Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for BYLVAY

Active ingredient: Odevixibat

Sponsor: Ipsen Pty Ltd

July 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time profile
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
F_{rel}	Relative bioavailability
IBAT	Ileal bile acid transporter
PD	Pharmacodynamic(s)
PFIC	Progressive familial intrahepatic cholestasis
PI	Product Information
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetic(s)
RMP	Risk management plan
SD	Standard deviation
SE	Standard error
SBA	Serum bile acid
$t_{1/2}$	Elimination half- life
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
UDCA	Ursodeoxycholic acid
V/F	Volume of distribution

BYLVAY (odevixibat) submission

Type of submission:	New chemical entity
Product name:	BYLVAY
Active ingredient:	odevixibat
Decision:	Approved
Date of decision:	24 March 2025
Date of entry onto ARTG:	26 March 2025
ARTG numbers:	BYLVAY odevixibat 200 microgram capsule bottle (419590) BYLVAY odevixibat 1200 microgram capsule bottle (419592) BYLVAY odevixibat 400 microgram capsule bottle (419591) BYLVAY odevixibat 600 microgram capsule bottle (419593)
, *Black Triangle Scheme*	Yes
Sponsor's name and address:	Ipsen Pty Ltd, Level 5, 627 Chapel Street South Yarra VIC 3134
Dose form:	Opaque, hard capsules contain white to off-white pellets containing odevixibat
Strength:	odevixibat 200 micrograms, 400 micrograms, 600 micrograms, or 1200 micrograms.
Container:	HDPE bottle with a child-resistant polypropylene closure
Pack size:	Each pack contains 30 hard capsules
Approved therapeutic use for the current submission:	BYLVAY is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older
Route of administration:	Oral
Dosage:	40 micrograms/kg. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	Category D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Proposed indication

This AusPAR describes the submission by Ipsen Pty Ltd (the Sponsor)[1] to register BYLVAY (odevixibat) for the following proposed indication:

> *BYLVAY is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.*

Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a life-threatening group of inherited disorders associated with significant morbidity. The age of presentation varies by PFIC subtype (1-6), but typically the disease occurs in infancy and early childhood with failure to thrive and progressive liver disease. PFIC1 and PFIC2 together represent approximately two-thirds of cases of PFIC, and PFIC3, approximately one-third. Symptoms develop early with a median age at onset of approximately 3 months; 78% of patients develop jaundice before 12 months of age and in association with abnormal liver transaminase concentrations patients develop severe pruritus and may also develop fat-soluble vitamin deficiencies.

The underlying pathology in PFIC is gene mutation. In PFIC1, also known as Byler disease, the mutation is in the P-type ATPase gene (ATP8B1, FIC1). In PFIC2, the defect is in ABCB11, the gene coding for sister P-glycoprotein (SPGP), also known as bile salt export pump (BSEP); PFIC3 involves mutations in the ABCB4 gene coding for multidrug resistance protein-3 P-glycoprotein (MDR3 or PGY3). Considerably less common defects include protein-truncating mutations in the TJP2 gene that expresses tight junction protein 2 (PFIC4).

Current treatment options

There is an unmet need for treatment for patients with PFIC. Pharmaceutical options are limited to symptomatic medical therapies for itch, for example colestyramine and ursodeoxycholic acid. Colestyramine has an approved indication in Australia for "Relief of pruritus associated with partial biliary obstruction" and has limited clinical trial data in children. Ursodeoxycholic acid (UDCA) has an indication in "the treatment of chronic cholestatic liver diseases", predominantly focused on primary biliary cirrhosis and primary sclerosing cholangitis, also with limited clinical trial data in children. Off-label treatment of persistent pruritus with rifampicin may also be trialled. Surgical options for unremitting itch include surgical biliary diversion, and ultimately patients may require liver transplantation.

Clinical rationale

Odevixibat is a small molecule that acts as a potent, selective inhibitor of the ileal bile acid transporter (IBAT, also known as the apical sodium/bile acid transporter [ASBT]). IBAT is a luminal epithelium glycoprotein expressed mainly in the distal ileum that co-transports sodium and bile acids, moving bile acids from the lumen of the small intestine across the apical brush border membrane. The bile acids are shuttled to the basolateral membrane, ultimately returning to the liver via portal venous blood (enterohepatic circulation). Minimal passive reabsorption of bile acids occurs throughout the intestine, active transport via IBAT is the major mechanism for bile acid reabsorption. Effectively blocking the action of IBAT decreases the reuptake of bile

[1] A sponsor is a person or company who does one or more of the following: a) exports therapeutic goods from Australia, b) imports therapeutic goods into Australia, c) manufactures therapeutic goods for supply in Australia or d) elsewhere arranges for another party to import, export or manufacture therapeutic goods

acids and therefore bile acid concentrations in the circulation. Elevated serum bile acid (SBA) concentrations are thought to contribute to the severe pruritus associated with cholestatic disease.

Regulatory status

Australian regulatory status

This product is a new chemical entity for Australian regulatory purposes. Odevixibat has been supplied in Australia under a compassionate use program. At the time of submission of request for orphan designation (July 2023) eight patients were receiving odevixibat via the Special Access Scheme (SAS). The TGA granted orphan drug designation to odevixibat (BYLVAY) for the treatment of PFIC on 3 August 2023. This submission was submitted through the TGA's Comparable Overseas Regulator A (COR-A) process, using evaluation reports from the European Medicines Agency (EMA). The full dossier was submitted to the TGA.

International regulatory status

BYLVAY (sponsored by Albireo AB) was granted orphan designation by the US Food and Drugs Administration (FDA) on 31 October 2012 for "Treatment of progressive familial intrahepatic cholestasis" and was registered by the FDA on 20 Jul 2021.

BYLVAY was granted orphan designation by the EMA on 17 Jul 2012 for "Treatment of progressive familial intrahepatic cholestasis" and received marketing authorization on 16 July 2021.

Marketing authorization was granted under exceptional circumstances following accelerated assessment, as the product was considered of major public health interest.

BYLVAY was granted orphan designation by the Japan Ministry of Health, Labour and Welfare on 23 May 2023.

BYLVAY is also authorised for marketing in Great Britain, Canada and Israel.

Registration timeline

Table 1 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1. Registration timeline for BYLVAY (odevixibat), submission PM-2023-03749-1-1

Description	Date
Designation (Orphan)	3 August 2023
Submission dossier accepted and evaluation commenced	3 October 2023
Evaluation completed	16 April 2024
Registration decision (Approved)	24 March 2024
Registration in the ARTG completed	26 March 2024
Number of working days from submission dossier acceptance to registration decision*	121 days

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

Australian-specific data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA, were also assessed. There is no objection to registration of BYLVAY, when the outstanding GMP clearance has been established.

Odevixibat is a white to off-white crystalline solid. The drug substance has two chiral centres and is manufactured as a single stereoisomer with the (S,R)-configuration.

Solubility is pH dependent and the drug substance is insoluble in aqueous buffers pH 1 to 4.

The polymorphic Form 1 was established as the stable solid-state crystalline form of the drug substance. It is noted that the crystalline fraction of Form 1 is dependent on the drying conditions used in the final stage of the manufacturing process.

Odevixibat sesquihydrate, its starting materials and all reagents used in the manufacture of the drug substance were assessed for any genotoxic alert structures. All potentially genotoxic impurities identified are adequately controlled or eliminated during the manufacturing process in accordance with ICH guidelines. A nitrosamine risk assessment has also been performed and concluded that the manufacturing process does not present a risk of formation of

N-nitrosamines. The analytical methods used to analyse the drug products were adequately described and validated.

Four strengths of the BYLVAY odevixibat (as sesquihydrate) immediate release hard capsules are proposed for registration, namely 200 µg, 400 µg, 600 µg and 1200 µg. The capsule strengths are easily distinguishable from one another in terms of colour and printed text.

Two concentrations of 'odevixibat pellets' are prepared: 5 mg/g (or 0.5% w/w) and 1.5 mg /g (or 1.5 w/w) odevixibat pellets.

- 200 µg and 400 µg: these capsule strengths are manufactured from the common odevixibat pellets of 5 mg/g (0.5% w/w) by adjusting the fill weight of the pellets into different size capsules, and are direct scale, and
- 600 µg and 1200 µg: these capsule strengths are manufactured from the common odevixibat pellets of 15 mg/g (1.5% w/w) by adjusting the fill weight of the pellet into different size capsules and are direct scale.

The capsules are manufactured by Patheon France, France using conventional manufacturing processes.

BYLVAY odevixibat (as sesquihydrate) hard capsules (all strengths) are packaged in 50 mL HDPE bottles (for 200 and 600 µg) or 30 mL HDPE bottle (for 400 and 1200 strengths) and closed with tamper-evident PP child resistant closure, in pack sizes of 30 capsules for all strengths. Satisfactory assurances of compliance with the requirements of TGO95- Child Resistant Packaging Requirements for Medicines have been provided.

There were no objections to approval from a quality perspective

Nonclinical evaluation summary

The non-clinical Evaluator had no objection to registration of odevixibat. The scope of the submitted Module 4 dossier was in accordance with the relevant TGA-adopted guideline (ICH S3 [R2]).[2] Most pivotal toxicity studies were conducted under GLP conditions using the proposed clinical route (oral) and dosing regimen (once daily). This evaluation report has used the assessments and considerations detailed in the EMA nonclinical evaluation reports. The evaluation concluded that:

- The pharmacology studies were adequate to support the use of odevixibat for the proposed indication.
- No clinically relevant hazards were identified in safety pharmacology studies.
- Odevixibat may alter the exposure of co-administered drugs that are CYP3A4/5 substrates.
- Odevixibat was generally well-tolerated in all species. Toxicities were reversible and associated with localised pharmacological effects on the gastrointestinal tract (e.g. diarrhoea).
- Odevixibat did not show any potential for genotoxicity or carcinogenicity.
- Unexplained cardiovascular malformations were seen in rabbits at low systemic (and therefore clinically relevant) exposures. A risk to human embryo-fetal development cannot be excluded. Accordingly, Pregnancy Category D was recommended for odevixibat.

Clinical evaluation summary

Relevant guidelines or guidance documents referred to by the Delegate [3]are listed below:

- European Medicines Agency, Committee for Medicinal Products for Human Use, Guideline on clinical trials in small populations (CHMP/EWP/83561/2005), 27 July 2006.
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population - Scientific guideline (EMA/CPMP/ICH/2711/1999), 06/10/2017.
- European Medicines Agency, Committee for Proprietary Medicinal Products, Points to consider on applications with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99), 31 May 2001.

Summary of clinical studies

The delegate reviewed the clinical assessment reports prepared by the COR and additional long-term data provided in response to a request for information. The primary data in support of the efficacy of odevixibat were derived from Study A4250-005, a completed Phase 3, randomised, double-blind, placebo-controlled, 24-week study of two dose levels of odevixibat, 40 and 120 µg/kg/day, conducted in paediatric patients with PFIC1 or PFIC2, aged between 6 months and 18 years and weighing at least 5kg. Participants were required to have SBA concentrations ≥ 100 µmol/L, and a documented history of severe pruritus. The primary efficacy endpoint was the

[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals - Scientific guideline. 2013

[3] A "Delegate" refers to a person within the TGA who has been conferred the authority to make decisions about the approval of therapeutic goods for supply in Australia, under section 25 of the Therapeutic Goods Act.

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

Long-term efficacy data are presented from Study A4250-008, an ongoing, open-label, 72-week extension study of odevixibat 120 µg/kg/day, including participants aged between four months and 26 years at enrolment with any type of PFIC. A total of 114 study participants had received at least one dose of odevixibat in Study A4250-008 at data cutoff date of 31 July 2022. All 114 patients were included in the full analysis set; 63 patients had completed the 72-week treatment period, 25 patients were ongoing on treatment in the 72-week treatment period and 26 had discontinued treatment prior to Week 72. Supportive efficacy data for the proposed indication are provided by the results of the 4-week Phase 2 study A4250-003, which evaluated multiple dose levels of odevixibat up to 200 µg/kg/day in 10 patients with cholestatic pruritus.

The safety of odevixibat has been evaluated in a total of eight clinical studies, including five Phase 1 studies in healthy adults, one Phase 2 study in paediatric patients with cholestatic liver disease, including PFIC, and two Phase 3 studies conducted in paediatric patients with PFIC.

Pharmacology

Pharmacokinetics

The pharmacokinetics (PK) of odevixibat were 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 absorption/distribution/metabolism/excretion 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.

Non-compartmental methods were used to determine the pharmacokinetic parameters of odevixibat in the phase 1 studies. Odevixibat is poorly absorbed and plasma levels were not quantifiable in several patients, therefore the pharmacokinetic parameters of odevixibat could not be determined for all participants.

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 82.9% was recovered from the faeces. Also, in single and multiple-dose studies A4250-001 and A4250-003, the relative bioavailability of odevixibat was estimated to be low.

Noncompartmental pharmacokinetic data obtained in drug-drug interaction study A4250-013, in healthy adult volunteers, is presented in Table 2.

Table 2. 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)
$AUC_{0\text{-}t}$(h*ng/mL)	2.04 (42.8); 21

Plasma PK parameter	Odevixibat (N=21)
$AUC_{0\text{-}inf}$(h*ng/mL)	2.45 (30.4); 19
C_{max}	0.435 (40.6); 21
T_{max}	2.50 (1.00-5.00); 21
$t_{1/2}$	2.36 (2.00); 19
CL/F	3060 (955); 19
V_z/F	9940 (7280); 19

AUCs and C_{max} are presented as geometric mean (geometric CV%), Tmax is presented as Median (Min, Max); other parameters are presented as mean (SD)

Exposure to odevixibat was lower in both the fed state (decrease of 72% and 62% in C_{max} and $AUC_{0\text{-}24}$, respectively) and when dosed as a sprinkled formulation on apple sauce (decrease of 39% and 36% in C_{max} and $AUC_{0\text{-}24}$, 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 pharmacodynamic (PD) marker, C4. As a PK/PD relationship could not be established, and because younger children were unlikely to be able to swallow whole capsules, thereby requiring "sprinkled" capsule contents, EMA agreed to recommend that odevixibat can be administered with food.

Plasma protein binding of odevixibat was high, >99.7% at 4 µM and >99.97% at 40 µM (unbound fraction <0.3%). The mean body weight adjusted apparent volumes of distribution (V/F) in paediatric patients for the 40 and 120 µg/kg/day dose regimens were 40.3 and 43.7 L/kg, respectively.

Based on population PK modelling, the mean half-life of odevixibat in paediatric patients was about 2.4 hours. The half-life is highly variable and could often not be determined using non-compartmental data, owing to the frequency of samples with undetectable levels.

The pharmacokinetics of odevixibat were adequately assessed. Odevixibat is poorly absorbed and its main action is locally in the gut.

Population pharmacokinetic data

The population PK (popPK) analysis ALBI-PMX-A4250-1167_PPK 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 adult 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. 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 (K_{a1} and K_{a2}, respectively). Covariates included in the final model were bodyweight on apparent clearance (CL/F), P-gp inhibitors and liver impairment on CL/F, body weight on V/F, dosage form and formulation on relative bioavailability (F_{rel}), and formulation on K_{a1}. The estimated typical (CL/F), volume of distribution (V/F) and elimination half- life ($t_{1/2}$) of odevixibat in a 70-kg subject were 2180 L/h, 2510 L and 47.9 min, respectively.

The exposure of odevixibat in paediatric patients with PFIC was calculated for the 40 and 120 µg/kg/day dose levels (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 estimated to

be 0.211 and 0.623 ng/mL, respectively, and the mean AUCs were 2.26 and 5.99 ng*hr/mL, respectively.

Due to the low bioavailability of odevixibat, the variability of the PK parameters is relatively high. The applicant concluded that it was not possible to estimate 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 EMA SmPC includes a statement that the C_{max} and AUC_{0-t} increase with increasing doses; however due to the high between-subject variability of approximately 40%, it is not possible to estimate dose proportionality accurately.

Special populations

Limited PK data are available to compare the effects of hepatic dysfunction on odevixibat PK, as few patients with PFIC have normal hepatic function. 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.

Pharmacodynamics

The PD of odevixibat were evaluated in Studies A4250-001 and A4250- 003 by assessment of changes from baseline in SBA, 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.

In the multiple ascending dose cohorts (odevixibat 1mg daily, 3mg daily, or 1.5mg bd vs placebo) mean decreases from Day 1 pre-dose in FGF19 concentrations 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. Comparable mean increases from Day 1 pre-dose in C4 concentrations 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 mean concentrations 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 participants 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.

In study A4250-003 a reduction in SBA 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 further decrease in total SBA. Individual responses varied from a 98% reduction 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.

A dedicated QT study was not conducted. Non-clinical data indicated a low potential for adverse effects on the cardiovascular system. 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.

Efficacy

The pivotal study in support of this application was A4250-005, a double-blind, randomized, placebo-controlled phase 3 study in children with PFIC types 1 and 2. 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.

Inclusion criteria

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

1. Male or female, with clinical diagnosis of PFIC1 or PFIC2, aged ≥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 SBA concentration (the average of 2 samples at least 7 days apart, Visits 1 and 2) ≥100 µmol/L (40 µg/mL) prior to randomisation
4. Had a history of significant pruritus and caregiver-reported observed scratching (recorded in an 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.

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 (BRIC), 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

Treatment

Patients received oral odevixibat at a dose of 40 µg/kg or 120 µg/kg, or placebo, for 24 weeks.

Concomitant medication

Treatment with UDCA, rifampicin, and/or antihistamines was allowed provided the patient was on a stable dosage for at least four 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 for at least four weeks before enrolment until treatment discontinuation.

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.

The secondary objectives of the study were to evaluate the effect of odevixibat on serum ALT concentration, growth, sleep disturbance, and the need for surgical treatment (biliary diversion or liver transplantation) as well as to assess the safety and tolerability of repeated daily doses of odevixibat for 24 weeks.

The primary efficacy endpoint (for the EU, and for Australia) was the proportion of patients experiencing at least a 70% reduction in SBA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment. SBA concentration at baseline was calculated as the average of the last 2 values prior to the first dose of odevixibat. The end value was calculated as the average of the values at Weeks 22 and 24 after the start of treatment. Several secondary and exploratory efficacy endpoints were also considered including the proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument;[4] the proportion of patients achieving a positive pruritus assessment for >50% the time during the 24-week treatment period, change from baseline to week 12 and to week 24 in SBA, change from baseline to week 12 and to week 24 in growth, change from baseline to week 24 in PELD/MELD scores.

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 rest of world (RoW)), sex (male and female), race (Caucasian and non-Caucasian), ethnicity (Hispanic, non- Hispanic, and unknown), baseline SBA level (≥250 and <250 µmol/L), Child-Pugh classification (A, B, C), BSEP type of PFIC2 patients, and the use of UDCA and rifampicin

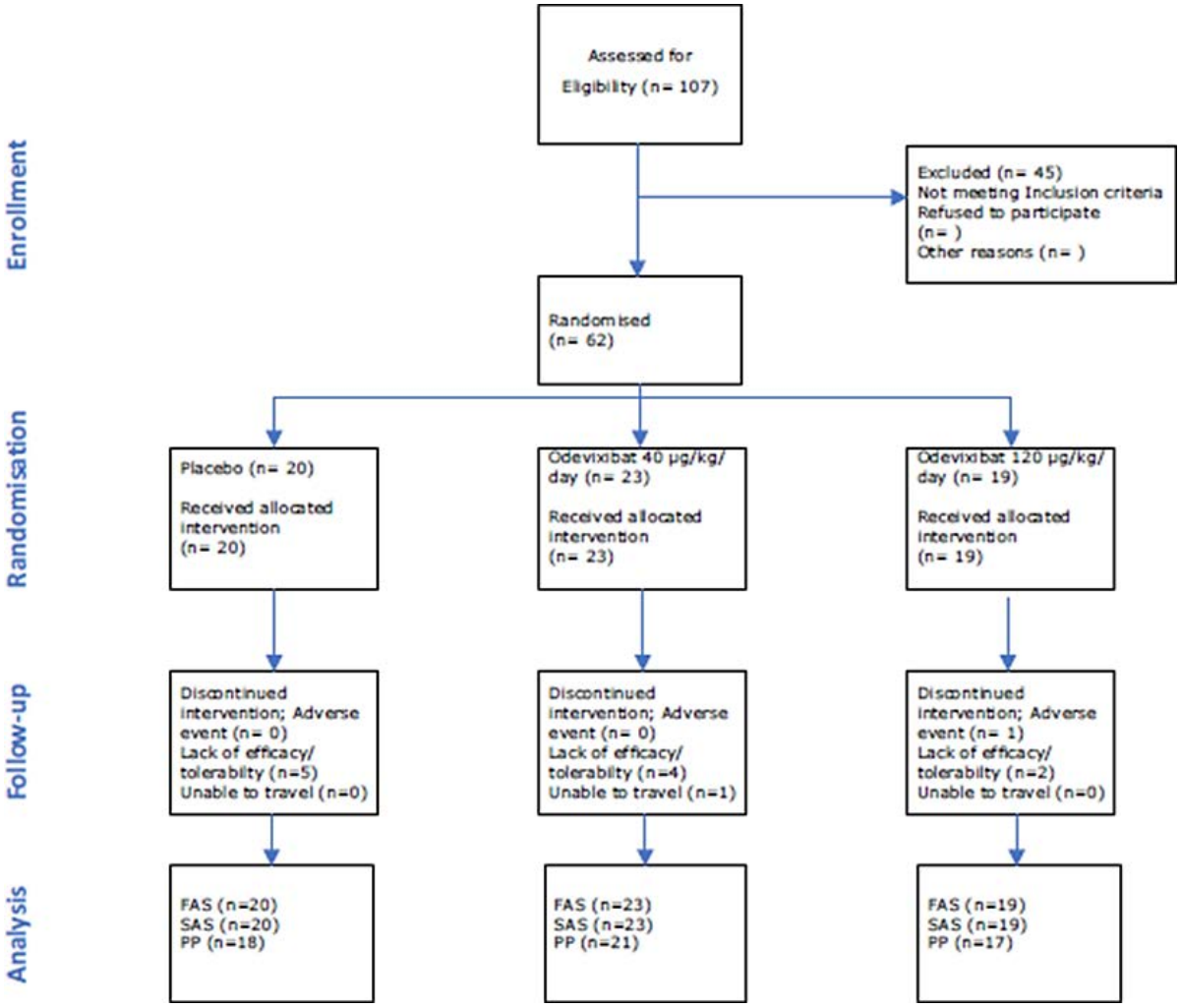
[4] Albireo ObsRO is the sponsor-developed observer reported pruritus outcome reporting tool; Albireo PRO is the related patient-reported pruritus reporting tool, suitable for use in PFIC patients aged 8 years or older. The PRO asked patients about their itching during the day and night-time hours and the ObsRO asked caregivers about the patient's scratching and other related behaviours observed during the daytime and night-time hours. The pruritus assessment was the primary clinical endpoint of the study required by the FDA.

(alone or either). Statistical analysis was performed only if the sample size was ≥ 10 in each treatment group.

Results

A total of 62 study participants were randomised into three treatment groups. Participant flow is summarised in the Figure 1.

Figure 1. Participant flow in study A4250-005.



Within the limits of small participant numbers, demographic and baseline disease data were comparable across the three groups. The mean (±SD) and median ages (years) of participants randomized to 120 µg/kg/day (5.2±4.2y, 4.9y resp) were nominally greater than in the 40 µg/kg/day (3.9±3.7y, 3.2y) and placebo groups (3.8±3.8y, 2.8y). Children aged between six months and five years represented most study participants (75.8% overall), with fewer aged six to 12 years (19.4% overall, 3-5 in each treatment group) or 13 to 18 years (4.8% overall, 1 in each treatment group). Over 80% were Caucasian, and more than half were recruited in Europe (n=35), compared to the United States (n=8) and rest of the world (n=19).

The mean (±SD) and median duration since diagnosis (years) across all groups were 2.9±3.3y and 1.45y respectively. Most participants had PFIC2 (45, 72.6%). Almost all had a reported history of significant pruritus, and almost 90% (n=55) were being treated with UDCA and/or rifampicin for symptoms.

At baseline, SBA 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 (Table 3).

Table 3. Efficacy results for the pivotal study, A4250-005.

Analysis	**Primary Analysis**			
Analysis population and time point	Full analysis set (FAS)			
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	0.0015	0.0174
	Secondary endpoint: Proportion of positive pruritus assessment.	**Comparison groups**	**40 µg/kg/day**	**120 µg/kg/day**
		LS Mean Difference (SE) (Odevixibat - Placebo)[b]	28.23 (9.182)	21.71 (9.892)
		95% CI [b]	(9.83, 46.64)	(1.87, 41.54)
		One-sided Adjusted p-value[c]	0.0019	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 (Odevixibat - Placebo)	0.467	0.287
		95% CI[a]	(0.2290, 0.7045)	(0.0344, 0.5401)
		One-Sided Unadjusted p-value[d]	0.0002	0.0391

CI: confidence interval
a. Miettinen-Nurminen (score) CI is reported adjusting for stratification factors.
b. The analysis was based on an ANCOVA model with rounded AM baseline score, PM baseline score as covariates, and treatment group and stratification factors (PFIC type and age category) as fixed effects.
c. 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.
d. Based on the Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors.

For the primary endpoint, a closed test procedure was used to compare the proportion of patients who responded (the proportion with at least a 70% reduction in SBA concentration from baseline or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks) to odevixibat all doses combined with placebo, and then odevixibat 40 µg/kg vs placebo and odevixibat 120 µg/kg vs placebo. The proportion of responders was significantly greater in both odevixibat-treated groups compared to placebo. Overall, 14 of 42 participants in the combined treatment group (10 of 23 participants receiving 40 µg/kg/day odevixibat and four of 19 participants receiving 120 µg/kg/day) were considered responders, compared to no patient on placebo.

Based on Cochran-Mantel-Haenszel test, adjusting only for stratification by PFIC type, the p-values for the respective comparisons were: combined vs placebo 0.0015, 40 µg/kg/day vs placebo 0.0003 and 120 µg/kg/day vs placebo 0.0174). The results in the FAS were supported in the PP population.

The results of the primary endpoint were supported by the secondary endpoint, the proportion of positive[5] pruritus assessments over the 24-week treatment period based on the ObsRO instrument. The proportion of positive assessments was significantly greater in both odevixibat-treated groups compared to placebo. In the combined treatment group 53.51±5.0% (mean ± SE) of assessments were positive, compared to 28.7±5.2% in the placebo group (p=0.0019). In the 40 µg/kg/day group 58.3±6.2% of assessments were positive (p=0.0016) and in the 120 µg/kg/day group 47.7±8.1% of assessments were positive (p=0.0016).

Other secondary and exploratory endpoints were generally supportive. 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 to placebo. For patients receiving odevixibat, the proportion of SBA 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. Overall, the responsiveness to treatment of patients with PFIC1 was variable. The SmPC and consequently the Australian PI include advice that the efficacy of odevixibat may be reduced in some patients, and therefore response should be monitored and alternative treatment considered if efficacy is not considered optimal after six months continual treatment. Positive effects on pruritus were seen in patients with PFIC1 as well as PFIC2.

Table 4. Descriptive statistics and estimate variability

	Treatment group		
	placebo	40 µg/kg/day	120 µg/kg/day
Number of subjects	20	23	19
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)

[5] A positive pruritus assessment is defined as a scratching score of ≤1 or at least a 1 point drop from baseline on the Albireo PRO (for children older than 8 years) or the Albireo ObsRO score (for children younger than 8 years). The scratching score was calculated based on an algorithm that considered responses to up to 9 questions, which may have required a rating answer or yes/no answer. The final score ranged from 0 to 4, with calculated scores being rounded to the nearest whole number.

	Treatment group		
	placebo	40 µg/kg/day	120 µg/kg/day
APRI score (mean [SE])	0.038 (0.1343)	-0.140 (0.0718)	0.043 (0.2327)

Study A4250-008 was an open-label extension study to evaluate long-term efficacy and safety of 120 µg/kg/day odevixibat in children with PFIC, including two children with benign recurrent intrahepatic cholestasis (BRIC). Enrolments were in two cohorts, Cohort 1 enrolled participants with PFIC1 and PFIC2 who had previously participated in A4250-005, and Cohort 2 enrolled participants with any type of PFIC. The treatment duration was 72 weeks (following an eight week screening period for patients in Cohort 2), with opportunity to continue in an optional extension period, allowing patients to continue on study drug until the drug is commercially available. As of Protocol Amendment 6, patients entering Cohort 2 start treatment at 40 µg/kg/day. Patients not tolerating the 120 µg/kg/day dose after a minimum of one week had the option to down-titrate to 40 µg/kg/day. A total of 114 patients including 56 patients in Cohort 1 and 58 patients in Cohort 2 had received at least one dose of odevixibat in Study A4250-008 at the data cutoff date for the interim report of 31 July 2022. All 114 patients were included in the full analysis set. The interim report supported the findings of the pivotal study, as patients from study A4250-005 who subsequently enrolled in A4250-008 maintained low SBA concentrations for up to 72 additional weeks while taking odevixibat. Furthermore, mean SBA concentrations at 24 weeks, and at up to 72 weeks in patients enrolled in Cohort 2, and in patients who had received placebo in study A4250-005, were significantly reduced from baseline. Fourteen patients in this study underwent surgical intervention (includes 3 patients who underwent biliary diversion surgery and 11 patients who underwent liver transplantation surgery). Five of the 14 patients had their surgery after completing the 72-week treatment period.

The evaluation concluded that odevixibat demonstrated a clear clinically relevant effect on the main symptom of PFIC e.g. reduction of pruritus. In addition, clinically relevant reductions in SBAs were observed. The data did not yet allow a conclusion that odevixibat could contribute to delays in requirement for surgical biliary diversion or liver transplantation, although improvements in serum transaminases and in liver histopathology (not discussed in this summary) were seen. A long term follow up study is intended to address this question.

Safety

The exposure data presented with the initial submission to TGA was based on the 24 week Study A4250-005; and preliminary data from the 72 week extension study A4250-008, which included 53 eligible participants rolled over from Study A4250-005, and a second cohort of 16 patients with PFIC of any type at data cutoff date 15 July 2020. Additional exposure data was provided from participants in dose-finding study A4250-003. An updated summary of safety data included an additional 7 participants enrolled in Study A4250-008 with data cutoff date 4 December 2020.

Based on the original submission across all study participants treated with odevixibat in the Pooled Phase 3 group, the median duration of exposure as of the 4 December 2020 cut-off was

53.1 weeks and ranged from 1 to 128.1 weeks. Overall, 44 (52%) of the 84 patients had received

≥52 weeks of treatment with odevixibat.

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; four patients who received protocol-allowed second courses account for the longer exposure durations. Treatment compliance in this study was 96%.

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 (83% and 84%, 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 21 patients (25%) 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.

A summary of treatment-emergent adverse events (TEAE) in the Phase 3 studies is presented in Table 5. There were no TEAEs of death, the most frequent TEAEs by SOC were gastrointestinal disorders (predominantly diarrhoea and vomiting), infections and infestations (upper respiratory tract infections) and investigations (liver-related including increased bilirubin, ALT, INR). Across all treatment populations, TEAEs assessed as drug-related were reported for 35 (42%) of participants enrolled in A4250-005 or and/or A4250-008, of which none were considered serious.

Table 5. Treatment-emergent adverse events in the Phase 3 studies

	Study A4250-005 (By Treatment)			Studies A4250-005/ A4250-008 pooled[a]	
Patients with Any:	Placebo (N=20) n (%)	40 µg/kg/day (N=23) n (%)	120 µg/kg/day (N=19) n (%)	SCS Data Odevixibat All Doses (N=77) n (%)	120-Day Data Odevixibat All Doses (N=84) n (%)
TEAEs	17 (85.0)	19 (82.6)	16 (84.2)	61 (79.2)	71 (84.5)
Drug-Related TEAEs	3 (15.0)	7 (30.4)	7 (36.8)	32 (41.6)	35 (41.7)
Severe TEAEs	2 (10.0)	1 (4.3)	2 (10.5)	8 (10.4)	8 (9.5)
Serious TEAEs	5 (25.0)	0	3 (15.8)	7 (9.1)	9 (10.7)
Drug-Related Serious TEAEs	0	0	0	0	0
TEAEs Leading to Study Treatment Interruption	1 (5.0)	3 (13.0)	6 (31.6)	17 (22.1)	21 (25.0)
TEAEs Leading to Study Treatment Discontinuation	0	0	1 (5.3)	4 (5.2)	5 (6.0)
Drug-Related TEAEs Leading to Study Treatment Discontinuation	0	0	1 (5.3)	1 (1.3)	2 (2.4)
TEAEs Leading to Death	0	0	0	0	0
Liver-Related TEAEs[b]	4 (20.0)	5 (21.7)	6 (31.6)	25 (32.5)	27 (32.1)
Liver Decompensation TEAEs[b]	0	0	0	1 (1.3)	1 (1.2)
All-Cause Mortality[c]	0	0	0	0	0

AE: adverse event; CRF: case report form; SCS: Summary of Clinical Safety; SUR Safety Update Report; TEAS: treatment-emergent adverse event.

[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.

[b] Liver-related TEAEs and liver decompensation TEAEs were collected and indicated on the AE CRFs.

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

The COR Evaluator noted that it was difficult to separate whether liver-related TEAEs were disease-related or drug-related. Cholestasis and elevated hepatic biochemical parameters, most excursions in ALT, AST, and total bilirubin values were considered by the investigators to be related to the underlying disease. Special attention should be paid to additional monitoring of uptake of fat-soluble food components (among others Vitamins A, D, E, K), interactions with fat-soluble medicinal products, hepatotoxicity, and diarrhoea.

The Evaluator emphasised that the safety database was limited and that further study data were required to establish a robust risk/benefit balance for odevixibat. Risks during pregnancy, breast-feeding and in neonates were unknown.

Additional safety data was provided with the Interim Study report for A4250-008 (31 July 2022 cut-off), but an updated integrated summary of safety was not requested or provided.

The median study drug exposure at data cutoff date for the interim report was shorter in participants in Cohort 2 (59 weeks) compared to 116 weeks in patients in Cohort 1 who had received odevixibat 40 or 120 µg/kg/day in Study A4250-005. Exposure times ranged from a minimum of 4.3 weeks to a maximum of 189.3 weeks. Mean and median exposures were similar (84.2 weeks, 78.6 weeks respectively).

Overall, by the end of July 2022, 103 (92%) of the 112 participants in study A4250-008 (excluding the two individuals with BRIC) had experienced at least one TEAE during the study including 100% of 21 patients who had received 40 µg/kg/day, 100% of 16 patients who have received 120 µg/kg/day, and 95% of 19 patients who had received placebo in Study A4250-005. In Cohort 2, 86% of 56 participants had experienced at least 1 TEAE. Severe events were reported in 13 participants (12%) overall, including one patient who had received odevixibat 40 µg/kg/day in Study A4250-005, one patient who had received odevixibat 120 µg/kg/day in Study A4250-005, one patient who had received placebo in Study A4250-005 and ten patients in Cohort 2.

Regarding TEAE of special interest, eight (7%) participants experienced nine TEAEs of vitamin D deficiency, five (5%) experienced seven TEAEs of vitamin D decreased, four (4%) experienced four TEAEs of vitamin E deficiency, two (2%) patients experienced two TEAEs of vitamin K deficiency and one (1%) patient experienced two TEAEs of vitamin E decreased. The most frequently reported TEAE of interest was vitamin D deficiency. All TEAE reports of fat-soluble vitamin deficiency/vitamin level decreased were mild to moderate in intensity and most events were assessed as unrelated to study drug.

The underlying pathophysiology of PFIC is hepatic. Based on this, hepatic adverse events were reviewed and adjudicated by an independent Drug Safety Monitoring Board (DSMB) for the clinical trial. Only one participant, in Cohort 1, was adjudicated by the DSMB as having a hepatic TEAE (increased ALT and increased total bilirubin) related to investigational product.

TEAEs assessed by the investigators as treatment-related (drug-related) were reported in 36% of the participants. The incidence of treatment-related TEAEs was comparable in patients who had received 40 µg/kg/day (48%), 120 µg/kg/day (56%) and placebo (37%) in Study A4250-005, and in Cohort 2 (25%, noting the shorter duration of exposure in the latter two groups). By SOC, treatment related TEAEs were most frequently reported in laboratory investigations, gastrointestinal disorders, and hepatobiliary disorders. By preferred term the most frequently reported treatment related TEAEs were blood bilirubin increased, diarrhoea and serum ALT increased.

One serious treatment related TEAE was reported, an episode of gastroenteritis in one participant. No treatment related deaths have been reported.

Based on the dossier submitted to the EMA, while treatment-emergent adverse events (TEAE) were very common (affecting over 80% of study participants in high dose (120 mcg/kg) odevixibat, low dose (40 mcg/kg) odevixibat and placebo groups in the pivotal study A4250-005), drug-related TEAEs affected around one in three participants in the active treated groups, of which none were considered severe adverse events, and only one resulted in study treatment discontinuation, in a participant on the higher dose protocol. There were no deaths during any of the reported studies.

The most frequently reported TEAEs (≥10% overall) among patients who received odevixibat, with corresponding incidence for patients who received placebo, were diarrhoea (31% vs 5%), pyrexia (29% vs 25%), upper respiratory tract infection (19% vs 15%), vomiting (17% vs 0%), ALT increased (14% vs 5%), and blood bilirubin increased (12% vs 10%).

The additional information from interim study report A4250-008 (31 July 2022 cut-off) satisfactorily supplemented the safety data. The key findings from this study supported the initial safety profile of odevixibat in patients with PFIC.

Other

Real world evidence (RWE) includes data regarding the usage, or the potential benefits or risks, of a therapeutic good derived from sources other than traditional clinical trials. RWE were included in the submission as post-marketing safety reports, which did not identify any new or concerning safety signals.

The secondary clinical endpoints of pruritus assessments and sleep disturbance assessments (the latter not addressed in this overview) were predominantly based on observer reported outcomes (ObsRO), although in older children a similar patient reported outcome assessment tool (PRO) could have been applied. These tools were developed and validated by the European sponsor of the drug (Albireo) with regulatory input from the EMA utilising the PRIME pathway with scientific advice procedures. This tool has not to date been used in the assessment of any other treatment specific to PFIC or more generally of pruritus.

Risk management plan evaluation summary

Ipsen Pty Ltd submitted EU-RMP version 5.0 (dated 26 June 2023; DLP 31 January 2023) and ASA version 1.0 (dated 31 August 2023) in support of this application. The summary of safety concerns in the ASA is consistent with the EU-RMP and is acceptable from an RMP perspective. The sponsor proposes routine and additional pharmacovigilance activities. Additional pharmacovigilance activities include Extension Study A4250-009 and a Prospective registry-based study. This is consistent with the EU-RMP and is acceptable. Routine risk minimisation activities only are proposed. This is acceptable as odevixibat is an oral medicine which will be prescribed by specialists to a small population and is sufficient to manage the proposed safety concerns.

Safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6.

Table 6. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	ü	ü*	ü	-
Important potential risks	Hepatotoxicity	ü	ü*	ü	-
	Embryofoetal toxicity	ü	-	ü	-
	Interactions with fat-soluble drugs	ü	ü*	ü	-
Missing information	Long-term use	ü	ü*	-	-
	Use during pregnancy and use in breastfeeding women	ü	-	ü	-

*Extension Study A4250-008 and Prospective Registry-based Study A4250-019

Risk-benefit analysis

PFIC is a diagnosis applied to a heterogeneous group of autosomal recessive genetic disorders, all of which result in cholestasis with impaired bile acid secretion and transport. The accumulation of the components of bile within the liver, including bilirubin and bile acids, can lead to portal hypertension, liver failure, cirrhosis, and hepatocellular carcinoma. As hepatic levels of components of bile increase, they are excreted into the systemic circulation leading to the development of jaundice and severe pruritus.

The diagnosis of PFIC is suspected in a child (often newborn) with cholestasis of hepatocellular origin and with rapid appearance of liver failure in most cases. Symptoms develop early, especially in the most common type, PFIC2, with a median age at onset of approximately three months; 78% of patients develop jaundice before 12 months of age.

In Australia there is no pharmaceutical treatment approved for the treatment of PFIC. The therapeutic choices are restricted to nonspecific 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 included off-label use of UDCA, rifampicin, hydroxyzine, antihistamines, and naltrexone, but none of these therapies have proven benefits for the long-term prognosis of patients with PFIC.

During odevixibat treatment, a significant reduction in SBA concentrations was accompanied by a statistically and clinically significant reduction in pruritus at both low and high doses, but

without a clear dose-response effect. Secondary and exploratory endpoints, including improvements in liver transaminases, hepatic function, growth and quality of life measures were supportive. Whether long-term treatment with odevixibat will also delay or diminish the requirement for surgical treatment including biliary diversion and liver transplantation is yet to be seen.

From a safety perspective, at present there is little evidence that odevixibat is likely to have significant toxic effects. However, signals for unexplained cardiovascular abnormalities in animal models suggest potential embryofetal effects which demand further follow up. In the absence of additional information, odevixibat should not be used during pregnancy or breast-feeding.

Conclusions

While some uncertainties remain around the long-term safety of odevixibat, this is a treatment that provides a significant benefit to patients with PFIC, particular PFIC2, with some evidence of efficacy in other forms of PFIC.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register BYLVAY (odevixibat) for the following indication:

> *BYLVAY is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older*

Specific conditions of registration

BYLVAY (odevixibat) is to be included in the Black Triangle Scheme. The PI and CMI for BYLVAY must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The BYLVAY EU-Risk Management Plan (RMP) (version 5.0, dated 26 June 2023 data lock point 31 January 2023), with Australian Specific Annex (version 1.0, dated 31 August 2023), included with submission PM-2023-03749-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Product Information and Consumer Medicines Information

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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