reduction of serum bile acids: For patients in Cohort 1 of study 008 the mean (SE) changes in serum bile acids levels from study 005 baseline to Week 22/24 were -160.7 µmol/L (41.4), a decrease of 64.0% for those patients who had received 40 µg/kg/day in study 005, -150.6µmol/L (58.2), a decrease of 50.4 %, in patients who had previous received 120 µg/kg/day. For patients who had received placebo in study 005, mean change with odevixibat 120 µg/kg/day was -156.4 µmol/L (33.7), a decrease of 58.1%, and for 14/23 the treatment naïve patients in Cohort 2 the change was -65.3µmol/L (28.4), a decrease of 30.4%.

Reduction of pruritus: After 24 weeks of treatment in study 008 the mean (SE) proportion of positive pruritus assessments in patients who previously received 40 µg/kg/day (n=21) was 39.6% (8.7), and 27.4% (7.0) for patients who had received 120 µg/kg/day (n=16). For the patients) previously on placebo (n=19) this was 59.3% (9.2). For the naïve patients in Cohort 2 (n=11) the proportion was 78.4 (9.9).

Changes in liver pathology and biochemistry: The baseline values for PELD/MELD, APRI and FIB-4 scores were all indicative for patients not likely to have fibrosis or have minimal fibrosis (e.g. PELD/MELD values negative; APRI scores <0.5 and FIB-4 <3.25). For PELD/MELD the mean (SE) changes from baseline study 008 to Week 24 were 0.29 (0.45) and -0.41 (0.30) in patients who had

received 40 µg/kg/day or 120 µg/kg/day in study 005. For patients who had received placebo in study 005 this was -1.41 (0.87). For the patients in cohort 2 (n=11) the change was 2.28 (1.50).

Marginal improvements were observed under continued odevixibat treatment in study 008 in patients previously treated with odevixibat in study 005. Only for 10 patients fibroscan data were available; the data indicates some improvement in fibrosis.

Growth: For patients in Cohort 1 who had previously received odevixibat in study 005, mean (SE) change from baseline to Week 48 in study 008 in height z-score were 0.55 (0.21), 0.35 (0.20) 40 µg/kg/day and 120 µg/kg/day, respectively. For patients in Cohort 1 who had received placebo and in Cohort 2 patients, mean (SE) changes in height z-score were 0.75 (0.21), and 0.14 (0.22), respectively.

Other endpoints: For both studies the other clinical secondary and exploratory efficacy results were consistent and pointed in the same direction for improvement under odevixibat treatment.

Choice of starting dose: Post hoc analyses to compare the results for the primary analyses of pruritus and serum bile acids across the 40 and 120 µg/kg/day groups showed that there was 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 (2-sided p-value = 0.5008) or in the proportion of serum bile acid responders (2-sided p-value = 0.1083). Based on additional comparison of clinical data in patients switching from 40 (n=20) to 120 µg/kg/day and those initiated and maintained on 120 µg/kg/day shows that 40 µg/kg/day is the most appropriate starting dose, as reflected in the SmPC. Of the nine patients who did not respond to 40 µg/kg/day, four additional patients responded when switched to 120 µg/kg/day. This is reflected in the SmPC since dose escalation can be considered in case of inadequate after 3 months of treatment.

3.3. Uncertainties and limitations about favourable effects

Study 008: Only 11 of 23 patients in study 008 cohort 2 had data available at Week 22/24 at the time of the data cut-off. One patient required surgical biliary diversion, and one patient received liver transplantation due to lack of improvement in pruritus. There is limited data on the long term use of odevixibat. The applicant has committed to submit final results for Study 008 by July 2023.

Changes in liver pathology and biochemistry: For the changes in liver pathology and biochemistry only about one year of follow-up data in a limited number of patients is available (i.e. short-term). Hepatotoxicity is an important potential risk and is included in the RMP.

Delay in SBD/OLT: There is currently no direct evidence that odevixibat is delaying SBD and or OLT, as discussed in section 3.7.3.

Hepatic impairment: Patients with mild to moderate liver dysfunction were recruited to the clinical programme, whereas no patients with severe hepatic impairment were recruited. The absence of clinical data in patients with severe hepatic impairment is stated in the SmPC SmPC with recommendation for additional monitoring for adverse reactions when odevixibat is administered to these patients.

3.4. Unfavourable effects

From the 84 PFIC patients included in the Pooled Phase 3 group (study 005 and 008 combined), 44 (52%) of the 84 patients received ≥52 weeks and 26 (31%) received ≥76 weeks of treatment with odevixibat as of the cut-off date (04 December 2020).

In the Pooled Phase 3 group, 35 (41.7%) patients experienced a drug-related TEAE. The incidence of drug-related TEAEs in Study 005 in the 40 and 120 µg/kg/day groups (30% and 37%, respectively) was similar to the Pooled Phase 3 group but was higher among odevixibat-treated patients compared with the placebo group in that study (15%). Most drug-related TEAEs were mild to moderate in intensity. The most common drug-related TEAEs in the Pooled Phase 3 group were blood bilirubin increased (14.3%), ALT increased (10.7%), and AST increased (6.0%).

Adverse event of special interest: Diarrhoea, (including diarrhoea, diarrhoea haemorrhagic, frequent bowel movements and faeces soft) were one of the most common TEAEs in patients treated with odevixibat, occurring in 18 (21.4%) of 84 patients in the Pooled Phase 3 group. In Study 005, these diarrhoea events occurred in 39% and 21% of patients in the 40 and 120 µg/kg/day groups, respectively, and in 5% of patients in the placebo group.

Treatment-emergent SAEs were reported in 9 (10.7%) of the 84 patients in the Pooled Phase 3 group. In Study A4250-005, there were no SAEs reported in patients who received 40 µg/kg/day; 3 patients (16%) in the 120 µg/kg/day group and 5 (25%) in the placebo group experienced SAEs. Two (20%) of the patients with PFIC in Study A4350-003 experienced SAEs. None of the treatment-emergent SAEs were assessed by the investigator as related to study drug. There were no deaths in the Phase 2 or Phase 3 studies.

Analysis of the vital signs and physical examination did not reveal clinically relevant changes. ECGs were obtained from healthy volunteers (N= 150) no clinically significant findings were reports, and all QT intervals were ≤500 ms. Further, no patients reported Torsade de Pointes or QT prolongation as an AE in the phase 2 or 3 studies.

Age nor gender appeared to affect the overall observed safety and tolerability profile.

The incidence of TEAEs in Europe (76%) and RoW (88%) was generally similar.

Patients with PFIC1 compared with PFIC2 had a higher incidence of TEAEs in the most common SOCs of GI disorders (60% versus 47%).

Treatment-emergent AEs leading to interruption of study treatment were reported in 21 patients (25%) in the Pooled Phase 3 group. Discontinuation of treatment was reported in five patients (6%) in the Pooled Phase 3 group, this included 1 patient in the 120 µg/kg/day group and four patients during the extension phase (120 µg/kg/day). The TEAE leading to treatment discontinuation (diarrhoea) was assessed as drug-related; all other TEAEs leading to discontinuation were reported as unrelated to odevixibat.

3.5. Uncertainties and limitations about unfavourable effects

The primary evaluation of the safety and tolerability of odevixibat in the proposed indication is based on the two Phase 3 studies 005 and 008 (Pooled Phase 3 Group) including a total of 84 patients with PFIC. Given the limited number of patients at the time of authorisation, safety would need to be supported by long-term data. For this reason, the final safety report generated by the applicant-initiated extension study (008) is of interest and the applicant committed to provide the results by July 2023.

From the 84 patients included in the Pooled Phase 3 Group, 44 (52%) patients received ≥52 weeks and 26 (31%) received ≥76 weeks of treatment with odevixibat as of the cut-off date (04 December 2020). The follow-up is considered too short to assess the long-term safety profile (among others genotoxicity).

As the underlying disease is only insufficiently managed with other treatment options, the signs and symptoms of the disease may obscure the adverse events profile of odevixibat. From a pharmacodynamic

point of view, various GI-tract adverse events could be expected (e.g. cganges of liver function tests and/or increased diarrhoea). The lack of safety data considering clinically significant or severe diarrhoea is considered a risk for patients treated with odevixibat. Further, follow-up to learn more about the frequency, seriousness, and best treatment options is considered necessary. Hence, the CHMP was of the opinion that further, more in-depth safety related information should be collected, especially on diarrhoea, hepatotoxicity and liver function related measures, fat-soluble vitamins and nutrients. Thus, the CHMP requested a post-authorisation registry study that will monitor these parameters.

In toxicology studies with juvenile rats, dose-limiting focal hepatic toxicities (hepatocyte necrosis/apoptosis) were observed. This, however, was seen at an exposure 1200 times the exposure reported in humans. As at the lower exposure levels, no hepatotoxicity is reported and thus, this observation is considered not clinically relevant.

Except for a slightly higher frequency of the adverse events in the higher dose group 120 µg/kg/day group, no clear and consistent differences in the safety profile between the 40 and 120 µg/kg/day could be identified. It should be kept in mind that this conclusion is based on 23 and 19 patients, respectively.

No ECGs were collected in the Phase 2 or 3 studies. No patients reported Torsade de pointes or QT prolongation as an AE in the phase 2 or 3 studies. ECGs were obtained from healthy volunteers. No clinically significant findings were reports, and all QT intervals were ≤ 500 ms.

The non-clinical studies indicate that odevixibat may be teratogenic at clinically relevant concentrations. Therefore, adequate contraception is required in the treated patients. As no interaction study with oral hormonal contraception were conducted, it cannot be excluded that the absorption of oral contraceptives is affected by concomitant use of odevixibat (progestogens and ethinyl oestradiol are lipophilic substances, and entero-hepatic recirculation plays a role). Therefore, an interaction study with an oral hormonal contraceptive will be conducted, as requested by the CHMP, and the final study report is awaited by end of 2022.

In addition to this study, it is anticipated that patients treated with odevixibat will reach sexual maturity and given the potentially teratogenic effect of odevixibat, the applicant was requested by the CHMP to initiate a disease registry with the focus on documentation of the natural history of the disease, treatment efficacy, safety, including long-term outcomes, pregnancy, breastfeeding and new-borns in patients with PFIC.

3.6. Effects Table

Table 52: Effects Table for Bylvay (treatment of PFIC) (data cut-off: 31 august 2020)

Effect	Short Description	Unit	Odevixibat 40 µg/day/kg (n=23)	Odevixibat 120 µg/day/kg (n=19)	Placebo (n=20)	Uncertainties/ Strength of evidence	References
Favourable Effects							
sBA	Proportion of patients experiencing ≥ 70% reduction or reaching a level ≤70 µmol/L after 24 weeks of treatment in sBA	N %	10/23 43.5	4/19 21.1	0/20 0	**SoE:** Primary endpoint; statistical significantly difference odevixibat *versus* placebo; Proportion Difference Adjusting for Stratification Factors (Odevixibat - Placebo) (95% CI[a]): 40 µg: 0.441 (0.2361, 0.6464); 120 µg: 0.216 (-0.0050, 0.4380) **Unc:** None of the US patients was a responder.	Study 005
pruritus	Proportion of Patients Achieving a Positive Pruritus Assessment for >50% of the Time During the 24-Week Treatment Period[c]	N %	17/23 73.9	9/19 47.4	4/20 20.0	**SoE:** Secondary endpoint; Odds ratio (Odevixibat – Placebo) (95% CI) [One-sided Adjusted p-value[b]] 40 µg: 16.2 (2.540, 106.320) [0.0002] 120 µg: 3.1 (0.718, 18.700) [0.0391]	Study 005
PELD/MELD score	Changes in liver pathology (PELD/MELD) after 24 weeks of treatment Mean (SE)		-2.43 (0.98)	-1.10 (1.23)	-0.66 (1.14)	Exploratory endpoint. All endpoints pertaining to liver biochemistry point into the direction of small improvements. Data up to week 60 in study 008 indicates further improvement/stabilisation. **Unc:** There is no direct evidence that odevixibat delays SBD or OLT. Only short-term data on liver related parameters is available, long-term follow-up data is required to inform whether these results are maintained.	Study 005

Effect	Short Description	Unit	Odevixibat 40 µg/day/kg (n=23)	Odevixibat 120 µg/day/kg (n=19)	Placebo (n=20)	Uncertainties/ Strength of evidence	References
Height	Change in height (z-scores) from BL after 24 weeks of treatment	Mean (SE)	0.05 (0.105)	0.00 (0.163)	-0.16 (0.104)	Secondary endpoint Pooled data up to 48 weeks in study 005 and 008: 40 µg, 0.52 (0.134) and 120 µg, 0.66 (0.177).	Study 005
Unfavourable Effects							
Diarrhoea	Diarrhoea, (including diarrhoea, diarrhoea haemorrhagic, frequent bowel movements and faeces soft)	%	39.1	21.1	5.0	**Unc**: as the signs and symptoms of the disease and the safety profile are overlapping it is not clear in how far the actual safety profile can be observed against the background of an active disease.	Study 005

Abbreviations: sBA: serum bile acids; Unc: uncertainties; SoE: strength of evidence, SBD: surgical biliary diversion; OLT: orthotopic liver transplantation; MA: marketing authorisation.
Notes:

a) Clopper-Pearson exact CI is reported for the percentage of responders, and the exact unconditional CI is reported for the proportion difference without adjusting for stratification factors.

b) For an individual dose, the adjusted p-value is calculated as the maximum value of the unadjusted p-value for odevixibat all doses and the unadjusted p-value for the individual dose.
c) as requested during protocol advice (EMA/CHMP/SAWP/770832/2018)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint, the reduction of SBAs (a key pathological index of the disease) under continued odevixibat treatment has been demonstrated. Accumulation of SBAs in hepatocytes would lead to hepatic damage such as fibrosis, portal hypertension and finally cirrhosis. In a literature review, SBA levels of 25 to 35 ULN were reported in PFIC patients. After initiation of odevixibat treatment, rapid reduction of SBAs is observed. These are considered clinically relevant and they are in the same magnitude of SBAs reduction in patients after surgical biliary diversion.

The reductions in SBAs under odevixibat treatment were accompanied by clinically relevant reductions of pruritus (one of the main determinants of patient quality of life outcomes) in most patients. Other secondary endpoints such as sleep-related parameters all were consistent with and pointed in the same direction as the reduction of pruritus.

Treatment with odevixibat also led to a clinically relevant improvement in growth over time, indicating catch-up growth. The observed growth catch-up is comparable to the effects observed following surgical intervention (i.e. 1-year data post-biliary diversion surgery or liver transplantation). The results in growth catch-up are supportive for a disease-modifying indication.

Data on the exploratory hepatic endpoints (ASAT, ALAT, bilirubin, FIB-4, APRI, MELD/PELD) are suggestive for improvement or disease stabilisation. Further it is recognised that at data cut-off (4 December 2020) none of the patients – in whom odevixibat resulted in decrease of sBA or ASAT improvement of MELD/PELD or pruritis - was listed for transplant, contrary to the patients who failed on odevixibat of whom 2 patients underwent surgery. Further, measurements on hepatic and fibrosis parameters and limited data on fibroscans were presented. In general, a trend toward improvement was observed for the aforementioned measures. This, however, only applied to a very limited number of patients. Although these data are encouraging and all point in the direction of improvement of liver health, only data for about short-term follow-up is available. Long-term follow-up data to confirm stabilisation or improvement on the hepatic parameters is not available. In addition, there is no direct evidence that odevixibat treatment will delay SBD and/or OLT. Therefore, the data on hepatic parameters cannot be extrapolated and more data is to be collected in a post-marketing setting. For this reason, a registry-based efficacy study will be conducted, as a specific obligation, in order to investigate whether odevixibat delays surgery and/or OLT in the context of a marketing authorisation under exceptional circumstances. The variables that are required to address this question will be recorded in a registry (database*).* The general outline of the registry and the registry-based study protocol as provided by the applicant to date, are agreeable to the CHMP. Feasibility assessment for this study will be submitted within 3 months of EC decision.

In the clinical studies, only 5 patients with PFIC3 and 1 patient with MyoB5 mutation (i.e. PFIC6) were included (long term follow-up study cohort 2). Albeit the very limited data available for these patients in cohort 2, the applicant has extensively substantiated that extrapolation to a broad PFIC population is justified. 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) 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. Only 2 patients over 18 years of age

were included. Although the data is limited, it is expected that there is no difference in treatment effect based on the mode of action of odevixibat. Based on the extrapolation, the clear and clinically relevant improvements on the reduction of pruritus, SBAs and growth catch-up, and the short-term improvements on hepatic parameters, an indication for the treatment of PFIC in patients aged 6 months and older under exceptional circumstances is acceptable to the CHMP.

On the other hand, based on the safety findings (e.g. hepatic-associated events), it is observed that the reported hepatic-associated events are not necessary drug-induced but are probably the results of underlying disease. Therefore, these safety findings are not mentioned in the SmPC as AE.

The primary evaluation of safety is based on a total of 84 patients with PFIC. Given the limited number of patients, no robust conclusions on safety can be drawn. For this reason, the final safety report generated by the extension study 008 is of interest and will be provided to the CHMP. Also, more information on hepatic safety is considered necessary, especially data on fat-soluble drug and food components, which will be generated in a dedicated registry-based safety study. Diarrhoea (including diarrhoea, diarrhoea haemorrhagic, frequent bowel movements and faeces soft) were one of the most common drug-related AEs in patients treated with odevixibat. Diarrhoea may also lead to dehydration. Further, follow-up to on these events about the frequency, seriousness, and best treatment options is expected to be derived from this safety study.

The non-clinical studies indicated that odevixibat may be teratogenic at clinically relevant concentrations. As no interaction study with oral hormonal contraception has been conducted, it is currently unknown whether oral hormonal contraception can be safely used as a contraception method. This will be investigated post-marketing. The adequate use of contraception is sufficiently addressed in the SmPC with a recommendation to use a barrier contraceptive method. In addition, due to the potential teratogenic character of odevixibat pregnancies outcomes and follow-up of new-borns will be conducted in this disease registry.

3.7.2. Balance of benefits and risks

During odevixibat treatment, a significant reduction in serum bile acids accompanied by a significant reduction in pruritus was seen. Furthermore, patients started to catch up on their growth. Hepatic parameters and fibrosis scores were improving or were stable for the duration of the study (max. 72 weeks). The short-term data indicate the potency of odevixibat to delay disease progression and the need for surgery and/or OLT. As no direct evidence is available that odevixibat treatment will delay SBD and/or OLT, the provided data are lacking for a comprehensive demonstration of efficacy with clinical outcomes. To address this, a registry-based efficacy study will be conducted as a specific obligation in the post-marketing setting. Additional safety data pertaining to the severity of diarrhoea and fat-soluble vitamins and nutrients, together with pregnancy outcomes and follow-up of new-borns is to be collected post-approval.

3.7.3. Additional considerations on the benefit-risk balance

As comprehensive data on the delay of surgical biliary diversion and liver transplantation on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant on the basis that it is unlikely that the Applicant will be able to provide comprehensive efficacy data due to rarity of the indication. The CHMP agrees that due to the very rare prevalence of the disease, it is not expected that comprehensive efficacy data will be generated on the delay of surgical biliary diversion and/or liver transplantation within a reasonable time frame.

Although there is a suggestion that hepatic parameters showed some improvement (or at least some stabilisation) under continued odevixibat treatment, the current data do not allow full extrapolation of these observations to a delay in biliary surgery and/or OLT. The results were based on a placebo-controlled study; however, this study was considered to cover only short time period to draw any firm conclusions. As long-term data is lacking, the CHMP considered that additional efficacy data is required to investigate whether odevixibat indeed delays biliary surgery and/or OLT. The collection of these data, which is also based on recruitment rate of PFIC patients, is necessary and it will take a long time given the rarity of the disease. At the time of approval, it is not possible to establish a comprehensive clinical database based on clinical trial data to determine the long-term beneficial effect on liver survival (delay of SBD/OLT). PFIC is an orphan disease and robust confirmation of delay of relevant clinical outcome parameters like SBD/OLT is challenging, if not unfeasible. The clinical treatment pathway is very heterogeneous, dependent on healthcare professionals' preferences, and often also complicated by the additional conditions. Taken together, it can be concluded that the applicant cannot be reasonably expected to provide comprehensive indisputable evidence for the long-term clinical benefit. Therefore, the CHMP concluded that the collection of further data on long-term benefit should be conducted as part of an imposed specific obligation within a framework of an authorisation under exceptional circumstances.

Further, as it is anticipated that patients treated with odevixibat will reach sexual maturity and given the potentially teratogenic effect of odevixibat, the CHMP requested the applicant to initiate a disease registry, to collect data on the use during pregnancy, breastfeeding and in new-borns. These data on pregnancy should be investigated as a post-marketing measure. The CHMP also considered that additional safety data are necessary on the effect of odevixibat treatment on diarrhoea, hepatotoxicity and the effect on fat-soluble nutrients and drugs.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate, with the following specific obligation:

- *Post-authorisation registry-based efficacy study: In order to investigate whether odevixibat treatment delays surgical biliary diversion (SBD) and/or liver transplantation (OLT), with matched comparison against untreated PFIC patients, the MAH should conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) according to an agreed protocol. Annual interim reports are to be submitted along with the annual reassessments.*

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall B/R of Bylvay is positive provided general statement on conditions.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bylvay is favourable in the following indication:

Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older (see sections 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation

(EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Post-authorisation registry-based efficacy study: In order to investigate whether odevixibat treatment delays surgical biliary diversion (SBD) and/or liver transplantation (OLT), with matched comparison against untreated PFIC patients, the MAH should conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) according to an agreed protocol.	Annual reports are to be submitted as part of the annual reassessment.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that odevixibat is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/0377/2020) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.