25 July 2024
EMA/372096/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kayfanda

International non-proprietary name: Odevixibat

Procedure No. EMEA/H/C/006462/0000

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
AE	Adverse event
ALGS	Alagille syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASBT	Apical sodium-dependent bile acid transporter
AST	Aspartate aminotransferase
BMI	Body mass index
CaGIC	Caregiver global impression of change
CaGIS	Caregiver global impression of symptoms
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CMH	Cochran Mantel Haenszel
CPP	Critical process parameter
CQA	Critical quality attribute
CSR	Clinical study report
DoE	Design of experiments
DSC	Differential scanning calorimetry
DVS	Dynamic vapour sorption
EC	European Commission
eDiary	Electronic diary
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FT-IR	Fourrier transform infrared spectroscopy
GC	Gas chromatography
GC-HS	Gas chromatography headspace
GGT	Gamma-glutamyl transferase
GIC	Global impression of change
GIS	Global impression of symptoms
GMP	Good manufacturing practice
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
IBAT	Ileal bile acid transporter
ICE	Intercurrent event
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma - mass spectrometry
IPC	In-process control

IR	Infrared
ISE	Integrated summary of efficacy
KF	Karl Fischer titration
LALLS	Low angle laser light scattering
LDPE	Low density polyethylene
LoQ	Limit of quantitation
LS	Least square
MAH	Marketing authorisation holder
MCC	Microcrystalline cellulose
MMRM	Mixed-effect model for repeated measures
NCI	National Cancer Institute
NDMA	*N*-Nitrosodimethylamine
NMBA	*N*-Nitroso-*N*-methyl-4-aminobutanoic acid
NMR	Nuclear magnetic resonance
ObsRO	Observer reported outcome
ODWG	Organ Dysfunction Working Group
OOS	Out of specification
p-C4	Plasma 7α-hydroxy-4-cholesten-3-one
PDE	Permitted daily exposure
PedsQL	Paediatric Quality of Life Inventory
PFIC	Progressive familial intrahepatic cholestasis
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PO-SCORAD	Patient-oriented SCORing for atopic dermatitis
PP	Process parameter
PPS	Per-protocol set
PRO	Patient reported outcome
QbD	Quality by design
QC	Quality control
QoL	Quality of life
QTPP	Quality target product profile
RH	Relative humidity
RoW	Rest of world
SAP	Statistical analysis plan
SCE	Summary of clinical efficacy
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
TGA	Thermogravimetric analysis
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal

UPLC	Ultra-high performance liquid chromatography
US	United States
UV	Ultraviolet
VAS	Visual analogue scale
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ipsen Pharma submitted on 20 November 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Kayfanda, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 9 November 2023.

The applicant applied for the following indication:

Kayfanda is indicated for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older (see sections 4.4 and 5.1).

1.2. Legal basis

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).

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0515/2022 on the agreement of a paediatric investigation plan (EMEA-002054-PIP03-20-M02).

At the time of submission of the application, the PIP EMEA-002054-PIP03-20-M02 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Marketing authorisation under exceptional circumstances

The applicant submitted an application for a full marketing authorisation. However, the submitted data were not considered comprehensive by the CHMP, especially with regard to long-term safety and the applicant was requested during the procedure to discuss a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 as the condition (Alagille syndrome) is so rare, that the collection of comprehensive evidence within a reasonable

timeframe is not possible.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 June 2013	EMEA/H/SA/2645/7/2020/PA/SME/II	Dr Hans Ovelgönne and Dr Andreas Kirisits
19 December 2013	EMEA/H/SA/2645/2/2013/PA/PED/SME/III	Dr Elmer Schabel and Prof. Brigitte Blöchl-Daum
18 May 2017	EMEA/H/SA/2645/3/2017/PA/PED/SME/PR/III	Dr Elmer Schabel and Prof. Brigitte Blöchl-Daum
14 September 2017	EMEA/H/SA/2645/4/2017/PA/SME/PR/I	Dr Hans Ovelgönne and Dr Andreas Kirisits
15 November 2018	EMEA/H/SA/2645/5/2018/PA/PED/SME/PR/II	Dr David Brown and Dr Mogens Westergaard

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the starting material for synthesis.
- Acceptability of the proposed nonclinical programme
- Adequacy of the overall design of the pivotal clinical study to investigate efficacy and safety in patients with Alagille Syndrome: primary and secondary efficacy endpoints, acceptability as single pivotal study, the proposed way of documenting effects on the itching parameter, the proposed evaluation of the colonic release cholestyramine, the proposal to analyse the first secondary endpoint of pruritus as assessed by observer-reported scratching, using the Albireo ObsRO instrument in study A4250-005, and the proposal of a blinded analysis of Albireo ObsRO and PRO eDiary data to estimate a threshold of clinically meaningful change in monthly average.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	20 November 2023
The procedure started on	28 December 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 March 2024
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	28 March 2024

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 April 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	02 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 July 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on	19 July 2024
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 Kayfanda on	25 July 2024
The CHMP adopted a report on similarity on	25 July 2024

2. Scientific discussion

2.1. Problem statement

Claimed therapeutic indication:

Kayfanda is indicated for the treatment of cholestasis and pruritus in Alagille syndrome (ALGS) in patients from birth and older (see sections 4.4 and 5.1).

2.1.1. Disease or condition

Alagille syndrome is a rare, life-threatening, autosomal dominant genetic disorder with a wide variety of clinical manifestations affecting the liver, heart, skeleton, eyes, skin, central nervous system, kidneys, and facial features. In the majority of patients, the symptoms present early, often within the first 3 months of life, with chronic cholestasis and jaundice and/or with cardiac symptoms. Cholestasis is one of the most common features of ALGS, typically presenting with unremitting pruritus. The progressive liver damage due to cholestasis can lead to cirrhosis, with end-stage liver disease requiring transplantation before adulthood. The estimated liver transplant-free survival rate at the age of approximately 18 years for patients with ALGS ranges from 24% to 40% based on data from the Childhood Liver Disease Research Network and the Global Alagille Alliance Study Group.

2.1.2. Epidemiology

There are scarce epidemiological data on ALGS. Many sources give an estimated incidence of 1/70,000 births. This figure is based on a large study from Victoria, Australia (1979) of 790,385 children born in Victoria during the period of 1963-1974 in which 11 children had the condition now called Alagille syndrome, giving an incidence at birth of 1/70,000 or 0.139/10,000 live births. Better diagnostic tools,

including the advent of molecular testing, have indicated that a more accurate incidence is closer to 1/30,000 or a birth prevalence of 0.33/10,000 live births.

In publications presenting results across larger cohorts of patients with ALGS, there is a slight predominance of males (57% to 60%); the disease occurs globally, with cases reported across North and South America, Europe, Africa, Oceania, Asia, and the Middle East.

2.1.3. Aetiology and pathogenesis

ALGS is caused by defects in components of the NOTCH signalling pathway, one of the basic signalling pathways during foetal development, involved in both cell-type specification and organogenesis. In about 90% of patients, the disease is caused by mutations in JAG1, which is one of 5 NOTCH signalling ligands. A smaller number of patients (< 5%) have mutations in the gene for the NOTCH2 receptor. Human embryological studies reveal that JAG1 is highly expressed in the heart, kidneys, blood vessels, skeleton, and eyes. It is also clear in studies in mice that JAG1-NOTCH2 interactions are critical for intrahepatic bile duct development. Consequently, mutations in JAG1 and NOTCH2 affect multiple organs, though the clinical manifestations can vary.

2.1.4. Clinical presentation, diagnosis and prognosis

Table *1* outlines the multiple clinical manifestations that can occur in patients with ALGS, including the approximate frequency of presentation.

Table 1: Clinical manifestation in patients with ALGS

ORGAN SYSTEM	MEAN FREQUENCIES	CLINICAL PRESENTATION
Hepatic	~95%	Cholestasis with elevated serum bile acids, conjugated hyperbilirubinemia, and liver function tests; bile duct paucity; pruritus, hypercholesterolemia/ hypertriglyceridemia; cirrhosis; end-stage liver disease
Cardiac	~90%	Peripheral pulmonary stenosis, pulmonary/aortic stenosis, tetralogy of Fallot, ventricular/atrial septal defect, coarctation of the aorta
Facies	~90%	Dysmorphic features: prominent and broad forehead, deep-set eyes, prominent ears, triangular face with pointed chin, broad nasal bridge
Ophthalmologic	78%-90%	Ocular xanthelasma, posterior embryotoxon
Renal	~74%	Dysplastic kidneys, glomerular mesangio-lipidosis, renal tubular acidosis
Skeletal	~70%	Butterfly vertebrae, hemivertebrae, pathologic fractures of the long bones
Vascular	Up to 15%	Cerebral artery stenosis and aneurysms, Moyamoya syndrome, renal vascular abnormalities, vascular accidents, intracranial bleeding, middle aortic syndrome

ORGAN SYSTEM	MEAN FREQUENCIES	CLINICAL PRESENTATION
Skin	Not Reported	Disfiguring xanthomas, excoriation and scarring due to pruritus
Other	Not Reported	Failure to thrive, growth impairment, fat-soluble vitamin deficiency, immunodeficiency with recurrent infections, pancreatic insufficiency, steatorrhea, delayed puberty, developmental delays, thrombocytopenia, splenomegaly

As the clinical presentation of ALGS is variable, even within patients from the same family with the same genetic mutation, the diagnosis of the disease has traditionally been difficult. With the availability of genetic testing, the clinical diagnosis of ALGS is confirmed, or the diagnosis itself is made, by determination of a mutation within the sequence analysis of JAG1 or NOTCH2.

The abnormalities in the development of intrahepatic bile ducts in patients with ALGS lead to chronic cholestasis, with approximately 95% of patients initially presenting with cholestasis, usually within the first 3 months of life. The cholestasis manifests with jaundice, pruritus, elevations in hepatic biochemical parameters, and potentially disfiguring or disabling xanthomas as a result of cholestasis-induced dyslipidaemia. Cholestasis leads to fat malabsorption resulting in failure to thrive with growth failure, steatorrhea, and fat-soluble vitamin deficiencies leading to an increased risk of bone fracture, bleeding, and other sequelae. As cholestasis progresses, portal hypertension with oesophageal varices and ascites can develop with 40% of patients developing definitive portal hypertension by age 20. Thrombocytopenia is not uncommon as portal hypertension ensues, leading to splenomegaly which can result in splenic sequestration of platelets.

Intractable pruritus associated with ALGS occurs in 45% to 88% of patients, ranging from mild scratching when undistracted to cutaneous mutilation with bleeding and scarring; severe pruritus has been reported in up to 45% of patients. The impact of pruritus for patients with ALGS occurs early in childhood with a median age at onset of 12 months. The precise mechanism of cholestatic pruritus remains unclear, but elevated serum bile acid levels are most commonly considered as direct or indirect pruritic mediators. The pruritus is associated with skin lesions, difficulty with sleep, and mood disturbances.

Xanthomas have been reported in 24% of patients, first manifesting at a median age of 25 months. At the initial onset of the xanthomas, the median serum cholesterol level was 646 mg/dL (16.7 mmol/L). The xanthomas can be disfiguring leading to an impact on activities of daily living and QoL.

Patients with ALGS present with elevations in serum bile acids. These elevations likely reflect accumulation and increased hepatic bile acid levels due to impeded bile flow. Although there are limited data in humans due to the challenges of obtaining hepatic levels of bile acids, animal models, particularly the mouse, have played a significant role in the understanding of bile acid homeostasis and the mechanism of liver injury. Further, in other chronic cholestatic conditions, including biliary atresia and progressive familial intrahepatic cholestasis (PFIC), it has been shown that a reduction in serum bile acid levels is associated with prolonged native liver survival. Elevation of liver enzymes in serum, including ALT and AST, that is a result of damage or destruction of liver tissue or changes in cell membrane permeability, allowing leakage into serum, is also observed in patients with ALGS. The biological variability of levels of ALT within an individual patient can be quite large, even after adjusting for age, varying from 56% lower to 129% higher 95% of the time.

Patients with ALGS also have significant growth impairment. In a study of patients with ALGS who had cholestasis, mean height and weight z-scores were less than -1 across the population. The growth

deficit may be related to fat malabsorption resulting in failure to thrive. Malabsorption of fat-soluble vitamins can lead to other comorbidities, including increased bone fracture risk and bleeding. It has also been postulated that direct effects of decreased NOTCH signalling in the bone may contribute to the increased incidence of fractures in patients with ALGS.

2.1.5. Management

In the EU, maralixibat was approved for "the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older". Other current treatments, target the symptoms of the disease. Symptomatic treatment of pruritus includes off-label use of UDCA, cholestyramine, rifampicin, ondansetron, and/or naltrexone; these agents are only partially effective. However, there here is no authorised pharmacological therapy aimed at correcting the underlying genetic defect in ALGS.

As liver disease progresses and symptoms do not respond to medical management, many patients undergo surgical options. Partial biliary diversion or ileal exclusion to divert recirculation of bile acids between the liver and gastrointestinal tract have been shown to relieve symptoms such as pruritus and xanthomas and improve QoL. This procedure is reported in only about 5% of patients with ALGS; in these patients, reduced survival with native liver was observed. About 60% to 76% of ALGS patients have had a liver transplant by approximately 18 years of age; this procedure is used more often than surgical biliary diversion. In most cases liver transplant procedures were performed due to complications of persistent cholestasis, primarily refractory pruritus in 69% of patients, as well as growth failure (54%), and xanthomas (49%). Other factors reported were bone fractures, refractory fat-soluble vitamin deficiency, liver failure, and the manifestation of portal hypertension. However, liver transplantation is associated with post-operative mortality and requirement for lifelong immunosuppression.

2.2. About the product

Odevixibat (A4250) is a small molecule that acts as a potent, selective inhibitor of the IBAT, alternatively known as the ASBT.

In 2021, odevixibat (tradename Bylvay) was authorised for marketing by the US Food and Drug Administration (FDA) for the treatment of pruritus in patients 3 months of age and older with PFIC and by the European Commission and the United Kingdom (UK) Medicines and Health Care Products Regulatory Agency for the treatment of PFIC in patients aged 6 months and older. The approved starting dose is 40 µg/kg/day; if an adequate clinical response is not achieved after 3 months of therapy, the dose may be increased to a maximum of 120 µg/kg/day.

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 daily basis. Therefore, IBAT is a key regulator of the bile acid pool and an important element in enterohepatic circulation.

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 (Figure 1).

Odevixibat has minimal systemic exposure at therapeutic dose ranges.

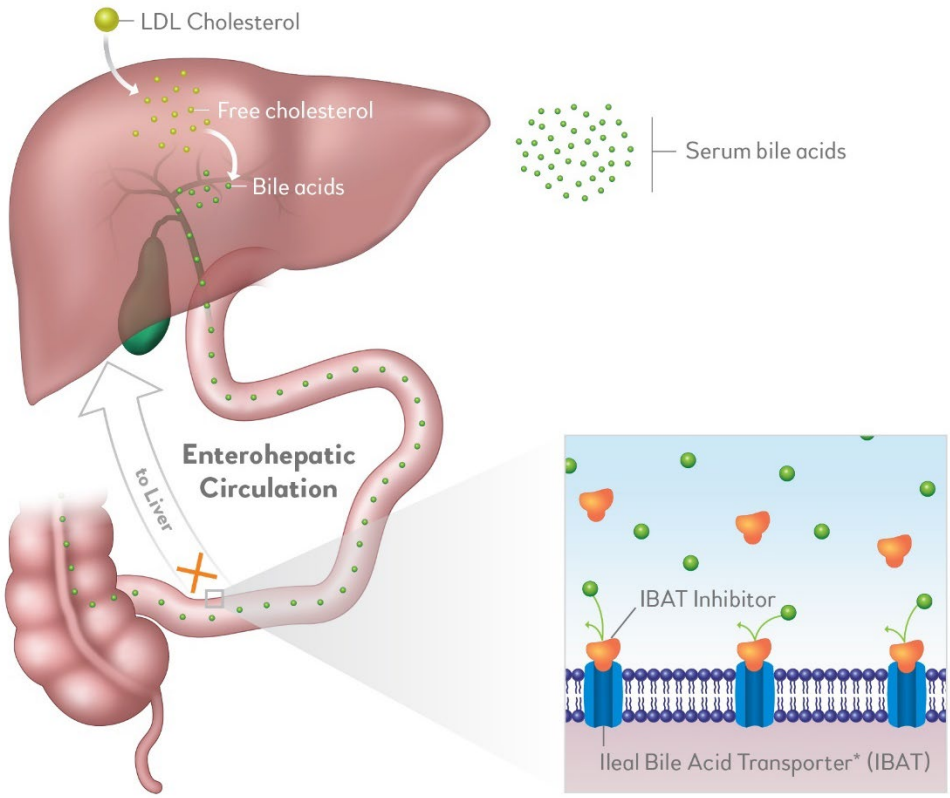


Figure 1: Role of IBAT in the enterohepatic circulation of bile acids

2.3. Type of application and aspects on development

The applicant submitted an application for a full marketing authorisation. However, the submitted data were not considered comprehensive by the CHMP, especially with regard to long-term safety and the applicant was requested during the procedure to discuss a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 as the condition (Alagille syndrome) is so rare, that the collection of comprehensive evidence within a reasonable timeframe is not possible.

2.4. Quality aspects

2.4.1. 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 (E172).

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.

2.4.2. 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:

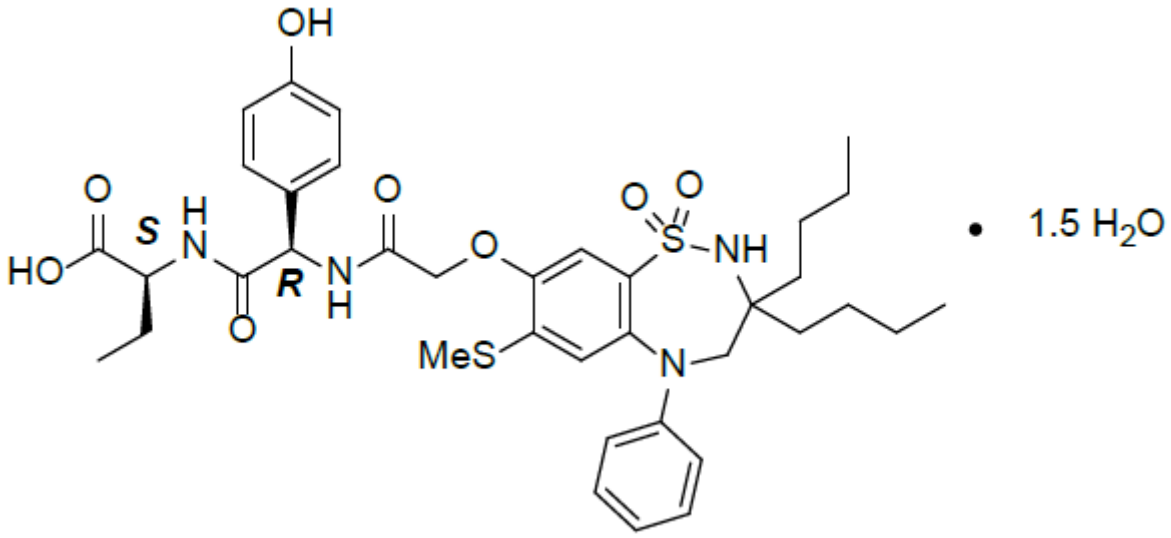


Figure 2: Active substance structure

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 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 synthesised convergently in 6 main steps followed by crystallisation using 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 characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. 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 was 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 non-compendial methods 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 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 (25ºC / 60% RH), for up to 12 months under intermediate conditions (30ºC / 65% RH), and for up to 6 months under accelerated conditions (40ºC / 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 conditions "Do not store above 25 ºC. Store in the original container in order to protect from light."

2.4.3. 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 2: Composition of oral capsules, 400 and 1200 µg

	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 3: Composition of oral capsules, 200 and 600 µg

	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 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 and 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 2.4.1 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. Consequently, 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.

The development of a discriminatory dissolution method for quality control (QC) purposes has been extensively described. 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. The current dissolution method, in conjunction with the totality of existing controls over raw materials, in-process, and finished drug product, is considered to be acceptable as a QC method.

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 (apple sauce, pureed bananas, pureed carrots, vanilla yoghurt, chocolate pudding, oatmeal porridge, and rice pudding) or into liquid (water, apple juice, grape juice, human breast milk, and infant milk formula). The pellet-soft food/liquid contents were gently mixed and incubated over a period of 2 hours under refrigerated (soft foods) or ambient (soft foods and liquids) conditions. No significant differences in assay values were found vs control samples. Visual inspection showed that the sprinkled pellets were still visible and intact for up to 2 hours in each soft food or liquid. This supports the methods of administration described in section 4.2 of the SmPC.

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 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.

Major steps of the manufacturing process have been validated by a number of studies, considering each stage of the process. Process validation of the pellet manufacturing process was performed at commercial scale on 3 consecutive batches of each odevixibat pellet strength (5 mg/g and 15 mg/g). Process validation for capsule manufacture was conducted on 3 consecutive batches of each strength. It has been demonstrated 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). The solvents used in the active substance process could potentially lead to formation of NDMA and NMBA should a nitrosating agent be present. The MAH chose to test for relevant impurities 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 12 production scale batches in total across the different strengths (3 batches of each strength). Samples were stored for up to 36 months under long term conditions (25ºC / 60% RH), for up to 36 months under intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 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. The proposed bracketing approach to test only 8 batches at each timepoint was deemed acceptable, although all batches were tested at 24-, 30-, and 36-month time points. Supportive data from 1 batch of capsules of each strength containing a high crystalline fraction was also provided.

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, but all remained within the proposed specification limits. 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 according to ICH Q1B. 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 36 months with the storage conditions "Store in the original package in order to protect from light" and "Do not store above 25 °C" 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.

2.4.4. 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.

2.4.5. 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.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The applicant submitted pharmacology, PK and toxicology studies in support of this application. A toxicological review and safety qualification of identified drug substance process-related impurities associated with odevixibat was also completed.

No additional non-clinical studies have been performed since the marketing authorisation of odevixibat for PFIC in 2021 (EMEA/H/C/004691/0000).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

2.5.2.1.1. In-vitro

In an *in vitro assay* (study 25881), the inhibition of the human, mouse, and canine ileal (apical) sodium/bile acid co-transporters (IBAT/ASBT) by odevixibat (or AZD8294 / AR-H064974) was tested. In addition, also the specificity of odevixibat for IBAT versus the human liver (basolateral) sodium/bile acid co-transporter and amino acid (α-aminoisobutyric acid) uptake transporter have been tested. All

receptors were transfected to HEK293T cells. The effect of varying concentrations of odevixibat on accumulation of 30 µM of radiolabelled, natural bile acid, glycocholic acid (GCA) was assessed.

Odevixibat was found to be highly specific for the ileal (apical) bile acid transporters with IC50 = 0.13, 0.12, and 1.4 nM for the human, mouse, and canine transporters. Specificity for the human liver (basolateral) sodium/bile acid co-transporter was 700-fold higher, IC50=93 nM. In addition, 3.125, 12.5, and 50 µM odevixibat resulted in 21%, 73%, and 84% inhibition of the sodium-stimulated uptake of 0.5 mM 14C-α-aminoisobutyric acid (AIB), respectively resulting in a Km-value for sodium-stimulated AIB-uptake in the HEK293 cells of 280 µM.

The applicant did not test the specificity for the rat and the rabbit ileal (apical) bile acid transporters, species used for toxicology studies, but based on sequence homology these species seem relevant.

2.5.2.1.2. *In vivo* studies

In study 24546, the effect of four different doses of odevixibat on the intestinal absorption of bile acid, using ^{75}SeHCAT (Tauro-23-[75-Se]Selena-25-homocholic acid) as a tracer was evaluated in female ApoE knockout mice. Doses from 0.01, 0.039, 0.156 to 0.625 µmol/kg odevixibat (that correlates with 7.409, 28.90, 115.58, or 463.06 µg/kg), respectively was administered to 3 mice per dose group, followed by oral administration of ^{75}SeHCAT (0.1 µCi per 0.1 mL per mouse) 30 min. later. The inhibition of odevixibat by the doses mentioned above on intestinal ^{75}SeHCAT absorption was 8%, 30%, 76% and 86%, respectively. The ED50 of the inhibitory effect was estimated to be 0.073 µmol/kg (54.09 µg/kg).

In study 24052-23, the effect of 4 IBAT inhibitors, among which is odevixibat, on cholesterol levels was assessed *in vivo* in ApoE/LDL-receptor double knockout mice (on a C57Bl/6 background) and compared to control (Study 24052 23). Each group consisted of 7 female mice of 25 weeks of age that were orally dosed with 0.625 µmol/kg/day IBAT inhibitor for 8 consecutive days. All IBAT inhibitors, including odevixibat, lower plasma levels of cholesterol. More specific, *odevixibat reduced plasma cholesterol levels by 40% (p=0.001) in ApoE knockout mice. This reduction was due to reductions in VLDL (45% to 61% reduction) and LDL (7% to 24% reduction) but* left the HDL form unaffected (2 compounds among which is odevixibat) or slightly affected (2 other compounds). In contrast, HDL is decreased in the toxicology studies. Plasma levels of triglycerides and ALAT are not affected, whereas the level of bile acid secretion into plasma is increased. It is not clear whether increase in serum bile acid levels is related to odevixibat in general or related to odevixibat treatment in this mouse model specifically. Overall, it can be concluded that all the IBAT inhibitors lower plasma cholesterol for one week treatment in ApoE/LDL-receptor knockout mice, with AR-H064974, odevixibat, being the most efficient. The unchanged HDL levels are contrary to what is observed in the toxicity studies, and the increased serum bile acid levels.

In study 24872, the duration of the inhibition of intestinal bile salts absorption after a single oral dose of 0.625 µmol/kg (463.08 µg/kg) odevixibat (AZD8294) was assessed in vivo in female ApoE knockout mice. Animals were administered by gavage with vehicle (4 groups of 3-4 mice) or odevixibat (4 groups of 3-4 mice) at 1PM, respectively. Both vehicle and odevixibat treated mice orally received a trace amount of bile acid marker ^{75}SeHCAT (0.25mCi/mouse) 0.5, 3, 6 or 10 hrs afterwards and sacrifice followed 24 hr later. The liver/gallbladder and the entire intestine were removed, and the faeces of each mouse during the 24-hour period were collected for body and faecal retention of bile acid marker ^{75}SeHCAT. The inhibiting effect of odevixibat on intestinal bile salts absorption remained at around 80% up to 3 hours after odevixibat administration. Afterwards the inhibition diminishes towards slightly lower that 30% at 10 hours after odevixibat administration.

To address the effect of bile acid depletion in a mouse model of cholestasis (study ARR4250000117), the dose of odevixibat was initially investigated in wild-type male mice of FVB/N background that were 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). The applicant indicated that the study report incorrectly stated the higher dose which was in fact 3-fold lower (0.01% w/w instead of 0.03% w/w). The administered dose level is, therefore, in line with the clinical context. Considering expected daily food consumption and weights for mice the daily dose was estimated at 16 mg/kg with a human equivalent dose (HED) of 1.3 mg/kg which is over 10-fold in excess of the clinical dose of 0.12 mg/kg/day.

Body weight, survival rate, serum liver enzymes or hepatic expression of pro-inflammatory gene tumour necrosis factor-alpha (TNF α) were not affected by odevixibat, excluding direct hepatotoxic effect. However, odevixibat did repress expression of ileal FGF15 and induced hepatic CYP7A1 expression by 2.5 to 3-fold. However, there was no increase in serum total bile acid levels, which might result from increased passive bile acid reabsorption from the colon, and no changes in bile salt export pump (BSEP) expression. The decrease in FGF15 and increase in CYP7A1 expression, is likely to result in increased bile acid biosynthesis, which is also observed in the clinic. It is not clear whether this will be a positive or negative effect.

In the second step the effect of odevixibat mediated bile acid depletion was addressed in male Mdr2-/- mice (n=5, 8 weeks old) receiving 0.01% (w/w) odevixibat in the diet for 4 weeks and compared to control groups (n=5/group) of untreated Mdr2-/- mice and norursodeoxycholic acid (norUDCA)-fed Mdr2-/- mice dosed at 0.5% (w/w), functioning as a positive control group. Survival and serum hepatic enzyme levels were assessed after 2 weeks or 4 weeks of feeding.

After 4 weeks:

A) liver weight/body weight ratio was increased (33%) in the norUDCA animals and decreased (33%) in the odevixibat-treated animals.

B) Serum ALT levels were significantly decreased in norUDCA and odevixibat groups compared to untreated controls.

C) Aspartate aminotransferase (AST) levels increased 5-fold in untreated controls, but only 2- to 3-fold in the norUDCA and odevixibat animals.

D) Alkaline phosphatase (ALP) levels decreased significantly in the odevixibat animals.

E) Levels of bile acids and bilirubin were similar between untreated control and odevixibat animal but contrasted to norUDCA animals (pos. control) with higher levels of serum bile acids (9-fold higher) and bilirubin (3-fold higher). Gallbladder size was only increased in norUDCA animals. Odevixibat reduced liver/body weight ratios, *serum markers of liver damage and cholestasis in Mdr2-/- mice*, especially when compared with norUDCA treated animals.

Odevixibat seems to have similar, maybe slightly better effect in terms of decreasing the liver enzymes as compared to norUDCA treated animals, but does not show the drawbacks from that therapy, namely, increased liver weight relative to body weight, increased serum bile acids and bilirubin levels and increased size of the gall bladder in Mdr2-/- mice. Although it is unclear why the effect of bile acid depletion is addressed in Mdr2-/- mouse model, the model likely represents one the types of the disease, type 3 that is related to deficiency in Abcb4 functioning. In a study from Baghdasaryan et al., (2016) the pharmacological effects of bile acid-lowering therapy of IBAT inhibitors were evaluated in this model and were translated to human.

As IBAT inhibitors may cause diarrhoea at higher doses, the effect of odevixibat on faeces of 4 dogs was evaluated in study 74519 upon oral administrated with 30 mg/kg odevixibat in combination with

rectal (intracolonic) administration of Cholestyramin suspension (to chelate bile acid from intestine) or exploration gel (placebo) administered as a single dose on 2 occasions (first 12 mL and the second time 22 mL) in a cross-over study design, four days apart. Animals that rectally received a placebo showed 1-6 episodes of soft to watery faces. Animals treated rectally with cholestyramine suspension to sequester the bile acid in the intestine, showed normal consistency in stools, except for one animal that had 2 times diarrhoea on day 1 after the rectal administration of 12 mL Cholestyramin suspension.

Odevixibat administration to dogs resulted in several episodes of diarrhoea in dogs, which could be treated by rectal administration of a suspension 22 mL (which appeared to be more effective than 12 mL) Cholestyramin suspension to sequester the bile acid from the intestine.

A charcoal propulsion test in the rat after single oral administration of odevixibat was considered part of primary pharmacology but is also regarded as a safety pharmacology study and was therefore conducted in accordance with ICH S7A and in GLP compliance, which is agreed. In study AA19205 the effect of odevixibat on total intestinal transit was examined in the conscious rat following oral administration of 1, 10, or 100 µmol/kg or 0.74, 7.41, or 74.09 mg/kg odevixibat (Study AA19205). A control group receiving vehicle and a group receiving 20 mg/kg reference item (morphine, SC administered) serving as positive control, were included. A charcoal meal was provided 70 minutes after administration of odevixibat and 45 min after administration of the reference item.

Odevixibat at the dose levels of 1, 10 or 100 µmol/kg (or the vehicle) administered orally did not have any significant effect on the total length of intestinal tract of male Wistar rats, nor did odevixibat significantly alter intestinal transit of conscious male Wistar rats twenty minutes after administration of a charcoal test meal (compared to vehicle-treated animals). The positive control, Morphine administered subcutaneously (20 mg/kg), did significantly delay intestinal transit of male Wistar rats twenty minutes after administration of a charcoal test meal (compared to vehicle-treated animals).

2.5.2.2. Secondary pharmacodynamic studies

To investigate whether odevixibat may also affect other enzymes, the bio-selectivity of odevixibat was tested in a limited panel of 17 enzyme and binding assays along with 2 tissue models provided by MDS Pharma Services, Taiwan. Not all enzymes were human enzymes (also from rat, mouse, and guinea pig) and the tissue models were derived from guinea pig, but it is considered that the chosen enzymes and the chosen tissue are all relevant for estimation the risk for secondary pharmacology of odevixibat in human.

The test was conducted with 1 µM odevixibat. It is considered that this is sufficient to assess secondary effects on enzymes of transporters that will only be exposed after low systemic exposure. However, whether it is sufficient to assess secondary effects on enzymes locally in the gut is not known. The local concentration has not been measured.

Odevixibat at 1 µM showed 66% inhibition of Protein Serine/Threonine Kinase, ERK2 (mouse recombinant enzyme) 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 re-tested at 0.1 to 10 mM in the ERK2 assay, no significant effect (>50%) was detected at any concentration, according to the applicant. However, it has to be noted that the dose response curve seems to have a bell-shape and the middle-tested concentration (1 µM) showed 49% inhibition. It is regarded that 49% is just beneath the border of 50% inhibition. Thus, the ERK2 inhibition is not regarded irrelevant. It is not clear what the local concentration is of the compound and whether it can enter the epithelial cells lining the gut. Further studies are, however, not deemed necessary given that

systemic exposure is low. Furthermore, long-term non-clinical studies, such as the rat carcinogenicity study, are more relevant for the risk estimation of GI toxicity.

2.5.2.3. Safety pharmacology programme

2.5.2.3.1. In vitro

Both odevixibat and AR-H064965 (another potential IBAT inhibitor) did not affect hERG channel activity at an unbound concentration of 1 µM (740.9 µg/L). It was noted in the report that the study was conducted in a GLP compliant facility but that the claim of compliance was not made. Therefore, this is not considered a GLP-compliant study. No effects on the hERG channel were seen in the assay at 1 µmol/L which based on the clinically measured odevixibat levels, and corrected for protein binding, is a concentration 100,000-fold higher than that seen clinically. Therefore, whilst no formulation analysis has been performed and the hERG assay was not GLP compliant, when taken in the context of this data and the absence of effects on ECG parameters in studies in dogs, these deficiencies can be accepted.

2.5.2.3.2. Rat

The potential for an effect of odevixibat on spontaneous locomotor activity was investigated in rat (8 animals per group) following a single oral administration of 0.741, 7.41, or 74.09 mg/kg odevixibat. Vehicle and Chlorpromazine (20 mg/kg) treatment groups were included in the study as negative and positive control respectively, providing the expected results and thus proving the validity of the used method. The absence of odevixibat in plasma samples from the vehicle treated group was confirmed. Based on the study data, a single oral dose of odevixibat of 1, 10, or 100 µmol/kg (0.741, 7.41, or 74.09 mg/kg) had no adverse effects on the spontaneous locomotor activity of animals at 1, 2, 6, and 30 hours post-dosing. Therefore, the no-observed-effect level (NOEL) in this study was considered to be ≥100 µmol/kg (74.09 mg/kg), the highest dose tested.

The potential for an effect of odevixibat on motor coordination by assessing performance on the rotarod, was investigated in rat (10 animals per group) following a single oral administration of 0.741, 7.41, or 74.09 mg/kg odevixibat. Vehicle and Chlorpromazine (10 mg/kg) treatment groups were included in the study as negative and positive control respectively, providing the expected results proving the validity of the used method. The absence of odevixibat in plasma samples from the vehicle treated group was confirmed. Under the experimental conditions adopted, odevixibat had no statistically significant effect on motor coordination 1, 2, 4, 6 or 24 hrs after odevixibat administration up to 74.09 mg/kg. Therefore, the no-observed-effect level (NOEL) in this study was considered to be ≥100 µmol/kg (74.09 mg/kg), the highest dose tested.

The potential of odevixibat to affect neuro-behavioural effect and body temperature was evaluated in rat (8 per group) following a single oral administration of 0.741, 7.41, or 74.09 mg/kg odevixibat. Vehicle and Chlorpromazine (20 mg/kg) treatment groups were included in the study as negative and positive control respectively, providing the expected results proving the validity of the used method. The absence of odevixibat in plasma samples from the vehicle treated group was confirmed. Odevixibat had no effect on body temperature. Odevixibat had no adverse neuro-behavioural effect at any dose level tested. The occasional noted statistically significant intergroup differences in some neuro-behavioural parameters were not considered odevixibat related because of lack of dose-response or consistency, none were considered likely to be attributable to test-article administration. Based on the study data, the NOAEL was considered to be ≥100 µmol/kg (74.09 mg/kg) by the oral route.

The potential of odevixibat to affect blood pressure and heart rate was assessed by telemetry in six conscious normotensive rats that all received an administration of vehicle, 0.741, 7.41, or 74.09 mg/kg (equivalent to 1, 10, or 100 µmol/kg) odevixibat and positive control, minoxidil (10 mg/kg) in that respective order. The absence of odevixibat in plasma samples from the vehicle treated group was confirmed. A dosage dependent increase in plasma drug concentrations was seen across the odevixibat dosage range tested. Odevixibat at doses of 1, 10, and 100 µmol/kg did not induce any statistically significant change in arterial blood pressure and heart rate (collected from both blood pressure and ECG signals) during a 24-hour period of measurement after dosing in conscious normotensive rats, whereas minoxidil, induced, as expected, a long-lasting hypotension associated with a marked tachycardia. The NOEL of odevixibat on arterial blood pressure and heart rate in conscious normotensive rats was considered to be ≥100 µmol/kg (74.09 mg/kg) by the oral route.

The potential of odevixibat to affect respiratory function (respiratory rate; peak inspiratory and peak expiratory flows; inspiration and expiration times; airway resistance; tidal volume; and minute volume) was assessed using whole-body plethysmography in conscious rat (8 animals/group) following a single oral administration of 0.741, 7.41, or 74.09 mg/kg odevixibat. Vehicle and carbamylcholine (30 mg/kg) treatment groups were included in the study as negative and positive control respectively, providing the expected results proving the validity of the used method. The absence of odevixibat in plasma samples from the vehicle treated group was confirmed. A dosage dependent increase in plasma drug concentrations was seen across the odevixibat dosage range tested. Odevixibat did not induce any pharmacologically relevant change in respiratory parameters (respiratory rate; peak inspiratory and expiratory flows; inspiration and expiration times; airway resistance; tidal volume; and minute volume) during a 4-hour period of measurement after dosing in conscious rats. A statistically significant and delayed decrease in inspiration time was observed at the dose of 1 µmol/kg at 240 minutes post-dosing, which was not considered pharmacologically relevant due to absence of dose dependency. The NOEL of odevixibat on respiratory parameters in conscious rats was at least 100 µmol/kg (74.09 mg/kg) by the oral route.

The potential of odevixibat to affect urinary output, urinary electrolyte balance, and glomerular filtration rate (creatinine clearance) was evaluated in rat (8/group) with saline following a single oral administration of 0.741, 7.41, or 74.09 mg/kg odevixibat. Vehicle and labetalol (10 mg/kg) treatment groups were included in the study as negative and positive control respectively, providing the expected results proving the validity of the used method. The absence of odevixibat in plasma samples from the vehicle treated group was confirmed. A dosage dependent increase in plasma drug concentrations was seen across the odevixibat dosage range tested. Odevixibat had no statistically significant effect on urine output, urinary pH, electrolyte balance, or glomerular filtration rate in the rat with a saline overload at any dose level tested. Therefore, the NOEL was ≥100 µmol/kg (74.09 mg/kg) by the oral route in this study.

2.5.2.3.3. Dog

The potential for odevixibat to affect haemodynamic was addressed in the anaesthetised dog with halothane. Twelve beagle dogs (6 males and 6 females weighing between 10.0 kg and 13.1 kg on the day of the study) were assigned into two groups. A control group (group 1) was dosed with vehicle (mannitol solution for infusion 50 mg/mL) and another group (group 2) was dosed with odevixibat at 3 increasing doses (0.001, 0.01, and 0.1 µmol/kg [0.741, 7.41, or 74.09 µg/kg]). Odevixibat at doses of 0.001, 0.01, and 0.1 µmol/kg (0.741, 7.41, or 74.09 µg/kg) did not cause statistically significant changes in cardiovascular parameters assessed (haemodynamic parameters and PR, QRS, QT, as well as QT interval duration corrected for heart rate using Fridericia's formula or Sarma's method and QT interval duration during pacing at 150 and 200 beats/minute) or on arterial blood gas parameters. The

absence of any effect on cardiovascular function in anaesthetised dogs, resulted in a NOEL of odevixibat on cardiovascular parameters of at least 0.1 µmol/kg (74.09 µg/kg) when intravenously infused in the anaesthetised dog.

2.5.2.4. Pharmacodynamic drug interactions

In the presence of a clinical study to the co-administration of odevixibat and bile acid sequestrants, non-clinical studies to address a potential pharmacodynamic interaction can be waived for odevixibat.

2.5.3. Pharmacokinetics

2.5.3.1. Analytical methods

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, 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 non-selective 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.

2.5.3.2. Absorption

2.5.3.2.1. In vitro

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.

2.5.3.2.2. Mouse Pharmacokinetics

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. Elimination half-life was between 1.9 and 4.5 h. No accumulation was observed after repeated dosing. No gender differences were observed.

2.5.3.2.3. Rat Pharmacokinetics

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 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 increase in dose. The increase in Cmax was also less than proportional to the increase in dose for 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 as well as AUC) were observed in both males and females at the low dose (12-50x exposure at day 1 and day 177), though this was only at 8-hour and 24-hour post-dose. Without these timepoints, the concentration-time curve of day 89 looks similar to those of day 1 and day 177. For the other dose groups and timepoints, accumulation was minimal to low (0.8-4.9). Elimination half-life was between 5 and 11 hours.

2.5.3.2.4. Dog Pharmacokinetics

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 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. 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.

2.5.3.2.5. Marmoset Pharmacokinetics

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.

2.5.3.3. 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 non-clinical 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 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 quantitative whole-body autoradiography (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.

2.5.3.4. 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 assumes 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 is not investigated.

2.5.3.5. 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 parent compound.

2.5.3.6. Pharmacokinetic drug interactions

The results of the *in vitro* studies on the drug interaction potential of odevixibat have been evaluated in the clinical assessment report.

2.5.3.7. Exposure in Safety Pharmacology Studies

In safety pharmacology studies, odevixibat was 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.

2.5.3.8. Exposure during reproductive and developmental toxicology studies

In an embryo-foetal development (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 pre- and post-natal development (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.

2.5.3.1. Juvenile toxicology studies

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, probably due to the immature metabolism in juveniles.

2.5.4. Toxicology

2.5.4.1. 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 interpretation of the studies is difficult due the lack of a control group and small number of animals. The toxicity profile of odevixibat is discussed in the repeated dose toxicity section.

Table 4: Single dose toxicity studies

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/kg/day)	**Exposure**		**Major (alt. Salient) findings**
			Cmax xg/ml	AUC xg/ml/h	
Single-dose toxicity studies (MTDs highlighted)					
CD-1 Mouse Oral gavage GLP (0153LM)	5 males	2000 mg/kg	N.D.	N.D.	Diarrhoea, transient BW loss at day 2
Han:Wistar Rat Oral gavage GLP (0662LR)	5/sex	2000 mg/kg	N.D.	N.D.	No major findings

2.5.4.2. Repeat dose toxicity

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

Two studies in mice of up to 13 weeks were performed to establish the dose for the subsequent mouse carcinogenicity study. There were no findings in female mice at doses up to 300 mg/kg/day. The high dose in males was less well-tolerated, with 4 mortalities due to treatment, and mainly GI tract adverse findings. Decreases in liver and gallbladder weight was also seen in the low dose males, however no macroscopic correlate was seen at this dose and therefore this is not considered toxicologically significant. Due to the adverse effects in males at 300 mg/kg/day, the NOAEL is set at 100 mg/kg/day, which results in exposure well above the maximal clinical exposure, with an exposure margin of at least 54.

A 7-day rat study was performed to investigate liver enzyme induction, of which there was no evidence up to the high dose of 1000 mg/kg/day. A 5-day rat study was performed to compare intestinal toxicity of odevixibat with another IBAT inhibitor, at doses up to 200 mg/kg/day. No intestinal toxicity was observed for either compound. The pivotal rat study of 26-weeks duration used doses of up to 300 mg/kg/day, while in a shorter 28-day study 2000 mg/kg/day was the high dose. Some minor changes of decreases in serum protein, glucose, calcium, and cholesterol were seen in the long-term study which could all be due to the high burden on the GI tract or secondary to the pharmacological effect of this mainly locally acting product. Other haematology findings were noted in the 28-day study, but since these are not seen in the long-term study they are considered of little relevance. Unlike mice, rats did not suffer from GI tract toxicity, but did show a decreased liver weight. Due to the lack of adverse effects, the NOAEL is the high dose of 300 mg/kg/day resulting in a safety margin of 86 and 162.

Dogs were administered odevixibat up to 39 weeks. The pivotal 39-week study was dosed up to 150 mg/kg/day, and the 13-week study up to 300 mg/kg/day. Main findings in the dogs were GI tract related (vomiting and diarrhoea), or due to the pharmacological effect (decreased cholesterol, LDL, HDL, gall bladder epithelial hyperplasia and vacuoles). However, a further finding that is not explained is a decrease in spleen weight 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. Whether this also occurs after 13 weeks of treatment is not known, since spleen weight was not measured in this study. The lack of dose-response, high inter-animal variation, lack of any macroscopic or microscopic correlate, and spleen weights within the historical control range all point to a non-test article-related finding.

Both in dogs and rats, there was a decrease in HDL levels. Although this is probably related to the pharmacological effect of odevixibat, it can be considered as adverse.

There were no effects on the cardiovascular system in dogs when tested in electrocardiograms after 13 weeks of treatment of up to 300 mg/kg/day odevixibat, with an exposure 2-fold higher than maximal clinical exposures.

A dose range study was also conducted in marmosets, with doses up to 259 mg/kg/day for 7 days. It was concluded that due to GI-tract effect and subsequent weight loss the high dose might be too high for long-term testing. However, the marmoset was not further used for toxicity testing of odevixibat.

In conclusion, odevixibat was well-tolerated in general in mice, rats, and dogs. Toxicity target organs were GI tract in mice and dogs, and spleen in dogs. In rats, no target organs were identified. Other effects were related to the pharmacological action of odevixibat as an IBAT inhibitor.

Table 5: Pivotal repeat-dose toxicity studies

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure**		**Major findings & NOAEL**
			Cmax ng/ml	AUC ng/ml/h	
Repeat-dose toxicity studies (NOAELs highlighted)					
CD-1 mice 13 weeks Oral gavage GLP (TEA0013)	12/sex/dose 18/sex/dose for TK	0	-	-	≥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) **NOAEL: F: 300, M: 100**
		10	M: 53.2 F: 38.4	M: 209 F: 256	
		100	M: 254 F: 198	M: 1440 F: 1350	
		300	M: 476 F: 527	M: 2760 F: 8860	
Wistar rat	12/sex/dose	0	-	-	

26 weeks Oral gavage GLP (TEA0001)	9/sex/dose for TK	10	M: 27.9 F: 23.8	M: 230 F: 311	≥10: ↓ glu (M), ↓ total protein/albumin, Ca (F), ↓ liver weight (M) ≥100: ↓ total protein, Ca, HDL (M) **NOAEL: 300**
		100	M: 63.9 F: 160	M: 680 F: 992	
		300	M: 464 F: 362	M: 4040 F: 2150	
Beagle dog 39 weeks + 4 weeks recovery Oral gavage GLP (8348308)	6/sex ctrl and high dose 4/sex low and mid dose 2/sex ctrl and high dose for recovery	0	-	-	≥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%) **NOAEL: <3**
		3	M: 1.34 F: 1.32	M: 10.2 F: 5.28	
		30	M: 23.6 F: 14.7	M: 32.1 F: 60.2	
		150	M: 44.6 F: 46.5	M: 91.1 F: 120	

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

Table 6: Supportive repeat-dose toxicity studies

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

2.5.4.3. Genotoxicity

Odevixibat was tested in a standard battery of in vitro and *in vivo* genotoxicity testing. All tests were negative. *In vivo* exposure was demonstrated by kinetic data. Odevixibat has no genotoxic potential.

Table 7: Overview of genotoxicity studies

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	Rat, micronuclei in bone marrow	2000 mg//kg/day (twice) 7 males/dose	Negative

Chromosomal aberrations *in vivo* GLP			

2.5.4.4. Carcinogenicity

Carcinogenicity of odevixibat was tested in a 104-week rat and 104-week mouse study 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. According to the CRO, 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 aging animals and thus not related to treatment. The observed non-neoplastic lesions in rats included increased incidence of urothelium hyperplasia in both sexes and increased incidence of basophilic foci of alteration in females starting from 10 mg/kg/day, as well as biliary hyperplasia, biliary cysts, and liver centrilobular hyperplasia in high-dose females. Both lesions showed dose-dependent increase in incidence and/or severity and are considered treatment-related. However, as these effects occurred at exposure levels significantly exceeding the anticipated human exposure, were not accompanied by concomitant changes in clinical chemistry, did not progress to neoplastic lesions and had no effect on survival or overall well-being, they are not considered clinically relevant. In mice, an increased incidence of gall bladder cystic hyperplasia and increased basophilic amorphous content was seen in both sexes, resulting in statistically significant trends for both effects. These changes are consistent with pharmacological effect of odevixibat and are not considered to represent a neoplastic risk.

Table 8: Overview of carcinogenicity studies

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).

2.5.4.5. Reproductive and developmental toxicity

2.5.4.5.1. Fertility and early embryonic development

In the pivotal GLP-compliant study with rats (AB21662) dosed up to 1000 mg/kg/day, the only observed effect on reproduction was a higher pre-implantation loss seen in both the control group and the treated groups compared to historical controls (21.5%, 12.87%, 12.71 and 14.13% vs. 3.4-11.3% in historical controls). However, as the effect was seen also in controls, and in the absence of the effects on the mean number of corpora lutea and number of implantations (corpora lutea: 14.4, 14.2, 13.6, 14.3; implantations: 11.7, 12.3, 12.1 and 12.5) this was considered a chance finding. Based on the results of the study, odevixibat does not show adverse effects on fertility and early embryonic development. The NOAEL for reproductive toxicity is the highest tested dose of 1000 mg/kg/day.

No information on AUC was provided, but the reference was made to the 6-month repeated dose toxicity study (TEA0001) in which AUC0-24 was 4040 and 2150 ng x h/mL in males and females, respectively, after 26 weeks of dosing with 300 mg/kg/day. Accumulation ratios for odevixibat were not significant (see TEA0001), varying between 0.8-3.0 between day 1 and day 177 (26 weeks). This suggests that no significant difference would be expected in AUC0-24 for a shorter treatment duration. As the expected exposure in the study would be clearly significantly higher than the intended exposure levels in humans, and no adverse effects were seen at the highest tested dose, the lack of information on the AUC is not considered to affect the reliability of the study.

2.5.4.5.2. Embryo-foetal development

Rat

In a dose-range finding (DRF) study (AB21160) with rats, the NOAEL for maternal and developmental toxicity was the highest tested dose of 1000 mg/kg/day. Clinical signs were limited to pale faeces noted between GD12 and GD18 in 2 high-dose females. A slightly higher mean post-implantation loss in the high dose group (15.81% vs. 7.43% in controls) was caused by a single female with 4 early resorptions (8 implantations, 50% implantation loss) and considered incidental, in view of the absence of the same trend in other high-dose females and as there was also one female with 4 early resorptions in controls. Pre-implantation loss was also higher in the 1000 mg/kg/day group (23% vs. 5.68% in controls, and outside the historical control range (mean 7.4%)), but this was again mostly caused by a single female with unusually high number of corpora lutea (19) and only 8 implantations (pre-implantation loss of 57.9%) and considered incidental.

In a pivotal Segment II EFD study with pregnant rats dosed up to 1000 mg/kg/day from GD6 to 17, a slight, but statistically significant, reduction in maternal body weight gain was seen in all dose levels from GD6 to GD9, correlated with the dose-dependent reduced mean food consumption. Recovery was seen afterwards with the terminal body weights similar among all groups; however, lower food consumption persisted throughout the treatment at 1000 mg/kg/day. Isolated findings of external, visceral, and skeletal malformations were considered not related to treatment in view of the absence of the dose-response and as the findings were not consistent between the foetuses. The higher incidence of delayed ossification of several bones (i.e. squamosal, metacarpal, sternebrae and caudal vertebral arches) and thick ribs at 1000 mg/kg/day as compared with the concurrent control and historical control data, is considered related to odevixibat treatment; however, the necropsy was performed on GD20 instead of GD21. As ossification depends on the gestational age of the foetus, changing dramatically near term, and considering that no effects were seen on the bones that are normally well ossified in the term foetus, the observed effects are likely transient in nature and not representative of a permanent structural change. Therefore, they were considered to be non-adverse.

Rabbit

In a pre-DRF study with non-pregnant rabbits treated with 100, 300 and 200 mg/kg/day odevixibat with wash-out periods, body weight loss was noted following administration of 100 and 300 mg/kg/day. Weight loss was also seen in one female treated with 100 mg/kg/day for one week. The dose level of 150 mg/kg bw/day was chosen for the DRF study in pregnant rabbits to try to induce clear but tolerable maternal toxicity.

In the subsequent DRF study with pregnant rabbits, severe maternal toxicity was seen at 150 mg/kg/day, with 3 out of 6 females sacrificed for humane reasons on GD 24. A severely decreased food consumption was seen for these females during the dosing period with no recovery afterwards (GD20-24), with a consequent body weight loss of 9% and reduction/absence of faecal output. These females were also found to have undergone a total litter resorption (100% post-implantation loss for 2 females) or early resorptions (6 out of 13 implantations for the 3rd female). On gross necropsy the findings were limited to pale liver with mottled appearance.

Clinical signs were seen at all dose levels and mainly consisted of decreased faecal output, correlated with decreased food consumption during the dosing period. Body weight losses were seen at all dose levels during GD6-9; that did not recover in some animals of the mid- and high dose groups post-dosing (GD20-24). Post-implantation loss was significantly increased at 150 mg/kg/day (out of 3 sacrificed females, 2 with complete litter resorptions and 1 with 6 early resorptions; out of the 3 remaining females, one with 2 late resorptions). There were 2 (2), 5 (3) and 2 (2) foetuses (litters) with hyperflexion of forepaw(s) in the low, mid-, and high-dose groups, in comparison to none in controls. As the incidence of this malformation exceeded historical control value (4.7%, 8.2% and 6.3%, resp., vs. 0.57% in historical controls), the relationship with the test substance cannot be excluded. Based on severe toxicity seen at 150 mg/kg/day the highest dose level for the subsequent pivotal study was chosen to be 100 mg/kg/day.

In a pivotal Segment II study (AB21159) with rabbits treated with 10, 30 and 100 mg/kg/day odevixibat during GD6-19, two females of the mid- and high-dose were sacrificed in extremis¬ after aborting/delivering early on GD 27 and 29 of gestation. Both females showed severe body weight loss and reduced food consumption prior to aborting/delivering early. Maternal toxicity was seen at all dose levels, consisting of reduced faecal output and a dose-related mean body weight loss during GD6-9. This correlated with the reduced food consumption which persisted until GD20 in the high-dose animals. One female at 100 mg/kg/day had 15 early resorptions, considered to be incidental by the CRO, which resulted in higher overall post-implantation loss at this dose level. However, as in the DRF study at a dose level of 150 mg/kg/day complete or partial litter resorption was seen in 4/6 females,

the relationship with the treatment cannot be excluded. There were 2 (2), 2 (1) and 3 (3) foetuses (litters) with hyperflexion of forepaw(s) in the control, 10 and 30 mg/kg/day groups, respectively, compared with none in the 100 mg/kg/day group. This finding was considered incidental by the study director, as it is known to occur spontaneously in this rabbit strain (historical control data: 0.19-0.57%). However, the same findings were reported in the dose-range finding study, and the observed incidences in the Segment II study exceeded the historical control values (1.2% and 1.3% at low- and mid-dose, respectively). Thus, the relationship with the treatment cannot be fully excluded. SmPC 5.3 informs the prescriber accordingly that in pregnant New Zealand White rabbits, early delivery/abortion was observed in two rabbits receiving odevixibat during the period of foetal organogenesis at an exposure multiple of ≥ 1.6 of the anticipated clinical exposure (based on total plasma odevixibat AUC_{0-24}). Reductions in maternal body weight and food consumption were noted in all dose groups (transient at the exposure multiple 0.5 of the anticipated dose).'

There were 2 (2) and 1(1) foetuses(litter) in the control and low-dose group with neural tube defects that were considered vehicle-related by the CRO. However, as these effects were not seen at mid- and high-dose levels, they are rather regarded to be spontaneous in nature.

There were 2 (2), 3 (2) and 2(2) foetuses (litters) with cardiovascular defects (primarily five-chambered heart, small ventricle and dilated aortic arch) in the low, mid-, and high-dose groups, compared to 0 in controls. The observed incidence was outside the historical control data range (i.e. 5-chambered heart: 0.4% vs 0-0.09%, small ventricle: 0.6% vs. 0-0.04%, dilated aortic arch: 0.9 vs. 0.04%). Although there was no dose-response, the effects were seen consistently across all dosed groups and are rare in nature (in particular five-chambered heart). Therefore, they are considered to be related to odevixibat treatment. The SmPC informs adequately about these findings in sections 4.6 and 5.3 of the SmPC. The use of Kayfanda during pregnancy and in women of childbearing potential not using contraception and during breast feeding is not recommended.

There were 6 (5), 7 (4), 6 (4) and 4 (3) foetuses (litters) with skeletal malformations in the control, 10, 30 and 100 mg/kg/day groups, respectively (primarily malformed sternebrae). These effects are known to occur incidentally in the tested strain; however, at a lower incidence than observed in the study. As vehicle-treated animals are also affected, this finding maybe vehicle-related.

It should be noted that the exposure at the low dose level was 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 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.

2.5.4.5.3. Prenatal and post-natal development, including maternal function

In the DRF study (AB22203) with rats treated from GD6 until PND 13, the NOAEL for both maternal and developmental toxicity was the highest tested dose of 1000 mg/kg/day. The mean percentage pre-birth loss was slightly higher in the 1000 mg/kg/day group compared to the controls (11.64% vs. 7.22%) but considered incidental since all individual values were within the concurrent control range (0 to 33%). Furthermore, the mean pup body weight was progressively slightly lower in treated groups when compared with control (-5 to -6% in males and -5 to -7% on PND 14), without any dose-relationship. However, the mean values remained within the historical control range from PND 1 to PND 14 for males and females in all groups, so this change was considered non-adverse. Based on this, the 1000 mg/kg/bw was chosen as the highest dose level for the pivotal study.

In the GLP-compliant Segment III study (AB22204) with rats dosed from GD 6 to PND 20 up to 1000 mg/kg/day, no treatment-related deaths or clinical signs were seen in F0 females. Two high-dose

females were sacrificed in extremis after not being able to deliver. At necropsy, 7 and 13 dead foetuses were found in the uterus, but macroscopic findings were otherwise unremarkable. In the absence of similar findings in other animals this was considered incidental.

In the F1 generation (20/sex/group) maintained, untreated, from ca. 3 weeks of age, for post-weaning development, behavioural tests and mating, no effects were seen which were considered toxicologically relevant. In neurobehavioral tests, mean swimming time and/or mean total number of errors for the memory trial were slightly higher in all treated females compared to concurrent and historical controls. At the low- and mid-dose those findings were principally caused by two females and thus considered incidental. At high dose, the effect of odevixibat could not be excluded; however, considering the high variability of individual data, the absence of the effect in males and the low mean intergroup difference with controls, it was considered not significant. Mean ambulatory activity and/or fine movements were greater for both sexes in all dose groups compared with the concurrent control. However, since all groups showed a normal habituation response, these effects were considered of no toxicological significance. Based on this, the NOAEL for maternal, developmental, and juvenile toxicity was the highest tested dose of 1000 mg/kg/day. This corresponds to a therapeutic margin of safety of about 104-fold.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

In the GLP-compliant DRF study with juvenile Sprague-Dawley rats dosed from day 14 till day 29 of age, the high-dose (300 mg/kg/day) animals had loose faeces which in general remained present until weaning. To a lesser extent this was seen at 100 mg/kg/day. After weaning (day 21) no clinical signs were seen. At microscopy, treatment-related changes were found in the liver and ileum of high-dose animals. In the liver, they consisted of minimal/slight focal hepatocyte necrosis in 3 males and 2 females, accompanied by minimal apoptosis in 2 males. In the ileum, the submucosa/muscle wall inflammation was also seen in four females, accompanied by a minimal inflammation in the submucosa/muscle wall in the colon in one of these females. Furthermore, uterine distension (slight or moderate) was seen in 1, 3, 4 and 5 animals of control, low-, mid- and high-dose groups, respectively. This could be indicative of the early onset of puberty; however, the oestrous cycle staging, which was performed subsequently, showed no difference between the treated animals and controls. This finding is therefore considered incidental.

The exposure in juvenile animals was significantly higher than in adult animals at the same dose levels (i.e. Cmax on day 29 of 3290 and 3950 ng/mL and AUC0-24 of 42300 and 55900 ng x h/mL in the 100 mg/kg/day males and females, respectively), which was considered to be related to immature gastro-intestinal tract of juvenile animals. Based on histopathological changes at 300 mg/kg/day, the highest dose level for the pivotal study was chosen to be 100 mg/kg/day.

In the pivotal GLP-compliant study (TEA0010) with juvenile Sprague-Dawley rats dosed from day 14 till day 63 of age with the 28-day recovery, adverse effects were limited to lose faeces in the high dose (100 mg/kg/day) pups until weaning. The NOAEL was considered to be the highest tested dose of 100 mg/kg/day. Peak and systemic exposure were markedly lower on PND 14 compared to PND 63, which is considered to be related to immature gastro-intestinal tract of juvenile animals. In rats, gastrointestinal system is less developed at birth relative to humans, with critical period of structural and functional growth and development continuing until weaning. Following a single administration on PND 14 at the 100 mg/kg/day dosage, 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.

2.5.4.6. Toxicokinetic data and interspecies comparison

The toxicokinetics of odevixibat were studied in mouse, rat, rabbit, dog, and marmoset. The absorption of odevixibat following oral (gavage) administration was relatively fast, with a Tmax of 1 to 4 h in animals and 1-5 hours in humans. Nevertheless, oral bioavailability is minimal (0.9 % in marmoset). In general, plasma concentrations of odevixibat increased in a proportional to sub-proportional manner. After repeated administration no to minimal accumulation is observed in animals and humans. In most species including humans, odevixibat is highly bound to plasma proteins (>99%, and 98% in rabbits). After IV administration, clearance, and steady state volume of distribution in marmosets were 7.5 mL/min/kg and 0.9 L/kg, respectively. The apparent oral volume of distribution (V/F) in humans was 9940 L, the apparent total clearance was 3060 L/h. Odevixibat is minimally metabolised in animals and humans. The majority is excreted via faeces: 88.6% in rats and 82.9% in humans, only 0.07% in rats and 0.002% in humans is excreted via urine. The majority is excreted as unchanged odevixibat (>96% in humans). Elimination half-life in animals ranges from 2-11 hours. In healthy adult humans, a plasma terminal half-life of 2.36 hours was observed. No apparent gender differences were observed.

In general, adequate exposure was maintained to evaluate safety in the toxicologic studies. Exposure multiples (based on Cmax of unbound odevixibat) at the NOAEL in the repeated dose toxicity studies were 13-429 in rat and mouse and 0.91-7 in dog. Also, in reproductive toxicology studies in rat exposure ratios were sufficient (47 and 15-3610 in rat EFD and rat PPND). However, the exposure multiple for developmental effects in rabbits was only <1.2 in the rabbit EFD.

2.5.4.7. Local tolerance

The absence of dedicated local tolerance studies is agreed since this aspect is covered by the repeated dose toxicity studies with oral administration.

2.5.4.8. Other toxicity studies

Odevixibat is not expected to generate an immune response and, therefore, antigenicity studies have not been performed. Due to the lack of adverse effects on the immune system, the lack of dedicated immunotoxicity studies is agreed. No studies on dependence, metabolites or excipients are required. There was no evidence of phototoxicity in rats treated with up to 1000 mg/kg/day for 3 days, followed by exposure to ultraviolet B, ultraviolet A, and visible light from a xenon lamp.

2.5.5. Ecotoxicity/environmental risk assessment

Table 9: 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 for neutral molecule at low pH log D_{ow} = 2.99 at pH 7	Potential PBT but not at environmentally relevant pH
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.2 (at low pH)	potentially B
	log D_{ow}	2.99 (at pH 7)	not 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	0.0001	µg/L	< 0.01 threshold

P.M.: pro memori

The applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline (2006 and 2018). The applicant has calculated the PECsw on the basis of a dose of 8.4 mg/patient/day. However, in the SPC a maximum dose of 7.2 mg/patient/day is given. Therefore, the calculations of the applicant can be considered as worst case. The Fpen refinement on the basis of public literature is in line with question 4 of the related Q&A document. The prevalence was based on three indications (PFIC, BA and ALGS). The current application is for the indication of ALGS only and the calculated PECsw (0.0001 µg/L) is well below the action limit of 0.01 µg/L.

The log Kow for the neutral compound is 5.2. Also, ion-correction calculations with the log Dows determined at pH 6 and higher confirm that the log Kow of the neutral molecule is higher than 5, thereby exceeding the trigger value of 4.5. 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, which is below the PBT assessment trigger value of 4.5. 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, a further PBT/vPvB assessment can be waived.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The primary pharmacodynamic studies provided adequate evidence that odevixibat acts as potent, selective inhibitor of the ileal bile acid transporter (IBAT), thereby inhibiting the reabsorption of bile acids from the gut. In a mouse model representative for type 3 PFIC, Mdr2-/- knockout mouse, odevixibat reduced liver/body weight ratios, serum markers of liver damage and cholestasis. Odevixibat performs slightly better in decreasing the liver enzymes as compared to norUDCA treatment in diseased Mdr2-/- mice.

The safety pharmacology studies demonstrated that odevixibat had no effects on the CNS, respiratory system, or renal/urinary system in rats, and had no effects on hERG channel conductivity or cardiovascular function in dogs.

Pharmacokinetics

From the pharmacokinetic point of view, the rat and dog were the most relevant species for non-clinical efficacy and safety studies. In general, the increase in exposure to odevixibat was sub-proportional to proportional to increase in dose.

Tissue distribution of odevixibat was investigated using a single oral dose of 5 µmol/kg in albino 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 small intestine). The concentration in blood was below the level of detection. According to the applicant, the dose used (5 µmol/kg, equivalent to 4 mg/kg) is in excess of the maximum recommended human dose of 0.162 µmol/kg (0.12 mg/kg).

Toxicology

Overall, the toxicology programme revealed primarily effects related to the pharmacological action of odevixibat. Odevixibat was generally well-tolerated in general in mice, rats, and dogs. Toxicity target organs were GI tract in mice and dogs, and spleen in dogs. In rats, no target organs were identified.

Odevixibat tested negative in a standard battery of *in vitro* and *in vivo* genotoxicity testing.

Carcinogenicity of odevixibat was tested in a 104-week rat and 104-week mouse study up to a dose level of 100 mg/kg/day. For a number of neoplastic lesions apparent positive significant trends were noted in both species in the provided studies. However, this either concerned the tumours which commonly occur in aging test species, or the observed tumours were seen at low incidence, in only one sex, or without dose-response relationship.

Odevixibat did not show adverse effects on fertility and early embryonic development. In the EFD study, cardiovascular defects were observed in rabbits outside the historic control range and were considered to be related to odevixibat treatment. The PPND and juvenile studies did not show clinically relevant toxicity. The risks of reproductive toxicity are adequately reflected in 4.6 and 5.3 of the SmPC.

Odevixibat did not show adverse effects on fertility and early embryonic development. In the EFD study, cardiovascular defects were observed in rabbits outside the historic control range and were considered to be related to odevixibat treatment. The PPND and juvenile studies did not show clinically relevant toxicity. The risks of reproductive toxicity are adequately reflected in 4.6 and 5.3 of the SmPC.

Environmental risk assessment

The applicant provided the same ERA as for the Bylvay PFIC MAA, which is considered valid for the ALGS indication. The Fpen refinement was based on the prevalence of three indications (PFIC, BA and ALGS) and the PECsw calculation took into account a dose of 8.4 mg/patient/day (more conservative than the maximum daily dose).

Odevixibat PEC surfacewater value is below the action limit of 0.01 mg/L. The neutral molecule, which is predominantly present at very low pH values, screens as a potential PBT/vPvB substance. The log Dow at environmentally relevant pH values is not close to the trigger value of 4.5. Hence, odevixibat is not a PBT substance at environmentally relevant pH values.

Therefore, odevixibat is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical pharmacology, pharmacokinetics, and toxicology of odevixibat have been sufficiently evaluated and support MAA for the ALGS indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

Study ID Study Dates[A] (Status)	Study Centres (Location)	Study Design	Objectives of the Study	Study Population	Dose Regimen/ Duration	No. of Patients treated	Sex Median Age Race
Clinical Studies in Patients with Alagille Syndrome							
A4250-012 26FEB2021 – 09SEP2022 (Complete)	21 (US, EU, UK, Turkey, Malaysia)	Phase 3, double-blind, randomised, placebo-controlled	Efficacy, safety	Patients with ALGS	Oral administration of 120 µg/kg odevixibat or matching placebo daily for 24 weeks	Odevixibat: 35 Placebo: 17	27M/25F 5.45 yrs. 43W/4B/3A/ 2 Other
A4250-015 03SEP2021 - Ongoing[c]	20 (US, EU, UK, Turkey, Malaysia)	Phase 3, open-label extension study	Efficacy, safety	Patients who completed Study A4250-012	Oral administration of 120 µg/kg/day odevixibat for 72 weeks	Odevixibat: 49	25M/24F 5.40 yrs. 40W/4B/3A/ 2 Other
A4250-003 25AUG2015 - 17MAR2017 (Complete)	6 (Europe)	Phase 2, open-label, single- and multiple-dose	Efficacy, safety	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	20 total 6 ALGS[b]	5M/1F 7.5 years NR

A: Asian; ALGS: Alagille syndrome; B: Black; EU: European Union; F: female; ID: identification; M: male; No.: number; NR: not reported; PFIC: progressive familial intrahepatic cholestasis; UK: United Kingdom; US: United States; W: white.

[a] First patient enrolled to last patient last visit.

[b] Only data from the 6 patients with ALGS are summarised; a total of 20 patients were enrolled; data from all patients were included in the clinical study report in the PFIC dossiers.

[C] Data included are through the data cutoff date of 09SEP2022.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology was investigated in five Phase 1 studies conducted in healthy adults (study A4250-001, A4250-004, A4250-013, A4250-022, A4250-J001), one mass balance study (study A4250-007), and three Phase 2/3 studies in paediatric patients with cholestatic pruritus (study A4250-003), in children with PFIC (sparse sampling; study A4250-005), and in children with ALGS (sparse sampling; study A4250-012). These studies were conducted to support dose selection and to characterise the single dose and multiple dose pharmacokinetics in children and adults, to evaluate the impact of food (study A4250-004) and to assess the interaction potential of odevixibat (study A4250-013 and A4250-022). Sparse PK sampling data from the phase 3 studies were included in popPK analyses.

Several *in vitro* studies were conducted to assess role of different transporters and CYP enzymes on the fate of odevixibat and the interaction potential of odevixibat.

For the analysis of odevixibat in plasma and urine, and in female human plasma, validated LC-MS/MS methods were applied, showing acceptable accuracy and precision.

For the analysis of [14C]-odevixibat concentrations of total radioactivity in plasma, whole blood, urine, and faecal samples liquid scintillation counting was applied. The method had acceptable accuracy and precision.

Validated LC-MS/MS methods with acceptable accuracy and precision were applied for the analysis of the co-administered drugs midazolam in plasma, levonorgestrel and ethinyl oestradiol in plasma.

Accuracy and precision during study sample analysis were within normal criteria. For odevixibat limited ISR data has been provided, however, this is acceptable, as in several studies, odevixibat plasma concentrations were not quantifiable. ISR data showed good reproducibility. Furthermore, study samples were analysed within the established stability periods.

For the PD markers C4 and individual bile acids (and total bile salts) in human plasma and faecal samples, FGF19 in human plasma and autotaxin/LPA in human plasma and serum, qualified methods were applied with overall acceptable accuracy and precision.

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 the popPK analysis, differences in absorption have been observed between Formulation A relative to Formulation B and C. Differences in solubility bioactive dissolution media were observed between drug substances with different crystallinity and possibly these may explain the observed differences in absorption between formulation. As formulation A has only been used in one early study and not in the Phase 2 or 3 studies in paediatric subjects the observed difference is not considered relevant for the interpretation of the clinical safety and efficacy data.

The sprinkle dosage form was associated with a 34.0% reduction in Frel relative to the capsule dosage form. Administration of odevixibat sprinkled on food (e.g. applesauce) is mainly intended for younger children, the slightly lower systemic bioavailability is not expected to result in clinically relevant differences in safety or efficacy as odevixibat is a locally acting drug.

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. Although an appropriately validated and sufficiently sensitive bioanalytical method was used to analyse the concentration of odevixibat in plasma, in about 50% of the study samples odevixibat was undetectable. These data indicate that there is very limited or no absorption of odevixibat following oral administration. The non-compartmental the 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 analyses developed by the applicant accounted for the samples below the limit of quantification (BLQ), the population model is considered more appropriate for the assessment of 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. The methodology used to construct the data set is considered acceptable and PK model appears to describe the observed data reasonably well.

PopPK analysis indicate that odevixibat is minimally absorbed following oral administration; absolute bioavailability data in humans are not available and estimated bioavailability is <1%.

Distribution

The exposure of odevixibat was calculated for the 40 and 120 µg/kg/day dose levels in paediatric patients with ALGS (study A4250-012) using popPK. The effect of disease status (ALGS vs. healthy subjects and patients with PFIC or other cholestatic diseases) was not statistically significant. In patients with ALGS, for the 120 µg/kg/day dose the trough values were below the limit of detection for 40% of the samples in ALGS. The mean Cmax value in a paediatric ALGS patient population for the 120 µg/kg/day dose is 1.13 ng/ml and the mean AUC value was 13.2 ng × h/ml. The mean V/F in ALGS patients is predicted to be 1160 l.

The food effect study showed that concomitant administration of a high-fat resulted in decreases of approximately 72% and 62% in Cmax and AUC0-24h, respectively compared to administration under fasted conditions. When odevixibat was sprinkled on apple sauce, decreases of approximately 39% and 36% in Cmax and AUC0-24h, respectively, were observed compared to administration under fasted conditions. The decrease in the bioavailability of odevixibat following administration with food, did not correlate with differences in the C4 concentration change from baseline. Although capsules were administered with food in the pivotal Phase 3 studies, based on these results no food-related dose adjustment of odevixibat is necessary and also not included in the SmPC.

The chemical compatibility was shown between odevixibat pellets and specified soft foods (i.e. applesauce, pureed bananas, pureed carrots, vanilla yoghurt, chocolate pudding, oatmeal porridge, and rice pudding) and liquids (water, apple juice, grape juice, human breast milk, milk protein formula Nan Pro 1, soy-based protein formula and hydrolysed formula Nutramigen LGG).

Odevixibat plasma protein binding was high, >99.7% at 4 µM and >99.97% at 40 µM (unbound fraction <0.3%). PopPK estimated apparent volume of distributions in paediatric ALGS patients is predicted to be 1210l.

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. The mean apparent total clearance CL/F in paediatric ALGS patients with moderate hepatic impairment for the 120 µg/kg dose regimens is 175 l/h and the mean half-life is approximately 4.75 hours.

Mass balance study A4250-007 showed that at least 83% of the dose is excreted in the faces. In faces 96% of the radioactivity was identified as parent compound showing that odevixibat is minimally metabolised.

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 accurately. However, the mean Cmax and AUC0-t tended to increase with increasing doses. Odevixibat has a short elimination half-life and no accumulation is observed. Due to the low and variable absorption it is not possible to estimate the dose proportionality accurately, however, Cmax and AUC0-t increase with increasing doses in a dose-proportional manner.

Odevixibat has 2 chiral centres and is manufactured as a single stereoisomer with the S,R-configuration. As odevixibat minimally absorbed and locally acting, interconversion is not expected to be relevant.

Odevixibat is identified as a substrate of P-glycoprotein (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. Possibly genetic polymorphism may contribute to the variability of the absorption. As the bioavailability is low in all subjects and the drug interaction study with itraconazole has shown that the impact on pGP inhibition is small there is no need to investigate the role of polymorphism of MBR1.

The population PK analysis has been used to been conducted to evaluate the influence of 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.

Hepatic impairment has an effect on the clearance of odevixibat, and a 77% lower CL/F was observed in patients with moderate liver impairment (Child-Pugh B) relative to patients with mild or no liver impairment. However, popPK indicated that the mean body weight adjusted CL/F in paediatric patients with PFIC with Child Pugh A for the 40 and 120 µg/kg/day dose levels (35.3 and 28.9 l/h/kg, respectively) were similar to that observed in healthy subjects (34.2 l/h/kg). A moderate hepatic impairment is not expected to result in any drug accumulation due to the short half-life. The impact of hepatic impairment is expected to be low due to the low bioavailability of odevixibat.

Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

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, 0.002% of the total radioactivity was recovered from the urine. The lack of data on moderate and severe renal impairment is acceptable as the renal excretion was minimal. The SmPC indicates that there are no available clinical data for the use of odevixibat in patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis, which is acceptable.

The population model was used to simulate the pharmacokinetics in paediatric PFIC patients < 1 year old. Simulations predict that the Cmax values in paediatric patients will remain below 1.06 ng/ml in most paediatric patients< 1 year old. As PK is comparable between paediatric PFIC patients and paediatric ALGS patients, this is also applicable to paediatric ALGS patients. 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, based on clinical efficacy and safety data. The use of PK modelling simulations in the youngest age group, without goodness of fit data in this age group, is acceptable as the bioavailability of odevixibat is very low and collection of PK samples is difficult in this age group. An assessment based on clinical efficacy and safety data is appropriate for this age group.

Pharmacokinetic interaction studies

The role of different transporters and CYP enzymes on odevixibat was explored in vitro. 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 above results a clinical interaction study was conducted to explore interaction with CYP 3A4. The DDI was conducted with itraconazole, an inhibitor of P-gp and midazolam, a sensitive substrate of CYP3A4. This study shows a 50-60% increase of odevixibat exposure upon concomitant coadministration with P-gp inhibitor itraconazole. These results are consistent with the observation that odevixibat is a substrate of P-gp, however, the magnitude of the increase indicates 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.

Odevixibat dosing for 7 days to healthy subjects, increased faecal bile acids and reduced plasma bile acids. There is a potential that odevixibat could impair absorption of lipophilic oral contraceptives by increasing faecal bile acid excretion, leading to a decrease in bile acid levels in the enterohepatic circulation. *In vivo* data showed that odevixibat decreased ethinyl exposure by about 17% and levonorgestrel by 12%.

Furthermore, decreased recirculation of bile acids, the absorption of fat-soluble vitamin deficiencies may be affected. A warning is included in the SmPC.

In the SmPC is mentioned that no interaction studies have been conducted with the most common concomitant medication, UDCA, and rifampicin. This is considered acceptable as no clinically relevant interactions are expected with UDCA and rifampicin.

2.6.2.2. Pharmacodynamics

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. 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.

Primary and secondary pharmacology

Pharmacodynamic endpoints have been included in the pivotal study for ALGS, A4250-012, namely serum bile acids, autotaxin and p-C4. Serum bile acids were a key secondary endpoint in the pivotal study and are described in the respective section. A short summary of the observed effects on autotaxin and p-C4 is presented here.

Changes from baseline over time in autotaxin and p-C4

Measurements of autotaxin and plasma 7α-hydroxy-4-cholesten-3-one concentration (p-C4), a marker of bile acid synthesis, were assessed for change from baseline to Weeks 12 and 24.

Elevated levels of autotaxin, the serum enzyme that converts lysophosphatidylcholine to lysophosphatidic acid, have been correlated with cholestatic pruritus and cholestasis. Mean (SD) change to Week 24 for autotaxin was -413.9 (439.22) ng/mL for the odevixibat group compared to a mean (SD) change of -44.6 (686.83) ng/mL in the placebo group.

For p-C4 levels, which is related to bile acid synthesis, a mean increase from baseline was observed over time during treatment with odevixibat. At Week 24, mean (SD) changes from baseline for this parameter were 11.543 (12.1865) ng/mL for odevixibat and 1.057 (9.6192) ng/mL for placebo.

Plasma 7α-hydroxy-4-cholesten-3-one (p-C4) levels are a marker for bile acid synthesis, which is highly regulated in the liver by endocrine and intracellular feedback mechanisms. During paediatric cholestasis, plasma C4 levels are typically lower than normal [Gonzales 2021; Thompson 2022; Zhao 2022]. This likely reflects accumulated bile acids in the liver due to the cholestasis, which in turn downregulates the need for new bile acid synthesis reflected by the decreased p-C4 levels.

In cohorts of healthy volunteers, mean p-C4 levels typically range between 13 – 18 ng/mL [Camilleri 2009; Galman 2011; Schneider 2021]. In 100 healthy children between 9 months and 18 years of age, mean C4 levels of 22.8 ng/mL were reported [Freudenberg 2013]. In contrast, p C4 levels obtained in paediatric patients with cholestatic diseases, where bile acids are expected to be accumulated in the liver, were typically < 10 ng/mL [Gonzales 2021; Thompson 2022; Zhao 2022]. This is consistent with the p-C4 levels observed in Study A4250-012 where the baseline p-C4 levels were 5.64 ng/mL in the odevixibat group and 6.86 ng/mL in the placebo group. After 24 weeks of treatment, the p-C4 levels in the odevixibat group were 18.9 ng/mL, which is in the range reported for healthy volunteers and children, while in the placebo group p C4 levels were approximately 8.4 ng/mL, remaining in the range reported for patients with cholestatic diseases.

Taken together, the initial increase in levels of p-C4 with odevixibat treatment is reflective of normalisation of bile acid synthesis due to restored hepatic bile acid homeostasis. These results are consistent with the mechanism of action of odevixibat: removing bile acids from the liver leads to an increase in p-C4 levels into a more normal range to counteract the reduction in serum bile acids, reflecting an improvement in cholestasis.

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 IC50 (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.

Consistent with the mechanism and site of action of odevixibat in the gastrointestinal tract no relationship between systemic exposure and clinical effects is observed. Also, no dose-response relationship could be established for the investigated dose range 10-200 µg/kg/day and the PD parameters C4 and FGF19.

2.6.3. Discussion on clinical pharmacology

To support the application, study A4250-012 in patients with ALGS has been conducted. The pharmacokinetics of odevixibat has been evaluated in an updated population pharmacokinetic study, which includes sparse PK samples collected in Study A4250-012.

The applicant provided an updated PK model with data from ALGS patients. This model appears to describe the observed odevixibat data reasonably well.

In the population PK study, it has been shown that hepatic impairment had a significant impact on the pharmacokinetics of odevixibat. The simulated exposure was similar between ALGS patients with moderate hepatic impairment and PFIC patients with moderate hepatic impairment; however, much higher than simulated for patients with no or mild hepatic impairment. As hepatic impairment is common in both patient groups, exposure differences are expected between patients with different degrees of hepatic impairment.

A total of 5 children with moderate hepatic impairment were included in the initial dataset. The limited PK data available in patients with hepatic impairment indicate that the clearance of odevixibat is decreased in patients with Child Pugh A and B compared to subjects with a normal hepatic function. As requested, the binning was optimised according to available sampling times. Although the population PK model is able to describe the median odevixibat concentrations adequately, the results should be interpreted with caution considering the low number of samples with measurable concentrations of odevixibat.

The updated model confirms that hepatic impairment significantly impacts the pharmacokinetics of the absorbed fraction of odevixibat. Patients with moderate hepatic impairment (Child-Pugh B) presented a 77.0% lower CL/F relative to patients with mild hepatic impairment (Child-Pugh A) or no hepatic impairment and the plasma exposure of odevixibat was 5-9-fold higher in subjects with moderate hepatic impairment. However, popPK indicated that the mean body weight adjusted CL/F in paediatric patients with PFIC with Child Pugh A for the 40 and 120 µg/kg/day dose levels (35.3 and 28.9 l/h/kg, respectively) were similar to that observed in healthy subjects (34.2 l/h/kg). A moderate hepatic impairment not expected to result in any drug accumulation due to the short half-life. The impact of hepatic impairment is expected to be low due to the low bioavailability of odevixibat. Patients with severe hepatic impairment (Child-Pugh C) have not been studied. This mentioned in the SmPC for the attention of the prescriber.

No dedicated PD studies have been conducted for ALGS, although PD endpoints were included in the pivotal phase 3 study. These include serum bile acids, autotaxin and p-C4.

Serum bile acids are generally considered to be a major contributing factor to one of the most important symptoms of ALGS, pruritus. In addition, since the MoA of odevixibat is the enhancement of bile acid clearance via the gut, this is a logical PD endpoint to include. As it was also a key secondary endpoint in the studies, a discussion on serum bile acids is included in the clinical efficacy section.

Although a causal relationship has not been established, autotaxin has been implicated as a pruritic agent. The deceases in autotaxin levels with odevixibat treatment are therefore seen as supportive. p-C4 levels were markedly (10-fold) increased in odevixibat-treated patients compared to placebo, indicative of a normalisation of bile acid synthesis as the p-C4 levels moved towards the normal range.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of odevixibat has been adequately characterised in paediatric patients with ALGS, of 6 months and older. The simulated exposure was similar between ALGS patients with moderate hepatic impairment and PFIC patients with moderate hepatic impairment; however, much higher than simulated for patients with no or mild hepatic impairment. However, body weight adjusted clearance was comparable between moderate impaired and normal hepatic function.

In line with the known PD effect of odevixibat, decreases in serum bile acids and autotaxin were observed. Increased p-C4 levels indicated a normalisation of bile acid synthesis. The PD data is supportive of the proposed indication.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

The dose-finding study A4250-003 included both PFIC and ALGS patients.

Methods

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 ALGS, PFIC, biliary atresia, and sclerosing cholangitis). The study included a screening period with a 7-day washout for patients on prior bile acid resins or other prohibited medications, a single dose administration treatment period with a 10-day follow-up, and a 4 week treatment period. Multiple dose cohorts were included 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. Doses of 10 to 200 µg/kg/day were evaluated.

The primary efficacy endpoint was the total serum bile acids change from baseline to end of the 4-week treatment period. Secondary efficacy endpoints included changes in pruritus and sleep-related parameters based on the following: visual analogue scale (VAS)-itch (scale: 0-10), Patient-Oriented SCORing for Atopic Dermatitis (PO-SCORAD) itching and sleep disturbance (scale: 0-10), and Whitington itch/pruritus scale (scale: 0-4). For all measures, decreases in scores represented improved symptoms.

Efficacy endpoints were analysed for the FAS, defined as treated patients who had baseline and weekly diary recordings at the end of the 4-week treatment period. As a post-hoc analysis, the primary and secondary efficacy endpoints were analysed separately for patients with ALGS. Due to the exploratory nature of this study, only descriptive statistics are presented.

Results

A total of 6 paediatric patients with ALGS were enrolled in the study. All 6 patients completed 1 dose cohort, i.e. they received a single dose followed by 4 weeks of daily dosing. Three of the patients received the 10 µg/kg/day dose of odevixibat, 1 received the 60 µg/kg/day, and 2 received the 200 µg/kg/day.

Five of the 6 patients with ALGS were male and one was female; their age ranged from 1 to 15 years with a median of 7.5 years.

The mean baseline serum bile acid level at screening was 237 µmol/L, and all patients had elevated levels of total serum bile acids at baseline, as required by study inclusion criteria (total serum bile acids > 2 × ULN [i.e. 20 µmol/L]).

Primary Efficacy Endpoint

After 4 weeks of treatment with odevixibat, mean serum bile acid levels across the 6 patients decreased by 46.3% from baseline (Table 14). In 5 of the 6 patients, including 2 who received 10 µg/kg/day, 1 who received 60 µg/kg/day, and 2 who received 200 µg/kg/day, reductions from baseline

in serum bile acid levels were observed ranging from 39% to 92%. In 1 patient, who received the 10 µg/kg/day dose of odevixibat, a small increase in serum bile acid levels of 4% was observed.

Table 10: Change from baseline to end of treatment in serum bile acids (ALGS subgroup)

Visit Statistic	Observed Value (µmol/L)	Observed Change (µmol/L)	Percent Change (µmol/L)
Baseline			
n	6	--	--
Mean (SD)	237.45 (195.138)	--	--
Median	190.45	--	--
Minimum, maximum	25.7, 563.8	--	--
Visit 5 (EOT)			
n	6	6	6
Mean (SD)	139.75 (157.814)	-97.70 (111.207)	-46.29 (31.239)
Median	61.30	-57.05	-46.98
Minimum, maximum	12.2, 352.7	-239.5, 14.5	-92.0, 4.3

Source: CSR A4250-003 Table 8.2.

Table 11: By-patient changes from baseline in serum bile acid levels

PATIENT ID/AGE/SEX DOSE	SERUM BILE ACIDS (µMOL/L)			PERCENT CHANGE FROM BASELINE
	VISIT 1 (BASELINE)	END OF TREATMENT	ACTUAL CHANGE FROM BASELINE	
101/ 15 yo/male 10 µg/kg/day	260.3	20.8	-239.5	-92.0
201/9 yo/male 10 µg/kg/day	116.1	70.8	-45.3	-39.0
601/6 yo/male 10 µg/kg/day	338.2	352.7	14.5	4.3
603/12 yo/F 60 µg/kg/day	25.7	12.2	-13.5	-52.5
405/1 yo/male 200 µg/kg/day	563.8	330.2	-233.6	-41.4
506/6 yo/male 200 µg/kg/day	120.6	51.8	-69.7	-57

Source: CSR A4250-003, Listings 2.1, 3.1, and 14.1.

Secondary Efficacy Endpoints

Overall, improvement was seen in patients with ALGS in all pruritus and sleep-related endpoints. Among the 6 patients with ALGS, mean changes from baseline to end of treatment were -2.4 (range -6.1 to 0.4) in VAS-itch score, 2.3 (range -6.7 to -0.03) in PO SCORAD itching score, 1.6 (range 5.49 to 0.73) in PO SCORAD sleep disturbance score, and 0.43 (range -1.6 to 0.83) in Whitington itch/pruritus scale score.

2.6.5.2. Main study

Study A4250-012: A Phase 3 Double-blind, Randomised, Placebo-controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients with Alagille Syndrome (ASSERT)

Methods

Study Participants

Main inclusion criteria

1. A male or female patient (of any age) with a genetically confirmed diagnosis of ALGS.
2. Patient must have had a history of significant pruritus and a caregiver reported observed scratching or a patient-reported pruritus score at an average of ≥ 2 (on a 0 to 4 scale), as measured by the Albireo ObsRO instrument in the 14 days prior to randomisation.
3. Patient must have had an elevated baseline serum bile acid level. Each of the serum bile acid levels obtained at Screening Visit 1 and Screening Visit 2 must have been greater than the upper limit of normal (> ULN).

Main exclusion criteria

1. Patient with past medical history or ongoing presence of other types of liver disease including, but not limited to, the following:
    a. Biliary atresia of any kind
    b. PFIC
    c. Benign recurrent intrahepatic cholestasis
    d. Suspected or proven liver cancer or metastasis to the liver on imaging studies
2. Patient with a past medical history or ongoing presence of any other disease or condition known to interfere with the absorption, distribution, metabolism (specifically bile acid metabolism), or excretion of drugs in the intestine, including but not limited to, inflammatory bowel disease.
3. Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period.
4. Patient had a liver transplant, or a liver transplant was planned within 6 months of randomisation.
5. Decompensated liver disease, history or presence of clinically significant ascites, variceal haemorrhage, and/or encephalopathy.

Treatments

Patients received odevixibat at a dose of 120 µg/kg/day or placebo once daily orally for 24 weeks. Both odevixibat and placebo were supplied as capsules that were identical in appearance and filling weight.

If, in the clinical opinion of the investigator, a dose modification was beneficial to manage any potential AEs, dose modification is permitted, and study drug may be continued at a reduced dose level of 40 µg/kg/day. Two dose reductions were permitted during the study. Any dose modification must be recorded in the clinical database.

During the study no drugs with effects on bile acid concentration in the GI tract or drugs with known effects on GI motility were allowed. 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 the patient was on a stable usage of the product at least 4 weeks before enrolment until treatment discontinuation.

Medications, including UDCA, rifampicin, and/or antihistamines, and other medications to treat pruritus, also were permitted provided the patient was on a stable dosage at least 4 weeks prior to enrolment, and no dosage change was planned during the treatment period. If a dosage change was required during the study, the medical monitor was to be consulted prior to that change. Topical treatment was allowed without restriction.

Objectives

The primary objective of the study was to demonstrate the efficacy of repeated daily doses of 120 µg/kg/day odevixibat in relieving pruritus in patients with ALGS.

The secondary objectives of the study were:

- To assess the impact of odevixibat on serum bile acid levels in patients with ALGS.
- To evaluate the safety and tolerability of odevixibat in patients with ALGS.

Outcomes/endpoints

Primary endpoint

Change from baseline in scratching to Month 6 (Weeks 21 to 24) as measured by the Albireo ObsRO caregiver instrument, based on the worst scratching score of the ObsRO.

Key secondary endpoint

- Change in serum bile acid levels from baseline through Week 24.

Secondary efficacy endpoints

- Change from baseline in pruritus to Month 6 (Weeks 21 to 24) as measured by the Albireo PRO instrument
- Percentage of patients achieving a clinically meaningful decrease in pruritus (pruritus responders) as measured by the Albireo ObsRO/PRO instruments
- Change from baseline through Week 24 in patient reported and observer reported itching and scratching severity scores, respectively, for the morning assessment, for the evening assessment. These endpoints will be assessed by combining age groups, and by age group, 0 to <8, 8 to <12, 12 to <18, and 18 years and over
- Change from baseline to Week 24 in sleep parameters as measured with the Albireo ObsRO/PRO instruments (e.g. tiredness and number of awakenings)
- Change from baseline to Week 24 in PedsQL subdomain scores
- Assessment of Global Symptom Relief to from baseline to Weeks 4, 12, and 24 as measured by patient, caregiver, and clinician GIS (PGIS, CaGIS, CGIS) items

- Assessment of Global Symptom Relief as measured by patient, caregiver, and clinician GIC (PGIC, CaGIC, CGIC) items at Weeks 4, 12, and 24
- Patient impression of treatment effect as recorded during exit interviews at Week 24
- Change from baseline to Week 24 in xanthomatosis as assessed by the Clinician Xanthoma Scale
- Change from baseline to Week 24 in serum ALT, AST, GGT and bilirubin concentration
- Change from baseline in biochemical markers and measures of bile acid synthesis (autotaxin, p-C4, only in patients >10 kg)
- Change from baseline in total cholesterol concentration

Sample size

Forty-five (45) patients <18 years of age were to be randomised at an experimental to control allocation of 2 to 1 in order to obtain approximately 36 completers, assuming an approximate drop-out rate of 20%. At a 1-sided significance level of alpha1-sided = 0.025, assuming a pooled standard deviation (SD) of 1.0, and a difference between the treatment groups of 1.2 in change of pruritus, favouring response, the power of the study is 0.909, using the exact method (Proc Power, SAS v.9.4, Cary, NC). The key secondary endpoint is also powered for a standardised treatment effect (treatment effect/SD) of 1.2.

After a minimum of 18 patients have completed the Week 16 visit, sample size re-estimation was conducted on the pooled SD of change from baseline to Week 16 (Weeks 13 to 16 assessments). The planned sample size re-estimation was conducted based on 17 patients having non-missing outcomes at Weeks 13-16 and 12 patients having non-missing outcomes at Weeks 21-24. Based on blinded pooled data, the observed SD at Week 16 and Week 24 was 1.11. The sample size was increased to target 48 completers (i.e. approximately 32 and 16 in the odevixibat and placebo groups, respectively, based on 2:1 randomisation). Given the low actual dropout rate at that time, 7 patients were added to the study.

Randomisation and Blinding (masking)

After completion of the screening period, eligible patients were randomised in a 2:1 fashion to receive odevixibat or matching placebo assigned by an Interactive Web Response System (IWRS). The randomisation codes were computer-generated by a biostatistician at Firma Clinical Research (Firma) and kept by an unblinded biostatistician at Firma, independent from the project team. A block size of 6 was used.

Subjects <18 years of age were randomised according to one age stratification factor, i.e. <10, and 10 to <18 years of age. This stratification factor is based on Kamath et al. (2020), showing an increase in the prevalence and severity of pruritus in children <10 years of age.

The study was with double-blind design so that both the investigators and the patients were unaware of the treatment assignment.

To ensure blinding, the study drug, and the matching placebo had the same shape, size, appearance, and filling weight. Patients received capsule(s) of odevixibat according to their dose group or capsule(s) of matching placebo once a day during the double-blind treatment period. Labels on the study drug containers did not identify the treatment to which a patient is randomised. Traceability of the treatment was ensured by the study drug number.

Statistical methods

SAP version 27 September 2022, with protocol version 2.0 date August 28, 2020.

Statistical testing strategy and multiplicity control

Statistical testing for the primary analysis of the primary endpoint was conducted with a 1-sided Type I error rate of 0.025. The key secondary efficacy endpoint was assessed for statistical significance if and only if the success criterion for the primary endpoint was met. Other secondary efficacy endpoints provided supportive efficacy information.

Analysis sets

The following analysis sets were specified:

Analysis set	Consists of	Analysis	Used for
Safety analysis set	All patients who received at least 1 dose of study drug	As received	Safety analyses
Full analysis set (FAS) <18 year of age	all randomised patients who received at least 1 dose of study drug treatment* excluding patients 18 years of age or older at randomisation for whom the ObsRO is not utilised	As randomised	Primary and key efficacy analysis
Full analysis set (FAS) All age groups	All randomised patients who received at least 1 dose of study drug treatment*	As randomised	All other secondary analyses
Per protocol (PP)	Subset of FAS: all randomised patients for whom no major protocol violation which may affect the study efficacy outcome is documented		Supportive data for efficacy analysis

*Allocation of patients to the PP analysis set will be performed before un-blinding of the study.

Analysis of primary efficacy endpoint: change in scratching severity score

For the analysis of the primary endpoint, the estimand strategy included all data collected through the end of study following the intercurrent event (ICE) of premature discontinuation of treatment prior to Week 24; data following the ICEs of biliary diversion surgery or liver transplant were excluded. This strategy to handle the intercurrent events was based on the following rationale:

The primary efficacy analysis was based on a mixed-effect model for repeated measures (MMRM) to summarise change from baseline for each 4-week average AM and PM scratching score. The model includes baseline age stratification, average AM + PM scratching scores, direct bilirubin; treatment group; time (in months as a categorical variable); and a treatment-by-time interaction.

The monthly (28-day) average for Months 1 through 6 in pruritus was calculated by taking the average AM and the average PM weekly scores, then averaging the AM and PM weekly scores, and finally calculating the monthly average by averaging the 4 weeks within the month. Baseline was calculated similarly for the 14 days preceding the start of treatment by taking the average AM and the average PM weekly scores, then averaging the AM and PM weekly scores, and finally calculating the average by averaging the 2 weeks. Change from baseline was calculated as the monthly score minus the baseline score.

The estimand targets a population of patients with ALGS. The FAS was used as the primary analysis population.

There was no imputation of missing data in the primary analyses of endpoints in this study as methods robust to missing data such as the mixed-effect model for repeated measures (MMRM) were used. Each week, at least 4 of 7 assessments needed to be completed for each of the AM and PM assessments. If these minimum assessments were not available, the week was considered missing. Monthly values were only calculated if at least 3 weeks could be calculated.

Sensitivity and supplementary analyses

The following sensitivity and supplementary analyses were pre-specified in the SAP, based on different missing data mechanisms, different populations, and different handling of the scratching scores:

Sensitivity analyses:
1: MMRM with control-based multiple imputations (MI)
2. Tipping point analysis, to explore whether missing data could have adversely impacted findings for the analysis of change from baseline in scratching score to Month 6 (Weeks 21-24) regardless of treatment adherence.
3: MMRM based on worst weekly scratching score for a month
4: MMRM with control-based MI based on the worst weekly scratching score for a month
5: MMRM with baseline score using 4 weekly average AM and PM scores in the 28 days prior to treatment start
6: MMRM of observed scratching at Month 6
Supplementary analysis
1: The same MMRM utilised for the main analysis will also be used for the PP analysis set.

Additional analyses including all data collected through the end of the study regardless of intercurrent events will also be performed.

Key secondary endpoint (hierarchically tested): change in serum bile acid levels

The same estimand strategy used for the primary endpoint was used in assessing this secondary endpoint. This key secondary efficacy endpoint would only be assessed for statistical significance if the success criterion for the primary endpoint was met.

The analysis for the key secondary endpoint was determined using a MMRM model with baseline age stratification, baseline serum bile acid level, treatment group, visits (Weeks 4, 8, 12, 16, 20, 24), and a treatment-by-visit interaction in the model. The primary comparison of the treatment difference is the change from baseline to the average of Weeks 20 and 24; the differences at Weeks 4, 8, 12, 16, 20, and 24 also were estimated and tested.

For the key secondary endpoint change in serum bile acid levels the following sensitivity and supplementary analyses were specified:

Sensitivity analyses:
1: MMRM with control-based MI
2. Tipping point analysis

Supplementary analysis
1: To evaluate the robustness of deviation from the normal and homoscedastic assumptions, a rank transformed ANCOVA model* was conducted, with missing data imputed by MI before ranking.
2. The MMRM model used for the main analysis was conducted for the PPS.

* with baseline age stratification, baseline serum bile acid level, and treatment group

A Pearson correlation coefficient was produced to evaluate the relationship between the primary endpoint (change from baseline in scratching score to Month 6 [Weeks 21-24]) and the key secondary endpoint (change in serum bile acid levels from baseline to the average of Weeks 20 and 24); results were displayed in a scatterplot

Other secondary endpoints: ALT, AST, GGT, total and direct bilirubin, total cholesterol, itching score, pruritis responders, pedSQL

Changes from baseline for the *continuous secondary efficacy endpoints*, including ALT, AST, GGT, total and direct bilirubin, total cholesterol, itching score (PRO) to Month 6 (Weeks 21-24), AM scratching/itching score and PM scratching/itching score (ObsRO/PRO) to Month 6 (Weeks 21-24), and sleep parameters (ObsRO and PRO), were analysed for the FAS using MMRM. The MMRM models include baseline value of the response variable, baseline age stratification, baseline direct bilirubin (for change in itching and scratching scores), treatment group, visit/time (in weeks/months) (depending on the assessments) and a treatment-by-visit interaction. The LS Mean change from baseline based on the MMRM is displayed using graphical presentations.

The proportion of patients achieving a clinically meaningful decrease in scratching score (pruritus responders) at Week 24 (or Week 12) was analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline age stratum. For this analysis, a pruritus responder is defined as a patient who reported a decrease in pruritus severity score from baseline equivalent to or greater than the threshold of meaningful change estimated from the blinded psychometric analysis (Section 9.7.1.3). Patients with missing data at Week 24 (or Week 12) were classified as non-responders.

A comparison of the change from baseline at Week 12 and Week 24 in the *PedsQL total score* (calculated as the average score of all answered items) and domain scores between the treatment groups was conducted using ANCOVA. The model includes terms for baseline, age category based on the age groups defined for the PedsQL (5 to < 8, ≥ 8 to < 13, ≥ 13 to < 18), and treatment.

Psychometric analysis of responder definition

A blinded analysis of Albireo ObsRO and PRO eDiary data was planned to be performed after 50% or more of the planned sample had completed the Week 24 Visit. The blinded analysis was used to estimate a threshold of clinically meaningful change (i.e. responder definition) in Albireo ObsRO and PRO pruritus scores. The analysis was performed by a group independent of both the study team and Albireo. Blinded data were used for this analysis; data were collapsed across treatment groups.

The thresholds for meaningful, within-patient change were estimated using distribution and anchor-based approaches (descriptive statistics), supplemented by ROC analyses, eCDF and PDF for Albireo ObsRO scores. According to the protocol, the anchor-based analyses were considered primary in the estimation of the meaningful change threshold. Other analyses were considered complementary and used to confirm the estimates that emerged from the anchor-based analyses.

Distribution-based analyses included the calculation of the SD and standard error of measurement of the baseline Albireo PRO and ObsRO scores.

Anchor-based analyses involved examining the degree of change in the Albireo PRO and ObsRO scores from baseline to Week 24 for patients who experienced a change in pruritus according to PGIC and symptom items. The potential anchors were evaluated through their correlations with the itching/scratching/sleep disturbance domain measures. The anchor with the highest correlation with the pruritus measures was used as the primary anchor. The smallest median value for the primary anchor that exceeded the values from the distribution-based analyses AND the lower bound of the 95% CI from the stable anchor category was selected as a candidate threshold value. Final meaningful change estimates were rounded to the nearest 0.5 value on the 0-4 scale to increase the interpretability of the threshold values.

The following definitions for meaningful change ("improved") were considered:

- Definition 1: improvement of at least 2 categories (Rating of "Very much better" or "Much better"/"Moderately better" of change in PGIS/CaGIS/CGIS scores)
- Definition 2: improvement of at least 1 category (Rating of "Very much better", "Much better"/"Moderately better" or "A little better" of change in PGIS/CaGIS/CGIS scores)
- Definition 3: improvement of 1 or 2 categories (Rating of "Much better"/"Moderately better" or "A little better") of change in PGIS/CaGIS/CGIS scores

Overall, moderate positive correlations (r = 0.525 to 0.629) were observed between Albireo ObsRO scratching items and the CaGIS scratching items, whereas in general, correlations were lower with the PGIS itch item (r = 0.168 to 0.323).

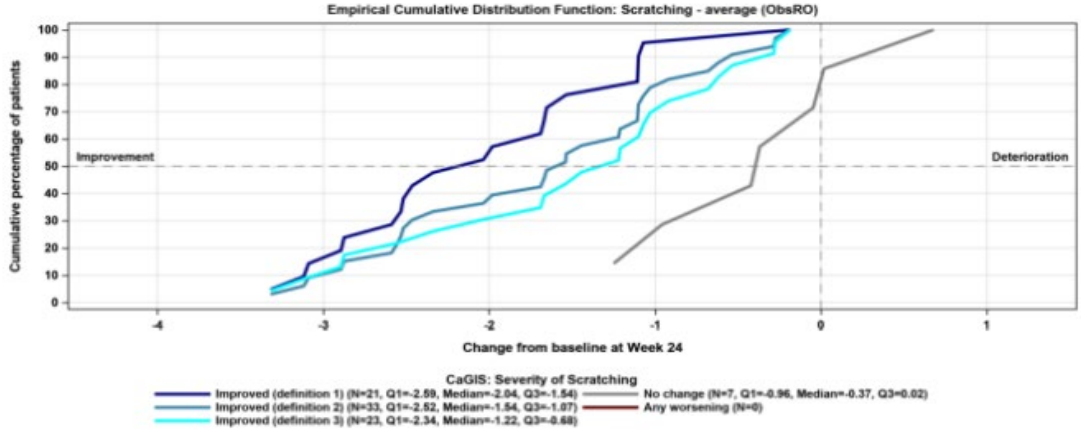
The 0.5 SD of the Baseline average and worst weekly Albireo ObsRO scratching scores was 0.28, and 1 SEM at Baseline was 0.30 for both scores. These values served as a lower limit for the meaningful change threshold that indicated the amount of change in the Albireo ObsRO scratching scores that could be due to measurement error alone.

The smallest absolute median Albireo ObsRO scratching average change value for the CaGIS that exceeded the values from the distribution-based analyses and the lower bound of the 95% CI from the stable anchor category was 1.22 and 1.29 at Week 24 for the ObsRO scratching average and worst weekly scores, respectively (**Table 12**). Similar to slightly higher thresholds of 1.51 and 1.29 for ObsRO scratching average and worst weekly scores, respectively, were observed at Week 12.

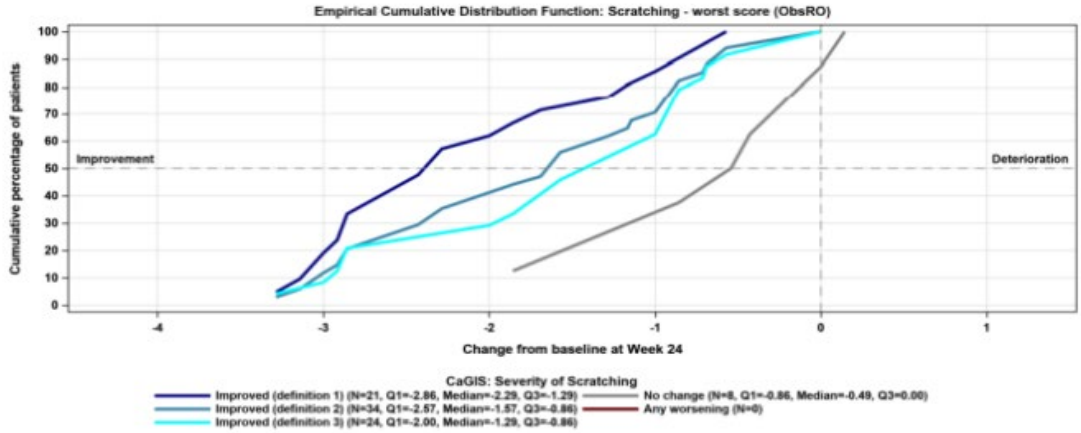
Table 12: Summary of anchor-based analysis of albireo ObsRO scratching average score

ANCHOR/ANALYSIS	STATISTIC	CHANGE FROM BASELINE TO WEEKS 9-12 (N)		CHANGE FROM BASELINE TO WEEKS 21-24 (N)
CaGIS: Improved - Definition 1	Mean, Median	-1.89,-1.92 (18)		-2.04,-2.04 (21)
CaGIS: Improved - Definition 2	Mean, Median	-1.60,-1.65 (34)		-1.67,-1.54 (33)
CaGIS: Improved - Definition 3	Mean, Median	**-1.47,-1.51 (28)**		**-1.51,-1.22 (23)**
CaGIS: No Change	(95% CI)	(**-1.01**; 0.07) (6)		(**-0.93**; 0.26) (7)
CGIS: Improved - Definition 1	Mean, Median	-2.18,-2.13 (16)		-2.09,-2.04 (21)
CGIS: Improved - Definition 2	Mean, Median	-1.68,-1.69 (34)		-1.75,-1.65 (35)
CGIS: Improved - Definition 3	Mean, Median	**-1.52,-1.58 (27)**		**-1.41,-1.22 (23)**
CGIS: No Change	(95% CI)	(**-1.18**; -0.15) (10)		(**-1.06**; 0.23) (7)
CaGIC: Improved - Definition 1	Mean, Median	-1.82,-1.71 (31)		-2.02,-1.98 (27)
CaGIC: Improved - Definition 2	Mean, Median	-1.78,-1.71 (32)		-1.88,-1.69 (31)
CaGIC: Improved - Definition 3	Mean, Median	**-1.22,-1.33 (10)**		**-1.21,-1.10 (11)**
CaGIC: No Change	(95% CI)	(**-1.19**; -0.12) (8)		(**-0.85**; 0.01) (10)
CGIC: Improved - Definition 1	Mean, Median	-1.94,-1.79 (24)		-1.96,-1.91 (28)
CGIC: Improved - Definition 2	Mean, Median	-1.68,-1.69 (32)		-1.80,-1.67 (33)
CGIC: Improved - Definition 3	Mean, Median	**-1.37,-1.23 (19)**		**-1.38,-1.11 (17)**
CGIC: No Change	(95% CI)	(**-1.51**; -0.10) (7)		(**-0.94**; 0.38) (7)
CaGIS	ROC curve value	-1.59		-1.54

A: Scratching (average score)



B: Scratching (worst weekly score)



CaGIS: Caregiver Global Impression of Symptoms, ObsRO: Observer-reported outcome.

Def1: Improvement of at least 2 categories. Def2: Improvement of at least 1 category. Def3: Improvement of 1 or 2 categories

Source: Appendix E: End-of-Text Figures (Interim analysis) Average itching: Figure 4.2.1.2.3. Worst weekly itching: Figure 4.2.2.2.3.

Figure 3: eCDF for Albireo ObsRO scratching score using GaGIS as anchor (week 24, monthly score)

In summary, according to the applicant, the blinded psychometric analysis results across all anchors and timepoints supported a threshold from 1.0 to 1.5 points.

Strong correlations (> 0.50) were observed between the ObsRO pruritus measure and the GIS/GIC anchors. The lower bound of the 95% confidence interval (CI) for the ObsRO pruritus measure in stable anchor groups (i.e. GIS change from baseline of zero and GIC answer of 'no change') was < 1.5. The upper bound of 1.5 points reduction was used for the primary analysis, while the lower bound of 1.0-point reduction was used for a sensitivity analysis.

Planned subgroup analyses

The following subgroup analyses were performed by using MMRM model with baseline serum bile acid, treatment group, visit and treatment-by-visit interaction. The approach to selection of the covariance matrix in the model followed the same approach as for the primary endpoint.

• Age group 1: 0 to <10 and 10 to <18 years (Based on the actual age)

- Age group 2: 0 to <2, 2 to <12, 12 to <18 years (Based on the actual age)
- Region (US, EU, and RoW)
- Sex
- Race (White vs. Non-White (including race as not reported))
- Ethnicity (Hispanic or Latino (including ethnicity as not reported), Not Hispanic or Latino)
- Baseline serum bile acid (≥ median and < median)
- The use of UDCA (Y, N)
- The use of anti-pruritus medication (Y, N)
- Child-Pugh classification (Class A, B, C)
- Hepatic impairment classification (no impairment, mild, moderate, or severe)
- Baseline direct bilirubin (>3 and ≤3 mg/dL and equivalent to >51.3 and ≤51.3 µmol/L)
- Genetic Testing for ALGS (JAG1 vs NOTCH2)

Results

Participant flow

A total of 52 patients were determined to be eligible and were randomised into the study, including 35 and 17 patients randomised to receive once daily odevixibat 120 µg/kg and placebo, respectively. All randomised patients were dosed and received their assigned treatment.

All 52 randomised patients completed the planned 24-week treatment period with 50 of the 52 patients electing to roll over to the long-term extension study A4250-015.

Recruitment

This was a multicentre study; patients were enrolled at 21 study centres, including 13 in the European Union - 5 in the United States (US), and 3 in the rest of world (RoW) (1 in the United Kingdom, 1 in Turkey, and 1 in Malaysia).

Date first patient enrolled: 26. February 2021

Date last patient completed: 09. September 2022

Conduct of the study

Amendments

The original protocol under which patients were first enrolled in the study was Protocol Version 2.0 (dated 28AUG2020); there were 5 country-specific amendments to the protocol. There were no major changes.

Protocol deviations

Overall, 5 (9.6%) of the 52 patients had important protocol deviations or other reasons that could affect efficacy evaluations. Therefore, data for these 5 patients were excluded from the PP analysis set.

Two patients, one in each treatment group, had missing pruritus scores at Month 6 due to insufficient collection of eDiary data between Weeks 21-24, and 1 patient, in the odevixibat group, had an average baseline scratching score of 1.9.

Two additional patients were excluded from the PP analysis set due to protocol-specified interruptions of odevixibat, including one patient with computed compliance of < 70% due to an interruption in treatment related to a TEAE of hepatic enzymes increased, and a patient who received treatment on < 50% of days during which the eDiary data was collected for the primary endpoint (i.e. Weeks 21-24) due to an interruption in treatment for TEAEs of platelet count decreased and macrocytic anaemia.

Protocol deviations related to the COVID-19 pandemic were reported in 6 (11.5%) patients overall, including 4 (11.4%) patients in the odevixibat group and 2 (11.8%) patients in the placebo group. These deviations were primarily related to visits conducted outside of the visit window.

Most patients had other key protocol deviations reported during the 24-week study. Not including those related to the pandemic or important deviations, key deviations categorised as major in the odevixibat and placebo groups were primarily related to patient compliance with study procedures or study drug dosing (8 and 3 patients in the odevixibat and placebo groups, respectively); the use of prohibited medications or unapproved dose changes made to concomitant antipruritic medications (7 and 3 patients, respectively); ICF procedures (i.e. incorrect completion of the form or issues with the timing of reconsent for new versions of the protocol/ICF) (6 and 1 patient[s], respectively); and visit window violations (i.e. laboratory and/or study procedures or tests not obtained or obtained outside of the scheduled window) (3 and 1 patient[s], respectively). All sites with ICF deviations were re-educated on ICF procedures and all patients and/or guardians subsequently completed and signed the appropriate ICFs.

Amongst the major protocol deviations categorised as related to compliance with study drug dosing were 4 patients, 2 each in the odevixibat and placebo, with an overall treatment compliance documented as <80% per final drug accountability.

Baseline data

The median age of the 52 patients was 5.45 years and ranged from 0.5 to 15.5 years. Most patients (39, 75.0%) were between 2 and 12 years of age; 8 (15.4%) were < 2 years old, and 5 (9.6%) were between 12 and 18 years of age. Overall, there was generally an equal representation of males and females (51.9% and 48.1%, respectively); the majority of patients were white (82.7%) and not Hispanic or Latino (84.6%).

The demographic characteristics were generally similar across the treatment groups. However, some imbalances were observed. In the odevixibat group, most patients were male (60.0%), while in the placebo group, most were female (64.7%). Fewer patients in the odevixibat group were < 2 years of age (8.6%) compared to the placebo group (29.4%).

Most of the 52 patients were enrolled at sites in the EU (36, 69.2%); 11 (21.2%) were enrolled at sites in the US, and 5 (9.6%) in the rest of world (RoW).

Patients in the odevixibat group had greater growth deficits with baseline median height and weight z-scores (-1.72 and -1.82, respectively) compared to the placebo group (-1.51 and -1.46, respectively). Median height and weight were 106.25 cm and 16.05 kg, respectively.

Baseline disease characteristics were generally similar across the treatment groups (**Table 13**). All 52 patients had genetic confirmation of ALGS. Most patients had the JAG1 gene mutation (48, 92.3%); 4 patients (7.7%) had a mutation in the NOTCH2 gene, including 3 patients who received odevixibat and 1 who received placebo. Median time since diagnosis was 5.5 years in the odevixibat group and 2.7 years in the placebo group.

Mean (SD) baseline pruritus score (AM + PM) in the 14 days prior to randomisation based on the ObsRO was similar in the odevixibat (2.80 [0.520]) and placebo (3.01 [0.636]) groups. Scores were also similar across the treatment groups for baseline AM and baseline PM scores.

Mean (SD) levels of serum bile acids were similar in the odevixibat (237.4 µmol/L) and placebo groups (246.1 µmol/L).

The majority of patients (51, 98.1%) were receiving antipruritic medications, including 46 (88.5%) patients who were receiving UDCA.

Table 13: Baseline disease characteristics

PARAMETER	PLACEBO N=17	ODEVIXIBAT N=35	OVERALL N=52
Genetic testing, mutation in:			
JAG1 gene	16 (94.1)	32 (91.4)	48 (92.3)
NOTCH2 gene	1 (5.9)	3 (8.6)	4 (7.7)
Time since diagnosis (years)			
n	17	35	52
Mean (SD)	3.79 (3.488)	5.77 (3.883)	5.13 (3.841)
Median	2.70	5.50	4.40
Minimum, maximum	0.4, 10.5	0.4, 15.3	0.4, 15.3
Scratching score (AM + PM), ObsRO			
n	17	35	52
Mean (SD)	3.01 (0.636)	2.80 (0.520)	2.86 (0.563)
Median	3.18	2.71	2.86
Minimum, maximum	2.1, 4.0	1.9, 4.0	1.9, 4
Serum bile acid level (µmol/L)			
n	17	35	52
Mean (SD)	246.1 (120.53)	237.4 (114.88)	240.2 (115.64)
Median	232.0	210.5	212.5
Minimum, maximum	56, 428	96, 510	56, 510
Serum bile acid level (µg/mL)			
n	17	35	52
Mean (SD)	100.5 (49.24)	97.0 (46.93)	98.1 (47.24)
Median	94.8	86.0	86.8
Minimum, maximum	23, 175	39, 208	23, 208
Serum bile acid level category[a]			
≥ 212.5 µmol/L (≥ 86.8 µg/mL)	9 (52.9)	17 (48.6)	26 (50.0)
< 212.5 µmol/L (< 86.8 µg/mL)	8 (47.1)	18 (51.4)	26 (50.0)
Baseline use of:			
Antipruritic medications	17 (100.0)	34 (97.1)	51 (98.1)
UDCA	16 (94.1)	30 (85.7)	46 (88.5)

SD: standard deviation; UDCA: ursodeoxycholic acid.

[a] Based on the median baseline serum bile acid levels across all 52 patients.

Source: Table 14.1.6.1.

Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria, which are based on serum total bilirubin and serum AST concentrations, were used for categorising hepatic dysfunction as mild, moderate, or severe classifications. Overall, 51 (98.1%) of the 52 patients had moderate hepatic impairment and 1 (1.9%) had severe hepatic impairment based on the Child-Pugh classification. Hepatic impairment classification based on the NCI ODWG indicated that 13 (25.0%), 18 (34.6%), and 21 (40.4%) of the 52 patients had mild, moderate, and severe hepatic impairment, respectively. In the

odevixibat group, 28 (80.0%) of 35 patients had moderate or severe hepatic impairment based on NCI ODWG compared to 11 (64.7%) of 17 patients in the placebo group.

Consistent with the underlying liver pathology in patients with ALGS, patients had elevated levels of hepatic biochemical parameters at baseline. Patients in the odevixibat group were more likely to have baseline levels of ALT >3 × ULN (23 of 35, 65.7%) compared to the placebo group (6 of 17, 35.3%) . For AST >3 × ULN at baseline, results were similar across the groups (40.0% and 41.2% for odevixibat and placebo, respectively) as were results for total bilirubin >2 × ULN (62.9% and 64.7%, respectively). Cholesterol levels at baseline were also elevated across the 52 patients.

Patients with ALGS are known to have fat-soluble vitamin deficiency. At baseline, median levels of vitamins A, D and E across all 52 patients were generally in the normal range, reflective of the vitamin supplementation the patients were receiving at baseline.

Numbers analysed

A total of 52 patients were randomised into the study, received their assigned treatment, and were included in the Safety Analysis Set and the FAS; 47 of the 52 randomised patients were included in the PPS. Reasons for exclusion from the PPS are discussed in **Table 14**.

Table 14: Patients excluded from per protocol analysis set (randomised patients)

PARAMETER	PLACEBO N=17 N (%)	ODEVIXIBAT N=35 N (%)	ALL PATIENTS N=52 N (%)
Patients excluded from PPS	1 (5.9)	4 (11.4)	5 (9.6)
Important protocol deviations:			
Missing pruritus score at Month 6 due to insufficient eDiary data collected during Weeks 21- 24	1 (5.9)	1 (2.9)	2 (3.8)
Failure to meet inclusion criteria of baseline pruritus ≥ 2	0	1 (2.9)	1 (1.9)
Other reasons for exclusion:			
Overall treatment compliance < 70%	0	1 (2.9)	1 (1.9)
Treatment duration < 50% of days with eDiary data collected during Weeks 21-24	0	1 (2.9)	1 (1.9)

eDiary: electronic diary; PPS: per protocol set.

Note: For detailed inclusion and exclusion criteria, see Section 9.3.

Source: Table 14.1.3.1.

Outcomes and estimation

Primary endpoint

Treatment with odevixibat 120 µg/kg/day for 6 months led to a statistically significant improvement in pruritus severity compared to placebo (**Table 15**).

Baseline scratching severity scores were comparable between the treatment groups with mean scores of 2.80 and 3.01 in the odevixibat and placebo groups, respectively. Based on the MMRM, the LS mean differences in changes from baseline to Weeks 21-24 in scratching severity score was (95% confidence interval [CI]) of -0.88 (-1.44, -0.33), one-sided p = 0.0012 between groups.

The improvement in scratching severity was observed early after the initiation of treatment with odevixibat. The improvements in scratching severity scores for the odevixibat group relative to placebo were observed at each of the 4-week intervals through the primary time point of Month 6.

Table 15: MMRM analysis of change from baseline in scratching severity score (AM and PM Scores Combined) from the ObsRO at month 6 (Weeks 21-24) (Full analysis set; study A4250-012)

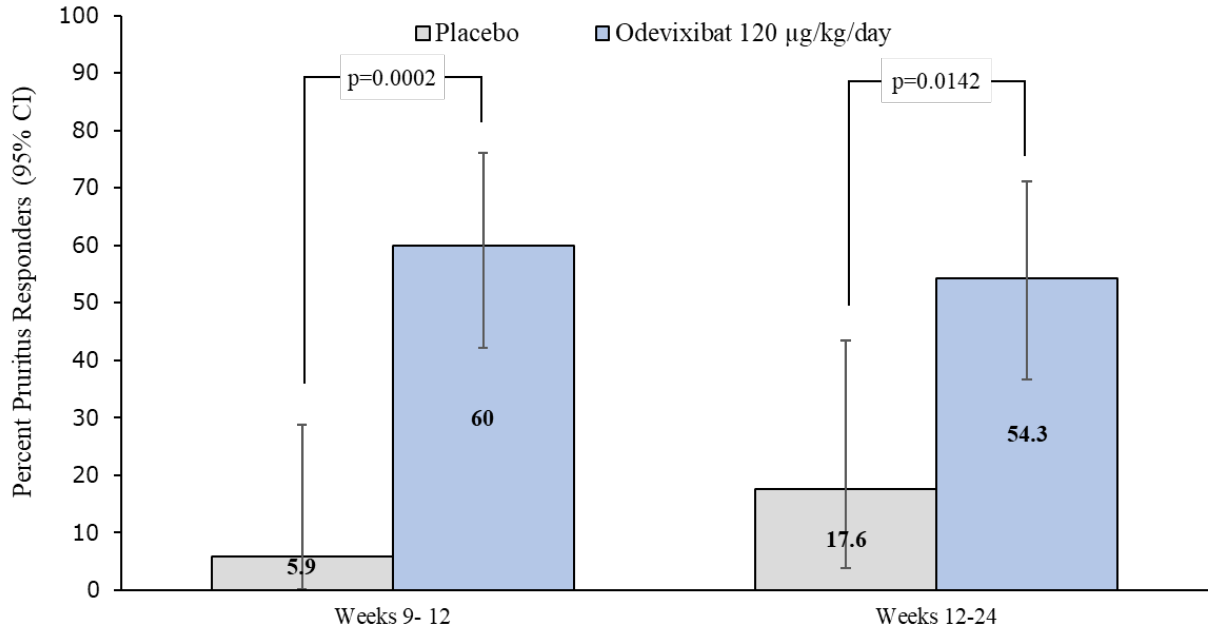
VISIT **STATISTIC**	**PLACEBO** **N=17**	**ODEVIXIBAT** **N=35**
Baseline		
N	17	35
Mean (SD)	3.01 (0.636)	2.80 (0.520)
Median	3.18	2.71
Minimum, maximum	2.1, 4.0	1.9, 4.0
Average of Weeks 21-24		
N	16	34
Mean (SD)	2.18 (0.981)	1.14 (0.913)
Median	2.17	0.99
Minimum, maximum	0.7, 4.0	0.0, 3.0
Change from baseline to Month 6 (Weeks 21-24)		
N	16	34
Mean (SD)	-0.76 (0.820)	-1.66 (0.966)
Median	-0.65	-1.59
Minimum, maximum	-2.3, 0.7	-3.3, 0.7
LS mean (SE)[a]	-0.80 (0.233)	-1.69 (0.174)
95% CI	(-1.27, -0.33)	(-2.04, -1.34)
LS mean difference (SE) (odevixibat-placebo)	-0.88 (0.277)	
95% CI	(-1.44, -0.33)	
One-sided p-value[a]	0.0012	

Results of the sensitivity analyses for the primary efficacy endpoint were consistent with the main analysis confirming the robustness of the results. A post-hoc sensitivity analysis was conducted on the primary efficacy endpoint to assess the potential impact of changes in concomitant antipruritic medications. Results were consistent with the primary analysis.

Responder analysis: meaningful reduction in scratching severity (secondary outcome)

Treatment with odevixibat led to a greater proportion of patients achieving a clinically meaningful reduction in scratching severity score when assessed at both ≥ 1.5-point and ≥ 1.0-point reduction thresholds compared to placebo at Weeks 9-12 and Weeks 21-24.

At Weeks 21-24, 54.3% (19 of 35 patients) were responders in the odevixibat group compared to 17.6% (3 of 17 patients) for the placebo group (Figure 4). Based on these data, the odds of being a responder with this level of decrease in scratching score was 5 times higher at Weeks 21-24 for patients who received odevixibat compared to those who received placebo.



One-sided p-values based on Cochran-Mantel-Haenszel test are presented.
Source: CSR A4250-012 Figure 14.2.7.1 and Table 14.2.11.1.1.

Figure 4: Bar chart of percent of responders (≥ 1.5-point decrease) for pruritus assessments (am and pm scores combined) at weeks 9-12 and weeks 21-24 based on monthly scores – albireo obsro instrument (fas)

The pruritus responder rate using a ≥ 1-point drop from baseline based on monthly scores at Weeks 21-24, was 80.0% (28 of 35 patients) for the odevixibat group compared to 35.3% (6 of 17 patients) for the placebo group.

As a post-hoc analysis, the proportions of patients with ≥ 2-point and ≥ 2.5-point decreases from baseline in monthly pruritus score were also assessed. Similar to the results for the ≥ 1.0-point and the ≥ 1.5-point reductions from baseline, a higher proportion of patients in the odevixibat group achieved ≥ 2- and ≥ 2.5-point reductions (31.4% and 20.0%, respectively) in their pruritus severity at Weeks 21-24 compared to placebo (11.8% and 0%, respectively).

Key Secondary Endpoint: Change in Serum Bile Acid Levels from Baseline to Weeks 20-24

Treatment with odevixibat 120 µg/kg/day for 24 weeks led to a reduction in serum bile acid levels compared to placebo (**Table 16**).

Consistent with values reported in patients with ALGS and the study inclusion criteria, all patients had elevated levels of serum bile acids at baseline. At Weeks 20-24, the mean serum bile acid level in the odevixibat group improved to 149.0 µmol/L, representing a mean change of -88.4 µmol/L, whereas in

the placebo group, the mean serum bile acid level increased from baseline to 270.7 µmol/L, representing a mean change of 24.6 µmol/L.

Based on the MMRM, the LS mean changes from baseline to Weeks 20-24 in serum bile acid levels were -90.35 and 22.39 µmol/L in the odevixibat and placebo groups, respectively, and the LS mean difference (95% CI) of -112.74 (-178.78, -46.69) µmol/L.

Following initiation of treatment with odevixibat, an early improvement was observed in serum bile acid levels. By Week 4, treatment with odevixibat led to an improvement in serum bile acid levels compared to placebo, with an LS mean (95% CI) difference of -99.41 (-164.33, -34.49) µmol/L. The improvements in serum bile acid levels for the odevixibat group relative to placebo were observed at each visit through Week 24.

Table 16: MMRM Analysis of change from baseline in serum bile acid levels at month 6 (Weeks 20-24) (Full analysis set; study A4250-012).

	SERUM BILE ACIDS (µMOL/L)	
VISIT STATISTIC	**PLACEBO N=17**	**ODEVIXIBAT N=35**
Baseline		
N	17	35
Mean (SD)	246.1 (120.53)	237.4 (114.88)
Median	232.0	210.5
Minimum, maximum	56, 428	96, 510
Average of Weeks 20 and 24		
n	17	35
Mean (SD)	270.7 (166.93)	149.0 (102.30)
Median	261.0	126.0
Minimum, maximum	42, 647	26, 377
Change from baseline to Weeks 20 and 24		
n	17	35
Mean (SD)	24.6 (131.63)	-88.4 (120.27)
Median	17.5	-91.0
Minimum, maximum	-246, 291	-350, 252
LS mean (SE)[a]	22.39 (28.463)	-90.35 (21.336)

VISIT STATISTIC	SERUM BILE ACIDS (µMOL/L)	
	PLACEBO N=17	**ODEVIXIBAT N=35**
95% CI	(-34.75, 79.52)	(-133.14, -47.56)
LS mean difference (SE) (odevixibat-placebo)[a]	-112.74 (32.864)	
95% CI	(-178.78, -46.69)	
One-sided p-value	0.0006	

Results of the sensitivity analyses on the key secondary efficacy endpoint were consistent with the main analysis showing the robustness of the results.

Other Secondary Efficacy Analyses

Change from Baseline to Month 6 in Itching Severity Score Based on the PRO

A total of 16 patients were ≥ 8 years of age and completed the PRO at baseline. Mean (SD) itching score (AM and PM combined) at baseline was 2.66 (0.553) in the odevixibat group and 2.14 (0.309) in the placebo group. Consistent with what was observed for the ObsRO, the improvement in mean itching score occurred early during treatment with odevixibat and was sustained through Weeks 21-24. After 24-weeks of treatment, the mean (SD) changes from baseline were -1.63 (0.975) in the odevixibat group compared to -0.78 (0.318) in the placebo group.

Night-time and Daytime Monthly Scratching Severity Scores – ObsRO and PRO

Consistent with the results of the primary pruritus endpoint, which was based on combined AM and PM scores, treatment with odevixibat also led to reductions over the 6-month treatment period in both night-time (AM) and daytime (PM) scratching severity based on the ObsRO and the PRO. The reductions in these pruritus symptoms occurred early in the course of odevixibat treatment and improved over time through Week 24 with little change observed for patients who received placebo.

Sleep Parameters

Consistent with the improvement observed in pruritus, treatment with odevixibat for 24 weeks led to improvements in sleep parameters for patients as measured by observer-reported information (**Table 17**).

Table 17: MMRM analysis of change from baseline in sleep parameters (ObsRO) at weeks 21-24 (FAS)

SLEEP PARAMETER	LEAST SQUARE MEAN (SE) (CHANGE TO WEEKS 21-24)		LEAST SQUARE MEAN DIFFERENCE (95% CI)
	PLACEBO N=17	ODEVIXIBAT N=35	
Percent of days with help falling asleep	-10.09 (9.205)	-43.44 (6.739)	-33.35 (-54.86, -11.85)
Percent of days with soothing	-6.34 (7.929)	-46.71 (5.812)	-40.37 (-58.77, -21.96)
Percent of days sleeping with caregiver	-8.27 (7.152)	-34.52 (5.357)	-26.25 (-43.27, -9.23)
Tiredness	-0.53 (0.196)	-1.13 (0.147)	-0.60 (-1.06, -0.14)
Percent of days seeing blood	-18.98 (5.954)	-27.95 (4.446)	-8.97 (-23.33, 5.39)
Number of awakenings	0.19 (1.315)	-2.70 (0.930)	-2.89 (-6.12, 0.34)
Percent of days taking medication to induce sleep	4.34 (5.782)	-2.79 (4.254)	-7.12 (-20.98, 6.73)

Source: Table 14.2.12.1.

Serum Cholesterol and Triglycerides

Treatment with odevixibat led to larger reductions in serum cholesterol levels over time compared to placebo. Changes from baseline in triglycerides were similar in both treatment groups.

Table 18: change from baseline to week 24 in serum cholesterol and triglycerides (table assembled by assessor)

SERUM CHOLESTEROL	PLACEBO	ODEVIXIBAT
Baseline	n=17	n=35
Mean (SD)	9.209 (4.7778) mmol/L	8.021 (1.9936) mmol/L
Median	8.390	7.430
Minimum, maximum	3.78, 21.52	4.92, 13.60
Change from baseline to Week 24		
LS mean (SE)[a]	0.67 (0.761) mmol/L	-0.91 (0.551) mmol/L
LS mean difference (SE) (odevixibat-placebo)[a]	-1.59 mmol/L	
95% CI	(-3.43, 0.25)	

SERUM TRIGLYCERIDES		
Baseline	N=16	N=35
Mean (SD)	1.933 (1.1725)	1.749 (0.8025)
Median	1.495	1.660
Minimum, maximum	0.66, 4.95	0.78, 3.88
Change from baseline to Week 24	N=16	N=33
Mean (SD)	-0.156 (0.7377)	-0.240 (0.8703)
Median	-0.085	-0.130
Minimum, maximum	-1.99, 1.54	-2.14, 2.56

Changes from Baseline Over Time in the Clinician Xanthoma Scale

All 52 patients were assessed for xanthomas at baseline and at Weeks 12 and 24. Among the 52 patients, 11 patients had xanthomas reported at baseline, including 9 (25.7%) of 35 patients in the odevixibat group and 2 (11.8%) of 17 patients in the placebo group.

In the odevixibat group, 27 (77.1%) of the 35 patients had no change from baseline in xanthomas to the last assessment, 7 (20.0%) patients showed improvements in xanthomas on treatment, and 1 (2.9%) patient worsened from a score of 0 to 1. In the placebo group, 14 (82.4%) of the 17 patients had no change from baseline in xanthomas, 2 (11.8%) patients had improvements in xanthomas to the last assessment, and 1 (5.9%) patient worsened from a score of 0 to 3.

Table 19: percentage of patients with xanthomas

	Placebo	**Odevixibat**
Xanthomas at baseline	2/17 (11.8%)	9/35 (25.7%)
Xanthomas at last assessment		
No change	14/17 (82.4%)	22/35 (77.1%)
Improvements	2/17 (11.8%)	7/35 (20.0%)
Worsening 0-1		1/35 (2.9%)
Worsening 0-3	1/17 (5.9%)	

Endpoints: markers of liver function

Note: Markers of liver function were not presented by the applicant as efficacy endpoints. Nevertheless, these are considered important in the substantiation of the indication "treatment of cholestasis". The following table is created by the assessor based on the tables derived from the CSR from study 012 (**Table 20**).

AST, ALT, Total bilirubin and GGT were all increased at baseline. No significant changes from baseline to week 24 were observed for any of these.

Table 20: Changes from baseline to week 24 in AST, ALT, total bilirubin and GGT

AST (U/L)			
		placebo	odevixibat
baseline	n	17	35
	mean (SD)	160.8 (90.80)	170 (80.51)
	median	131	149
	min, max	73, 427	57,411
week 24	n	17	35
	mean	150.5 (66.27)	216.8 (131.25)
	median	140	190
	min, max	75, 291	69, 575
Change from baseline to week 24	LS mean difference (SE)		55.13 (23.236)
	95% CI		(8.41, 101.86)
ALT (U/L)			
baseline	n	17	35
	mean (SD)	149.1 (84.15)	185.6 (83.2)
	median	114	173
	min, max	52, 403	39, 365
week 24	n	17	35
	mean	146.3 (65.74)	245.4 (120.62)
	median	123	237.5
	min, max	39, 274	88, 550
Change from baseline to week 24	LS mean difference (SE)		61.74 (21.883)
	95% CI		(17.77, 105.72)
Total bilirubin (umol/L)			
baseline	n	17	35
	mean (SD)	61.62 (57.022)	51.99 (43.380)
	median	40	33.9
	min, max	7.4, 195.1	12.8, 189.6
week 24	n	17	35
	mean	64.44 (59.701)	52.64 (42.272)
	median	55.6	37.15
	min, max	7.0, 192.4	11.5, 163.6
Change from baseline to week 24	LS mean difference (SE)		-3.81 (5.247)
	95% CI		(-14.36, 6.74)
GGT (U/L)			

baseline	n	17	35
	mean (SD)	535.5 (345.34)	366.3 (211.31)
	median	415.0	349.0
	min, max	78, 1275	46, 728
week 24	n	17	34
	mean	594.4 (461.14)	459.7 (269.64)
	median	392.0	412.0
	min, max	187, 2020	72, 1172
Change from baseline to week 24	LS mean difference (SE)		38.0 (73.53)
	95% CI		(-109.61, 185.60)

Ancillary analyses

N/A

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of efficacy for trial A4250-012

Title: A Phase 3 Double-Blind, Randomised, Placebo-Controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients with Alagille Syndrome (ASSERT)			
Study identifier	A4250-012 EudraCT Number 2020-004011-28		
Design	A double-blind, randomised, placebo-controlled, multicentre, Phase 3 study to investigate the efficacy and safety of odevixibat at a dose of 120 μg/kg/day administered once daily compared to placebo in patients with Alagille syndrome.		
	Duration of main phase:		24 weeks
Hypothesis	Superiority over placebo		
Treatments groups	Odevixibat		Odevixibat 120 μg/kg/day, 24 weeks, N=35
	Placebo		Placebo, 24 weeks, N=17
Endpoints and definitions	Primary endpoint	ObsRO	Change from baseline to Month 6 (Weeks 21-24) in average AM and PM scratching severity score as measured by the Albireo ObsRO caregiver instrument
	Key secondary	sBA	Change from baseline to the average of Week 20 and Week 24 in serum bile acid levels.
Database lock	29SEP022		
Results and Analysis			

Title: A Phase 3 Double-Blind, Randomised, Placebo-Controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients with Alagille Syndrome (ASSERT)			
Study identifier	A4250-012 EudraCT Number 2020-004011-28		
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): All randomised patients who received at least 1 dose of study drug. Patients were analysed as randomised. The FAS was the primary analysis set for efficacy analyses.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Odevixibat
	Number of subjects	17	35
	ObsRO Mean SD	 -0.76 0.820	 -1.66 0.966
	sBA Mean SD	 24.6 (131.63)	 -88.4 (120.27)
Effect estimate per comparison	Primary endpoint: ObsRO	Comparison groups	Odevixibat - placebo
		LS mean difference	-0.88
		95% CI	-1.44, -0.33
		One sided P-value	0.0012
	Key Secondary: sBA	Comparison groups	Odevixibat - placebo
		LS mean difference	-112.74
		95% CI	-178.78, -46.69
		P-value	0.0006
Notes			

2.6.5.3. Clinical studies in special populations

N/A

2.6.5.4. Supportive study A4250-015

Methods

Study A4250-015 is an ongoing, Phase 3, multicentre, open-label extension study to investigate the long-term efficacy and safety of the 120 µg/kg daily dose of odevixibat in patients with ALGS. Patients who completed the 24-week treatment period in Study A4250-012 were eligible for enrolment. For regulatory submission purposes, an interim analysis, based on the data cut-off of 09SEP2022, was performed to accompany the final analyses of Study A4250-012.

Day 1 of the study was planned to coincide with the Week 24 visit of Study A4250-012. However, if that was not possible due to logistical issues, patients could enrol in the open-label extension Study A4250-015 within 28 days of completion of Study A4250-012. The extension study includes a 72-week treatment period and a 4-week follow-up period. Patients return to the clinic 4, 12, 20, and 24 weeks after the first dose of odevixibat and thereafter every 12 weeks for follow-up assessments. Telephone contact with the patient/caregiver is conducted at Day 14, Week 8, and Week 16 to document concomitant medications, the occurrence of AEs, and compliance with dosing and the eDiary.

Efficacy and safety assessments conducted in this study are identical to those conducted in Study A4250-012. In addition, the study also includes an evaluation of the incidence of biliary diversion and liver transplant. Safety assessments conducted during the study include physical examination, vital sign measurements, clinical laboratory evaluations (including haematology, chemistry, urinalysis, fat-soluble vitamins) liver ultrasound and elastography (where available), review of concomitant medications and AEs, and completion of the fat-soluble vitamin questionnaire.

All efficacy analyses were conducted on the FAS, which was comprised of all patients who received at least 1 dose of study drug in Study A4250-015.

As the study is ongoing, summary information is provided for Weeks 12 and 24 of Study A4250-015; data from all available visits are presented in statistical outputs. Changes from baseline are evaluated using the baseline value from Study A4250-015. As in Study A4250-012, the primary efficacy variable was a change from baseline in scratching severity score based on the ObsRO, with a change from baseline in serum bile acid levels as a key secondary endpoint, results are summarised descriptively. Other secondary and exploratory variables analysed were also similar to those in Study A4250-012, and included sleep parameters, cholesterol, xanthomas, change from baseline in the stage of fibrosis by elastography (where available), symptom assessments, QoL measures, growth, and biomarkers. In addition, the incidence of biliary diversion and/or transplant was assessed.

The same estimand strategy used for the pivotal Study A4250-012 was used for this study. In Study A4250-015, no imputations were conducted for missing data. All data collected through the end of the study were included, except following the ICEs of the requirement for biliary diversion surgery or liver transplant. For this interim analysis, all changes over time were based on assessments conducted from baseline of Study A4250-015.

Results

As of the data cut-off date of 09. September 2022, a total of 50 patients had rolled over to the extension study from Study A4250-012, and 49 had received treatment with odevixibat, including 32 and 17 patients who had previously received odevixibat or placebo, respectively, in Study A4250-012. As of the data cut-off, 48 of the 49 patients were ongoing on treatment. One patient was reported to have discontinued treatment because the patient’s caregiver elected to withdraw from the study as they did not think the study medication was working.

As of the data cut-off date, the median duration of exposure to odevixibat 120 µg/kg/day in Study A4250-015 was 13.29 weeks and ranged from < 1 to 50.3 weeks. Most patients (36 of 49, 73.5%) had received ≤ 24 weeks of treatment at that time; 13 (26.5%) patients had received > 24 weeks with a maximum treatment duration of ~50 weeks in both study groups.

Efficacy Results

In the following section, efficacy data for Weeks 12 and 24, representing 36 and 48 weeks of overall treatment with odevixibat for patients who completed active treatment in Study A4250-012, and up to 24 weeks for patients who received placebo, are summarised.

Changes from Baseline in Scratching Severity Score Based on the ObsRO

Patients who had received odevixibat during Study A4250-012 entered Study A4250-015 with improved pruritus symptoms compared to treatment-naïve patients, with mean (SD) baseline scratching scores of 1.14 (0.938) compared to 2.22 (0.986) for those who had received placebo.

For patients who had received odevixibat in Study A4250-012, continued treatment with odevixibat led to further improvement in scratching severity (Figure 5). Mean (SD) changes from baseline in scratching severity score for this group of patients were -0.35 (0.467) at Weeks 9-12 and -0.45 (0.684) at Weeks 21-24.

For patients who received placebo in Study A4250-012, improvement in pruritus symptoms was observed early following the start of treatment with odevixibat, with continued improvement through Weeks 21-24. Mean (SD) changes in scratching severity scores to Weeks 1-4 were -0.82 (0.451) and to Weeks 9-12 and Weeks 21-24 were -1.43 (0.800) and -2.24 (0.508), respectively.

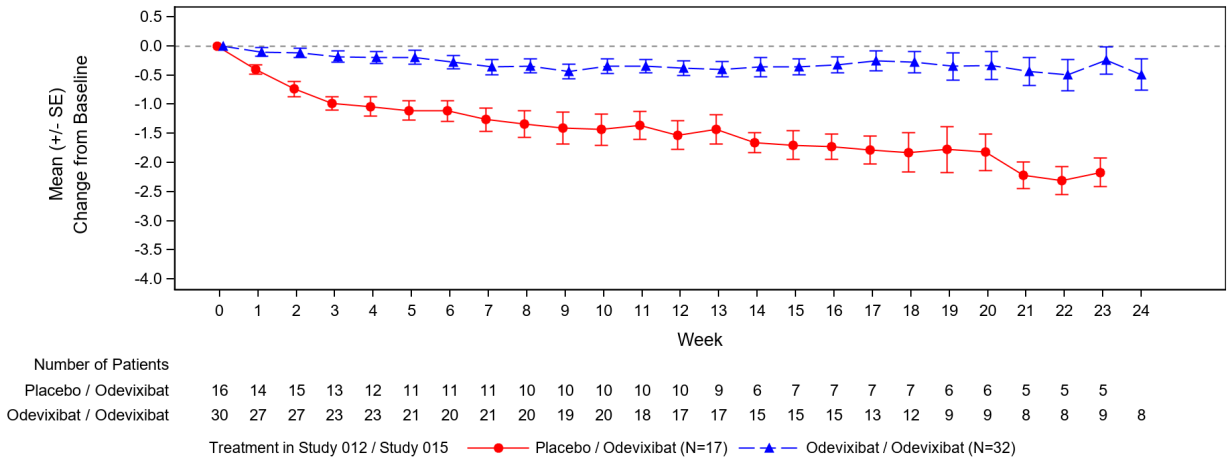


Figure 5: Mean (se) change from study a4250-015 baseline in weekly scratching severity score (am and pm scores combined) – albireo obsro instrument (fas)

Results for nighttime (AM scores) and daytime (PM scores) monthly scratching scores were consistent with those for the combined AM and PM scores.

Clinically Meaningful Improvement in Pruritus Through Week 24

Pruritus responder analyses based on the ≥ 1.5-point and ≥ 1.0-point drop in scratching severity scores were assessed from Study A4250-015 baseline for patients who had received placebo in Study A4250-012. Results for patients who had received odevixibat in Study A4250-012 are not summarised as these patients had already experienced improved pruritus scores on Study A4250-012 with a mean (SD) and median scratching score already near 1.0 (1.14 [0.938]) and 0.98, respectively).

For those patients who received placebo in Study A4250-012, 5 (50.0%) of 10 patients achieved a ≥ 1.5-point reduction, and 7 (70.0%) achieved a ≥ 1.0-point reduction in scratching severity score at Weeks 9-12 after starting treatment with odevixibat; at Weeks 21-24, all 5 patients (100%) with assessments achieved a ≥ 1.5-point reduction.

Changes from Baseline Over Time in Serum Bile Acid Assessments

Treatment with odevixibat 120 µg/kg/day led to reductions in serum bile acids concentration from Study A4250-015 baseline to Week 24 in patients who had received odevixibat in Study A4250-012 and in treatment naïve patients (Figure 6).

For patients who received odevixibat in Study A4250-012, further reductions in serum bile acid levels were observed with continued treatment. At Weeks 12 and 24, the mean (SD) change from baseline in serum bile acid levels were -17.4 (90.60) µmol/L and -70.9 (121.05) µmol/L, respectively.

For patients who received placebo in Study A4250-012, a rapid reduction in serum bile acid levels was observed after the initiation of treatment with odevixibat. By Week 4 of treatment, the mean (SD) change in serum bile acids was -111.2 (76.55) µmol/L. Mean levels of serum bile acids continued to improve through Week 24 with a mean (SD) change from baseline at that time of -120.5 (105.31) µmol/L.

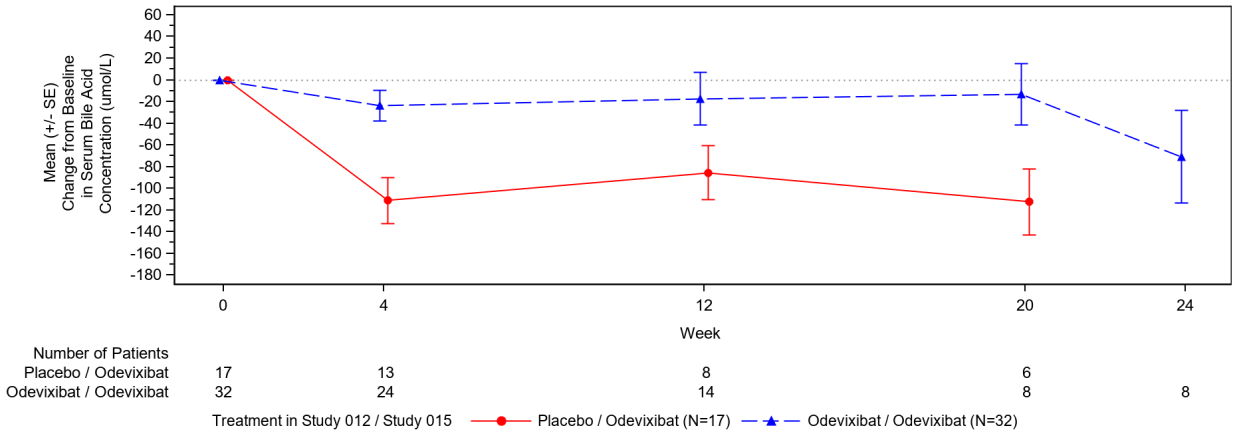


Figure 6: Mean (±se) change from study baseline in serum bile acid levels (µmol/l) by visit (full analysis set, study a450-015)

Changes from Baseline in Sleep Parameters

Consistent with the improvement observed in pruritus, treatment with odevixibat led to improved sleep for patients based on observer-reported information.

For patients who received odevixibat during Study A4250-012, the improvements in sleep parameters observed in that study were sustained over time during treatment in Study A4250-015. Mean (SD) changes from baseline to Weeks 21-24 (n = 6) for this group were -30.26% (47.237%), -14.19% (33.185%), 0.0% (3.912%), for percentage of days with help falling asleep, days with soothing, and days sleeping with the caregiver, respectively; and 0.02 (0.567) for daytime tiredness score.

Among treatment-naïve patients who first received odevixibat in Study A4250-015, improvement from baseline in most sleep parameters occurred early in the course of treatment and was sustained over time on treatment. Mean (SD) changes from baseline to Weeks 1-4 were -9.2% (21.9%), -11.9% (22.0%), and −11.7% (26.6%) for the percentage of days with help falling asleep, with soothing, and sleeping with the caregiver, respectively, and -0.44 (0.644) for daytime tiredness score, and at Weeks 21-24 (n=4) were -46.9% (54.2%) -38.7% (44.9%), -36.0% (41.8%), and -1.62 (0.974), respectively.

Global Impression of Symptoms and Change

Results for global symptom relief based on the GIS and GIC were consistent with the effects of odevixibat on the reduction in pruritus and improvement in sleep, with a high proportion of patients in both study groups reporting both pruritus and sleep were a little better, moderately better, or very much better at Weeks 4, 12, and 24.

For patients who had received odevixibat in Study A4250-012, CaGIC results showed improvements from baseline in both scratching and sleep in 16 (84.2%) of 19 patients at Week 4, in all 14 (100%) patients at Week 12 and all 6 (100%) patients at Week 24.

For patients who had received placebo in Study A4250-012, CaGIC results showed improvements in all patients assessed (100%) for scratching at Week 4 (n = 10), Week 12 (n = 8) and Week 24 (n = 3), and for sleep in 9 (90%) of 10 patients at Week 4 and all patients assessed as Weeks 12 and 24.

Quality of Life: Paediatric Quality of Life Inventory

Quality of life based on the PedsQL showed improvements to Weeks 12 and 24 in total score, family impact score, and all domain scores for patients who had received odevixibat and those who had received placebo in Study A4250-012.

For patients who had received odevixibat, caregiver-reported total score on the PedsQL improved from baseline to Weeks 12 and 24 of Study A4250-015 with a mean (SD) increases of 3.69 (8.606) and 10.54 (4.625). Results for mean (SD) changes in the total score were similar for patients who had received placebo (5.66 [7.174] and 8.28 [10.175] for Weeks 12 and 24, respectively). A review of the caregiver-reported domain scores indicated improvement at Weeks 12 and 24 for all 4 domains, including physical, emotional, school, and school functioning, in these patients.

For the family impact total score, mean (SD) change from baseline to Weeks 12 and 24 for patients who previously received odevixibat were 1.98 (12.332) and 6.60 (15.295), respectively, and for patients who previously received placebo, were 9.18 (13.143) and 9.72 (9.796), respectively. Review of the caregiver-reported domain scores for the family impact module indicated improvements at Weeks 12 and 24 for most of the 8 domains at both assessments, including physical, emotional, social, and cognitive functioning, family relationships, communication, worry, and daily activities.

Changes from Baseline Over Time in Cholesterol

At study entry, patients who received odevixibat in Study A4250-012 had improved cholesterol levels compared to treatment-naïve patients. At Weeks 12 and 24, cholesterol levels were maintained in patients who had received odevixibat (-0.262 [1.1679] mmol/L and 0.520 [1.3192] mmol/L, respectively) and were improved in those who had received placebo (-1.155 [1.2065] and -0.973 [0.6812] mmol/L) in Study A4250-012.

Changes from Baseline Over Time in the Clinician Xanthoma Scale

At the time of the data cut-off, 28 of the 49 patients had baseline and at least 1 post-baseline assessment for xanthomas. Of the 28 patients, 25 (89.3%) had no change from baseline, 1 (3.6%) patient improved, and 2 (7.1%) patients had worsening.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study A4250-012

The efficacy of odevixibat in ALGS patients is based on the results of one pivotal, double-blinded, randomised, placebo-controlled phase III study and a long-term extension study. In general, the design of the study is considered appropriate.

The study population includes male and female patients with ALGS who have pruritus and elevated baseline bile acid levels. Patients with biliary diversion surgery or liver transplant were excluded, as were patients with other types of liver disease. The eligibility criteria are considered appropriate.

The dosing regimen of odevixibat used during the studies is somewhat different from the authorised dose for Bylvay (PFIC) which is 40 ug/kg/day, with the possibility to escalate up to 120 ug/kg/day in case of insufficient response. In the pivotal ALGS study, patients were all treated with 120 ug/kg/day.

Drugs with effects on bile acid concentration in the GI tract or with known effects on GI motility were not allowed. Medications to treat pruritis were permitted, provided the patient was on a stable dosage and no dosage change was planned. This is acceptable.

Pruritus is regarded as one of the most debilitating symptoms of ALGS. Although causality was never unequivocally shown, it is generally considered that the main pruritic agent is elevated serum bile acid levels. The primary and key secondary objectives of the study are, therefore, acceptable.

The primary endpoint is the Change from baseline in scratching to Month 6 (Weeks 21 to 24) as measured by the Albireo ObsRO caregiver instrument, an observer/caregiver reported outcome to measure pruritus. This scale has been validated by the applicant for use in PFIC in earlier PFIC trials and is considered acceptable to measure pruritis. The results of the ObsRO are supported by the patient-reported instrument (PRO).

Based on a blinded interim analysis, the applicant aimed to establish a threshold for a clinically meaningful change in ALGS patients., although considered not optimal the CHMP agreed during scientific advise to use interim data in a blinded way due to the rarity of the disease,. CHMP also recommended including a justification for whether a 1-point drop has the same meaning across the scale. According to the applicant, the results of the blinded psychometric analysis across all anchors and timepoints supported a threshold from 1.0 to 1.5 points for the ObsRO. The upper bound of 1.5-points reduction was used for the primary analysis, corresponding to "at least a little better" on the PGIS/CaGIS/CGIS scale. Of note, in the PFIC dossier, a 1-point decrease in pruritus score was clinically meaningful.

As secondary endpoints, a wide variety of parameters is measured which are implicated in ALGS including serum bile acids (the main secondary endpoint, hierarchically tested), liver function, xanthomas, cholesterol, sleep and HRQoL (both related to the pruritus). These endpoints are considered useful to establish the impact of odevixibat on various aspects of the disease. Given the short duration of the study, no effects on survival with native liver can be measured. The chosen endpoints are considered acceptable and adequate to address the study objectives.

The study was designed to have 90% power to detect or refute a clinically relevant difference on population level, assuming a 1.2. change of pruritis. This is in line with the treatment effect observed in the PFIC trial, where a slightly smaller effect was observed. Sample size re-estimation was performed, based on non-comparative blinded data for which no alpha adjustment is required. The sample size was increased from 36 to 48 evaluable patients. It is considered that dropouts should have been accounted for in the sample size in line with the statistical analysis.

The methods for randomisation and blinding are acceptable.

Pruritis is analysed as the change in scratching severity score from baseline to month 6 (21-24 weeks), based on the worst scratching score on the full analysis set, including all data collected through the end of study regardless of treatment discontinuation and regardless of the change in pruritis medication (prohibited by the protocol), while excluding data following the intercurrent events (ICE) of biliary diversion surgery or liver transplant. The proposed primary analysis method will model outcomes following biliary diversion surgery or liver transplantation informed by the patients' outcomes prior to the surgery/transplant and by the trajectories of other patients in the trial.

The applicant mentions that changes in anti-pruritis medication during the study is prohibited (but it could still have taken place) and argues that use of anti-pruritus medication will not be considered as an intercurrent event in this study and all efficacy data after a change in anti-pruritus medication will be included in the analyses. CHMP did not agree with the decision not to consider it as an intercurrent event only because it is difficult to account for but views it as a potentially relevant intercurrent event that (implicitly) was handled with a treatment policy strategy, meaning for the intercurrent event anti-pruritis medication outcomes are included regardless of the use of anti-pruritic medication. However, as the potential impact will be assessed the approach will be taken into consideration.

The primary analysis model, a mixed model assumes that patients with missing data will have similar outcomes as patients without missing data based on covariates in the model. It is questionable if that will be the case, and this would require further substantiation. However, given the limited number of intercurrent events and missing data (and the planned sensitivity and supportive analysis, this issue was not further pursued. The analysis model includes baseline age stratification, average AM + PM scratching scores, and direct bilirubin; treatment group; time in months as a categorical variable; and a treatment-by-time interaction, as specified in the SAP.

The key secondary endpoint of serum bile acids was hierarchically tested; the results of all other secondary endpoints were not included in the testing strategy and were considered supportive and only descriptive analysis were used.

The planned subgroup analyses were considered relevant; however, overall numbers and numbers within subgroups are small.

Study A4250-015

Patients from the pivotal study could enrol in the long-term extension study to continue odevixibat treatment at a dose of 120 ug/kg/day. Patients who were on placebo could switch to odevixibat in this study. Besides the endpoints also measured in study 012, in the LTFU study, data on biliary diversion surgery and liver transplant is recorded. As the study lasts for 72 weeks, additional long-term data could be collected with this study. It is, however, doubted whether 72 weeks is sufficient to detect changes in the occurrence of surgery or liver transplant.

As this is an open-label study, the results have to be interpreted with caution as many Observer and patient-reported outcomes were used in this study which are prone to bias.

Efficacy data and additional analyses

Study A4250-012

Thirty-five patients were randomised to the odevixibat arm and 17 to the placebo arm. Two patients were screened but did not meet the inclusion criteria of the study. Patients were primarily included from study sites in the EU and the US; hence the data can be regarded as representative of the European population.

Amendments made to the protocol were country specific.

Overall, protocol deviations led to the exclusion of the PP population in 5 cases. Reasons included missing pruritus assessments (1 patient in placebo and 1 in odevixibat arm), compliance issues (1 patient in odevixibat arm) or treatment interruptions due to AEs in 2 patients. These exclusions are understood and are not considered to greatly impact the efficacy conclusions.

Patients in the odevixibat arm were slightly older, with fewer patients in the odevixibat group <2 years of age (8.6%) compared to the placebo group (29.4%). Time since diagnosis consequently also differed, with a median of 2.7 years in the placebo group and 5.5 years in the odevixibat group. Theoretically, this might translate to the patients in the odevixibat group having more advanced liver disease. However, this does not clearly show from the baseline disease characteristics, except for ALT which was slightly higher in the odevixibat group. In fact, GGT was lower in the odevixibat group compared to placebo. Overall, the observed imbalances in the placebo and odevixibat group are unlikely to have major impact on the conclusions, also since baseline pruritus score and serum bile acid levels were comparable. Virtually all patients had concomitant use of anti-pruritic medication. The applicant reports 10 major protocol deviations due to the use of prohibited medication or unauthorised dose changes. However, a requested sensitivity analysis showed that these protocol deviations have not impacted the pruritus outcome.

The primary endpoint was met. A significant difference in a decrease from baseline to week 24 in scratching score was observed for the odevixibat (-1.66) group versus the placebo group (-0.79), with an LS mean difference -0.88, 95% CI -1.44, -0.33, one-sided p-value 0.0012. All sensitivity and supplementary analyses of pruritus showed consistent results of both the direction and magnitude of effect. The effect observed in the per-protocol analysis was slightly higher.

The responder analysis conducted as secondary outcome is considered important to support interpretation of the clinical relevance of this effect on pruritus relief. A 1.5-point reduction was used for the primary analysis. After 24 weeks of treatment, 19/35 (54.3%) of odevixibat-treated patients reported a >1.5-point decrease in pruritus score, compared to 3/17 (17.6%) of the placebo patients. This is considered a benefit for the patients, corresponding to a score of at least "a little better". The applicant has provided argumentation that a 1-point reduction is likely to be perceived the same across the scale, independent of baseline value.

To assess the impact of the choice of the responder definition, the applicant has submitted additional responder analyses with a 2- and 2.5-point reduction classified as a responder. At Weeks 21-24, the proportion of pruritus responders with a $\geqslant$ 2.0point drop from baseline based on monthly scores was 31.4% (11 of 35 patients) for the odevixibat group compared to 11.8% (2 of 17 patients) for the placebo group. For the more stringent decrease from baseline in monthly pruritus score of $\geqslant$2.5-points, none of the patients in the placebo group met this criterion at Week 21-24 compared to 10 (28.6%) of the 35 patients at Week 21-24.

The key secondary endpoint showed rapid and sustained decreases in serum bile acids due to odevixibat treatment. The timing of the decrease coincides with the timing of the decrease in pruritus score, which supports the association between the biomarker and symptoms. The results of the sensitivity analyses support this conclusion. However, the clinical meaningfulness of the observed effect is not clear as it is not known what reduction in sBA would lead to an improvement in clinical endpoints. For the PFIC dossier, a responder analysis was chosen with a responder being defined as having at least a 70% decrease in sBA, or having sBA levels ≤70 µmol/L, which was considered as clinically relevant. The applicant has conducted analyses, assessing the effect on pruritus in patients with more or less than a 100 µmol/L decrease in sBA. Although other contributing factors to pruritus cannot be ruled out, a good correlation as observed with decreases in sBA of more than 100 µmol/L and pruritus relief.

A decrease in pruritus score based on the PRO was observed in 16 patients above 8 years of age. The mean change from baseline to weeks 21-24 in the placebo group was -0.78 (0.318) versus -1.63 (0.975) in the odevixibat group. This is the same order of magnitude as was observed with the ObsRO. This data could therefore be seen as supportive. In addition, the night-time and daytime monthly scratching scores were in line with the total scores for both the ObsRO and the PRO.

Improvements in sleep parameters were observed in the ObsRO, especially on the percentage of days the patient needed soothing or help to fall asleep. This is regarded as a benefit not only for the patients themselves but also for the caregivers for whom the care can be very burdensome. Numerical reductions in sleep parameters were also observed for the PRO; however, these were less pronounced.

The percentages of caregivers who reported improvements in global symptoms were consistently higher in the odevixibat group compared to the placebo group. By week 24, 87.5% and 78.1% of the caregivers reported improvements in scratching and sleep compared to 35.3% and 29.4% in the placebo group. This is considered a benefit and is supportive of the primary efficacy endpoint.

Patients with ALGS often present with dyslipidaemia. Numerical changes in favour of odevixibat were reported for the improvement of hypercholesterolaemia. No clear difference was observed in the improvement of hypertriglyceridaemia between the odevixibat and the placebo group.

Numerically, there seems to be a small difference in favour of odevixibat in the percentage of patients with xanthomas at baseline that improved to the last assessment. However, the numbers are small, and there was also more room for improvement in the Odevixibat group. Therefore, no robust conclusions can be drawn. For the majority of patients, no change was observed. It seems no new incidences of xanthomas were reported, except for 1 patient in the odevixibat group.

Numerical improvements were observed in PedsQL in favour of odevixibat. However, the clinical relevance of the observed numerical improvements cannot be established. Patients and caregivers did report a meaningful change since the start of treatment in favour of odevixibat (78.1%) versus 26.7% in the placebo group as measured by the patient and caregiver impression of treatment effect.

ALGS patients are known to have growth deficits. Growth parameters were included as exploratory endpoints in the study. No clinically relevant catch-up growth, or improvement in growth parameters could be attributed to odevixibat treatment.

No positive effects on liver values were observed during odevixibat treatment. AST, ALT, and bilirubin were all elevated at baseline, and stayed elevated after 24 weeks of treatment. As progressive liver damage is considered one of the hallmarks of cholestasis in ALGS patients, the absence of a clinically relevant improvement in liver function is disappointing, especially since approximately 60% of patients with ALGS will undergo a liver transplant before the age of 18.

Study A4250-015

As of the data cut-off date, 32 patients from the odevixibat group and 17 from the placebo group had rolled over. As of the data cut-off, 48 of the 49 patients were ongoing on treatment. One patient was reported to have discontinued treatment because the patient's caregiver elected to withdraw from the study as they did not think the study medication was working.

The duration of exposure varied from < 1 to 50.3 weeks, 36 of 49, (73.5%) had received ≤ 24 weeks of treatment and 13 (26.5%) patients had received > 24 weeks of treatment. This follow-up is still limited and few conclusions about long-term treatment can be drawn from this data.

Patients who had received odevixibat in study A4250-012 showed a small but continued improvement in pruritus score. For the patients switching from placebo to odevixibat, slightly greater improvements

were observed in pruritus, but this could be due to the open-label character of the study. Overall positive effects on HRQoL supported the positive changes in pruritus.

2.6.7. Conclusions on the clinical efficacy

Taken together, the presented data support clinically relevant but modest treatment effects on pruritus and associated sleep problems. The pharmacodynamic effect of odevixibat is supported by the sustained decrease in serum bile acids. No clear effects were observed on dyslipidaemia, xanthomas, and growth. More importantly, there was no indication of improvements in liver function markers, such as ALT/AST and bilirubin.

Considering all of the above, the indication claims on "treatment of cholestatic pruritus" is accepted from an efficacy perspective.

2.6.8. Clinical safety

The characterisation of the safety profile in ALGS patients is based on data from the completed Phase 3, randomised, double-blind, 24-week study that evaluated odevixibat at a dose of 120 µg/kg/day compared to placebo in 52 patients with ALGS (A4250-012) and from pooled analyses of data from Study A4250-012 and its ongoing open-label extension study (A4250-015). The open-label extension study includes patients who completed Study A4250-012 and who received odevixibat 120 µg/kg/day for up to 72 weeks. For the ongoing extension study, all available data as of the interim data cut on 09SEP2022 are included in this analysis.

Of importance for the assessment of safety, patients with ALGS are known to have multiple comorbidities, including malabsorption leading to fat-soluble vitamin deficiencies and steatorrhea with diarrhoea, coagulopathies, and hepatic impairment with deranged hepatic biochemical parameters (e.g. ALT, AST, total and direct bilirubin, ALP, GGT), clinical hepatitis, and exacerbation of cholestasis.

2.6.8.1. Patient exposure

In pivotal study A4250-012, all 52 randomised patients completed the planned 24-week treatment period, with 50 of the 52 patients electing to roll over to the longer-term extension study A4250-015. Forty-nine of these 50 patients were dosed as of the data cut-off date (09SEP2022).

In the Pooled Phase 3 group, median duration of exposure was 29.57 weeks and ranged from < 1 to 74.4 weeks. Overall, 36 (69.2%) of the 52 patients had received > 24 weeks of odevixibat, with 10 (19%) patients receiving odevixibat for > 48 weeks and 1 (1.9) patient receiving odevixibat for >72 weeks. Total patient-years of exposure to odevixibat was 31.5 years in the Pooled Phase 3 group (**Table 22).**

Table 22: Duration of study treatment (safety analysis set)

EXPOSURE PARAMETER	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17)	ODEVIXIBAT (N=35)	ODEVIXIBAT[A] (N=52)
Duration of exposure (weeks)			
N	17	35	52
Mean (SD)	24.26 (0.485)	23.94 (0.726)	31.65 (17.537)
Median	24.00	24.00	29.57
Minimum, maximum	23.7, 25.1	21.1, 26.0	0.7, 74.4
Total Patient-Years of	7.9	16.1	31.5
Duration category, n (%)			
≤ 4 weeks	0	0	4 (7.7)
> 4 - ≤ 8 weeks	0	0	2 (3.8)
> 8 - ≤ 12 weeks	0	0	1 (1.9)
> 12 - ≤ 16 weeks	0	0	3 (5.8)
> 16 - ≤ 20 weeks	0	0	1 (1.9)
> 20 - ≤ 24 weeks	9 (52.9)	22 (62.9)	5 (9.6)
> 24 - ≤ 28 weeks	8 (47.1)	13 (37.1)	8 (15.4)
> 28 - ≤ 32 weeks	NA	NA	5 (9.6)
> 32 - ≤ 36 weeks	NA	NA	4 (7.7)
> 36 - ≤ 40 weeks	NA	NA	4 (7.7)
> 40 - ≤ 44 weeks	NA	NA	4 (7.7)
> 44 - ≤ 48 weeks	NA	NA	1 (1.9)
> 48 - ≤ 60 weeks	NA	NA	7 (13.5)
> 60 - ≤ 72 weeks	NA	NA	2 (3.8)
>72 - 84 weeks	NA	NA	1 (1.9)

NA: not applicable; ND: not done; SD: standard deviation.

[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015.

Source: ALGS ISS Table 14.1.7

OLE update (07 FEB 2024 data cut-off):

A total of 50 patients were enrolled and received treatment with odevixibat, including 33 who had received odevixibat in Study A4250-012 and 17 who had received placebo, i.e. were treatment-naïve upon entry in Study A4250-015. Overall, 44 (88%) of the 50 patients completed the 72-week

treatment period and 6 (12.0%) patients discontinued treatment prior to that time, including 1 patient each due to adverse event (AE) and withdrawal of consent, and 4 patients due to other reasons (2 for lack of effectiveness, 1 for liver transplant and 1 who switched to alternate therapy). In total, 40 of the 44 patients who completed to Week 72 elected to enrol in the optional extension treatment period, 36 of whom are ongoing on treatment with odevixibat as of the data cutoff of 07FEB2024. Three patients did not enrol in the extension period as they were switched to commercially available odevixibat, and 1 patient was referred for liver transplant. Median duration of exposure to study treatment overall was 80.64 weeks as of the data cutoff. Most patients (42 of 50, 84.0%) had received > 72 weeks of treatment at that time. Maximum duration of treatment was 107.9 weeks (2 years).

2.6.8.2. Adverse events

In the Pooled Phase 3 group, 43 (82.7%) of 52 patients who received odevixibat in Studies A4250-012 and/or A4250-015 experienced at least 1 TEAE. In Study A4250-012, the overall incidence of TEAEs was similar in the odevixibat and placebo groups (74.3% and 70.6%, respectively) (Table 23).

Most TEAEs were Grade 1 or 2 in severity. Grade 3 TEAEs were reported in 7 (13.5%) of the 52 patients in the Pooled Phase 3 group. During Study A4250-012, events of Grade 3 severity were reported in 5 (14.3%) patients in the odevixibat group and 2 (11.8%) in the placebo group. There were no Grade 4 or 5 events in either Study A4250-012 or A4250-015.

The majority of TEAEs were reported as unrelated to the study treatment by the Investigators. Drug-related TEAEs were reported in 15 (28.8%) patients in the Pooled Phase 3 group. In Study A4250-012, the incidence of drug-related AEs was 22.9% in the odevixibat group and 17.6% in the placebo group. Drug-related TEAEs are summarised in **Table 25**.

Table 23: Overall summary of treatment-emergent adverse events (Safety analysis set, integrated data)

	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
PATIENTS WITH ANY:	PLACEBO (N=17) N (%) / E	ODEVIXIBAT (N=35) N (%) / E	ODEVIXIBAT[A] (N=52) N (%) / E
TEAEs	12 (70.6) / 42	26 (74.3) / 104	43 (82.7) / 173
Drug-Related TEAEs	3 (17.6) / 4	8 (22.9) / 17	15 (28.8) / 25
Severe (Grade ≥ 3) TEAEs	2 (11.8) / 3	5 (14.3) / 8	7 (13.5) / 11
Serious TEAEs	2 (11.8) / 5	5 (14.3) / 8	6 (11.5) / 11
Drug-Related Serious TEAEs	0	1 (2.9) / 2	1 (1.9) / 2
TEAEs Leading to Death	0	0	0
TEAEs Leading to Study Treatment Interruption	0	3 (8.6) / 4	7 (13.5) / 10
TEAEs Leading to Dose Reduction	0	1 (2.9) / 2	1 (1.9) / 2

PATIENTS WITH ANY:	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17) N (%) / E	ODEVIXIBAT (N=35) N (%) / E	ODEVIXIBAT[A] (N=52) N (%) / E
TEAEs Leading to Study Treatment Discontinuation	0	0	0

E = number of events; TEAE: treatment-emergent adverse event. [a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015. Source: ALGS ISS Table 14.3.1.1.

Common (≥ 5%) TEAEs reported in the odevixibat group in Study A4250-012 or in the Pooled Phase 3 group are presented in Table 24.

In the Pooled Phase 3 group, the most common types of events reported among patients who received odevixibat were events in the Infections and infestations SOC and Gastrointestinal disorders SOC. The most common TEAEs (occurring in ≥ 10% of patients) during treatment with odevixibat were diarrhoea (15 patients, 28.8%), pyrexia (11 patients, 21.2%), nasopharyngitis (8 patients, 15.4%), COVID-19 infection (7 patients, 13.5%), and abdominal pain (6 patients; 11.5%) **Table 24**.

A review of the EAIR (exposure adjusted incidence rates) for TEAEs did not indicate an increase in incidence rate with longer-term exposure to odevixibat, with an incidence of 3.99 events per patient-year (PPY) across all odevixibat treatment in the Pooled Phase 3 group and 3.93 for the odevixibat group during 24 weeks of treatment in Study 4250-012.

Table 24: Treatment-emergent adverse events (≥ 5% of patients in the odevixibat group in study A4250-012 or in the pooled population) by system organ class and preferred term (Safety analysis set, integrated data)

MedDRA SOC Preferred Term	**Study A4250-012 (By Treatment)**		**Studies A4250-012/ A4250-015 pooled**
	Placebo (N=17) n (%)	**Odevixibat (N=35) n (%)**	**Odevixibat[a] (N=52) n (%)**
Infections and infestations	**7 (41.2)**	**17 (48.6)**	**26 (50.0)**
Nasopharyngitis	1 (5.9)	2 (5.7)	8 (15.4)
COVID-19	4 (23.5)	5 (14.3)	7 (13.5)
Bronchitis	0	3 (8.6)	5 (9.6)
Upper respiratory tract infection	2 (11.8)	3 (8.6)	5 (9.6)
Respiratory tract infection	1 (5.9)	3 (8.6)	4 (7.7)
Gastroenteritis	0	2 (5.7)	3 (5.8)
Conjunctivitis	0	2 (5.7)	2 (3.8)

MedDRA SOC Preferred Term	Study A4250-012 (By Treatment)		Studies A4250-012/ A4250-015 pooled
	Placebo (N=17) n (%)	**Odevixibat (N=35) n (%)**	**Odevixibat[a] (N=52) n (%)**
Gastrointestinal disorders	**2 (11.8)**	**11 (31.4)**	**18 (34.6)**
Diarrhoea	1 (5.9)	10 (28.6)	15 (28.8)
Abdominal pain	1 (5.9)	4 (11.4)	6 (11.5)
Vomiting	1 (5.9)	2 (5.7)	3 (5.8)
General disorders and administration site conditions	**4 (23.5)**	**9 (25.7)**	**12 (23.1)**
Pyrexia	4 (23.5)	8 (22.9)	11 (21.2)
Asthenia	0	2 (5.7)	2 (3.8)
Investigations	**2 (11.8)**	**3 (8.6)**	**5 (9.6)**
International normalised ratio increased	2 (11.8)	1 (2.9)	3 (5.8)
Weight decreased	0	2 (5.7)	2 (3.8)
Respiratory, thoracic, and mediastinal disorders	**1 (5.9)**	**3 (8.6)**	**4 (7.7)**
Cough	1 (5.9)	3 (8.6)	4 (7.7)
Vascular disorders	***0***	***3 (8.6)***	***3 (5.8)***
Haematoma	0	3 (8.6)	3 (5.8)

[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015. Source: ALGS ISS Table 14.3.1.11.

Infections

The overall incidence of TEAEs in the Infections and Infestations SOC in the Pooled Phase 3 group was 50.0% (26 of 52 patients), with the most common types of infections being nasopharyngitis (8 patients; 15.4%), COVID-19 (7 patients; 13.5%), bronchitis and upper respiratory tract infection (each 5 patients; 9.6%), respiratory tract infection (4 patients; 7.7%), and gastroenteritis (3 patients; 5.8%). These types of infections are common in paediatric patients. All infections were assessed by the Investigator as unrelated to study drug.

Overall, the profile of infections seen in the odevixibat and placebo group in Study A4250-012 was similar (51.4% and 58.8% in the odevixibat and placebo groups, respectively). Furthermore, the profile of infections seen in the odevixibat group in Study A4250-012 was similar to that seen in the Pooled Phase 3 group.

OLE update:

Overall, 47 (94.0%) of the 50 patients experienced at least 1 treatment-emergent AE (TEAE) during the study, including 30 (90.9%) of the 33 patients previously treated with odevixibat in Study A4250-

012 and all 17 patients who received placebo. Most TEAEs were Grade 1 or 2 in severity and assessed as unrelated to study treatment. Events of Grade 3 severity were reported in 12 (24.0%) patients overall, including 5 (15.2%) of 33 patients who previously received odevixibat in Study A4250-012 and 7 (41.2%) of 17 who received placebo. Drug-related TEAEs were reported in 13 (26.0%) patients overall, including 6 (18.2%) patients and 7 (41.2%) patients who previously received odevixibat and placebo, respectively. There were no deaths during the study. Treatment-emergent SAEs were reported in 11 (22.0%) of the 50 patients; all were assessed as unrelated to odevixibat.

One patient discontinued treatment due to a TEAE of blood bilirubin increased. Treatment interruptions due to TEAEs were reported in 5 (10.0%) patients and dose reduction was reported 2 (4.0%).

Overall, 11 (22.0%) of the 50 patients experienced treatment-emergent SAEs. All SAEs by preferred term were reported in a single patient and all were reported as unrelated to treatment with odevixibat. The most commonly reported SAEs were in the SOC of infections and infestations, reported in 5 (10.0%) of the 50 patients, including 1 report each of pneumonia, gastroenteritis, rotavirus gastroenteritis, enterovirus infection, and chronic otitis media.

Gastrointestinal Disorders

The overall incidence of TEAEs in the Gastrointestinal disorders SOC in the Pooled Phase 3 group was 38.5% (20 of 52 patients). The most common gastrointestinal disorders in the Pooled Phase 3 group were diarrhoea (15 patients; 28.8%), abdominal pain (6 patients; 11.5%), and vomiting (3 patients; 5.8%). All other gastrointestinal disorders occurred in 1 or 2 patients only. Most gastrointestinal disorders among patients in the Pooled Phase 3 group were Grade 1 or 2 in severity. Three (5.8%) patients experienced a Grade 3 gastrointestinal disorder, including 1 (1.9%) case each of abdominal pain, constipation, diarrhoea, and haematemesis. Drug-related gastrointestinal disorders were reported in 11 (21.2%) patients, most commonly reported diarrhoea (6 patients; 11.5%). Other study drug-related gastrointestinal disorders occurred in 1 or 2 patients only, and included abdominal pain, upper abdominal pain, and vomiting (each 2 patients; 3.8%) and faeces discoloured, frequent bowel movements, haematemesis, and nausea (each 1 patient; 1.9%). In 3 (5.8%) patients in the Pooled Phase 3 group, a gastrointestinal disorder was reported as an SAE (see below).

In Study A4250-012, gastrointestinal disorders were reported with higher incidence among patients who received odevixibat (34.3%) compared to patients who received placebo (11.8%). As was the case in the Pooled Phase 3 group, diarrhoea was the most common gastrointestinal TEAE, with this event reported at a higher incidence in patients who received odevixibat (28.6%) compared to patients who received placebo (5.9%).

There was no increase in the incidence rate of these events with longer-term treatment.

Other TEAEs reported in ≥5% of patients

Other TEAEs reported in ≥ 5% of patients in the Pooled Phase 3 group included pyrexia (11 patients; 21.2%), cough (4 patients; 7.7%), and haematoma and INR increased (each 3 patients; 5.8%). Of these events occurring in the Pooled Phase 3 group, one case of pyrexia and one case of INR increase were assessed by the Investigator as severe, with this latter event also being serious.

A further review was conducted for the 3 cases of haematoma as this was the only potential sequalae reported in >5% of odevixibat patients with no patients reporting this event in the placebo group. All 3 reported cases were Grade 1 in intensity and assessed as unrelated to treatment by the Investigators. Investigation regarding causality of the events was conducted with all 3 of the haematoma events reported as related to trauma in young children by the treating physician. Further, review of INR levels, which were all < 1.2, and platelet counts, which were all in the normal range, did not yield any safety concerns.

Adverse Events of Grade 3 Severity

In the Pooled Phase 3 group, 7 (13.5%) of the 52 patients experienced a TEAE of Grade 3 severity. The incidence of Grade TEAEs in Study A4250-012 was similar in the odevixibat group (5 patients, 14.3%) and the placebo group (2 patients, 11.8%).

Gastrointestinal disorders and infections were the most common Grade 3 TEAEs, each occurring in 3 (5.8%) of 52 patients overall in the Pooled Phase 3 group. No individual Grade 3 TEAE by preferred term occurred in > 1 patient. One patient experienced a grade 3 event of haematemesis and INR increased, which is discussed in the SAE section.

No Grade 4 or Grade 5 events were reported in either Study A4250-012 or Study A4250-015.

Adverse drug reactions

Drug-related TEAEs reported in > 1 patient in the Pooled Phase 3 group are presented in **Table 25**.

In the Pooled Phase 3 group, drug-related TEAEs were reported in 15 (28.8%) of 52 patients during treatment with odevixibat. The only study drug-related TEAEs reported by > 1 patient overall were gastrointestinal disorders, including diarrhoea (6 patients, 11.5%) and abdominal pain, upper abdominal pain, and vomiting (each 2 patients; 3.8%).

In Study A4250-012, the overall incidence of drug-related TEAEs was similar in the 2 treatment groups reported in 8 (22.9%) of the 35 patients who received odevixibat and 3 (17.6%) of 17 patients who received placebo. In this study, there was a higher incidence of drug-related TEAEs in the gastrointestinal disorders SOC in odevixibat treated patients (20.0%) compared to placebo-treated patients (5.9%), primarily reports of diarrhoea.

Table 25: Treatment-related treatment-emergent adverse events occurring in > 1 patient in the pooled population, by system organ class and preferred term (Safety analysis set, integrated data)

	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
MEDDRA SOC PREFERRED TERM	PLACEBO (N=17) N (%)	ODEVIXIBAT (N=35) N (%)	ODEVIXIBAT[A] (N=52) N (%)
Patients with any Drug-related TEAEs	3 (17.6)	8 (22.9)	15 (28.8)
Gastrointestinal disorders	1 (5.9)	7 (20.0)	11 (21.2)
Diarrhoea	1 (5.9)	4 (11.4)	6 (11.5)
Abdominal pain[b]	1 (5.9)	1 (2.9)	2 (3.8)
Abdominal pain upper[b]	0	1 (2.9)	2 (3.8)
Vomiting	0	2 (5.7)	2 (3.8)

MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class; TEAE: treatment-emergent adverse event. [a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015. [b] These events occurred in different patients; thus, the overall incidence of abdominal pain/upper abdominal pain was 4 (7.7%) (CSR A4250-012 Listing 16.2.7.1 and CSR A4250-015 Listing 16.2.7.1).

OLE update:

Overall, 13 (26.0%) of the 50 patients experienced TEAEs assessed as treatment-related (**Table 26**). Diarrhoea and vitamin D deficiency were the only treatment-related TEAEs reported in > 1 patient. Treatment-related diarrhoea was reported in 5 (10.0%) of the 50 patients, and treatment-related vitamin D deficiency in 2 (4.0%) patients. All reports of treatment-related diarrhoea and vitamin D deficiency were Grade 1 or 2 in severity.

Table 26: Treatment-related treatment-emergent adverse events by system organ class and preferred term (Full analysis set, week 72 analysis)

SYSTEM ORGAN CLASS **PREFERRED TERM**	**PLACEBO[A]/ ODEVIXIBAT N=17 N (%)**	**ODEVIXIBAT[A]/ ODEVIXIBAT N=33 N (%)**	**TOTAL N=50 N (%)**
Patients with any TEAEs	**7 (41.2)**	**6 (18.2)**	**13 (26.0)**
Gastrointestinal disorders	**4 (23.5)**	**4 (12.1)**	**8 (16.0)**
Diarrhoea	3 (17.6)	2 (6.1)	5 (10.0)
Abdominal pain	0	1 (3.0)	1 (2.0)
Abdominal pain upper	1 (5.9)	0	1 (2.0)
Frequent bowel movements	1 (5.9)	0	1 (2.0)
Haematochezia	0	1 (3.0)	1 (2.0)
Nausea	1 (5.9)	0	1 (2.0)
Investigations	**3 (17.6)**	**2 (6.1)**	**5 (10.0)**
Alanine aminotransferase increased	1 (5.9)	0	1 (2.0)
Aspartate aminotransferase increased	0	1 (3.0)	1 (2.0)
Blood 25-hydroxycholecalciferol decreased	1 (5.9)	0	1 (2.0)
Blood bilirubin increased	1 (5.9)	0	1 (2.0)
Hepatic enzyme increased	0	1 (3.0)	1 (2.0)
International normalised ratio increased	1 (5.9)	0	1 (2.0)
Transient elastography[b]	0	1 (3.0)	1 (2.0)
Metabolism and nutrition disorders	**2 (11.8)**	**1 (3.0)**	**3 (6.0)**
Vitamin D deficiency	1 (5.9)	1 (3.0)	2 (4.0)
Vitamin E deficiency	1 (5.9)	0	1 (2.0)
Eye disorders	**1 (5.9)**	**0**	**1 (2.0)**
Vision blurred	1 (5.9)	0	1 (2.0)
Hepatobiliary disorders	**1 (5.9)**	**1 (3.0)**	**2 (4.0)**

SYSTEM ORGAN CLASS PREFERRED TERM	PLACEBO[A]/ ODEVIXIBAT N=17 N (%)	ODEVIXIBAT[A]/ ODEVIXIBAT N=33 N (%)	TOTAL N=50 N (%)
Hepatic fibrosis	1 (5.9)	0	1 (2.0)
Hepatomegaly[b]	0	1 (3.0)	1 (2.0)
Nervous system disorders	**1 (5.9)**	**0**	**1 (2.0)**
Headache	1 (5.9)	0	1 (2.0)
Skin and subcutaneous tissue disorders	**0**	**1 (3.1)**	**1 (2.0)**
Pruritus	0	1 (3.1)	1 (2.0)

2.6.8.3. Serious adverse event/deaths/other significant events

Diarrhoea Events, including Clinically Significant Diarrhoea

All reports of diarrhoea were evaluated to determine if any met the criteria for clinically significant events as follows: 1) diarrhoea with duration ≥ 3 days without other aetiology; 2) diarrhoea of Grade ≥ 3 severity or reported as an SAE; or 3) diarrhoea with concurrent dehydration requiring treatment with rehydration and/or other treatment intervention.

Overall, 11 (21.2%) patients in the Pooled Phase 3 group met the criteria for clinically significant diarrhoea. In Study A4250-012, 6 (17.1%) patients in the odevixibat group and 1 (5.9%) patient in the placebo group had clinically significant diarrhoea.

The median number of clinically significant diarrhoea episodes per patient was 1.0 across all patients in the Pooled Phase 3 group and was 1.0 each in the odevixibat and placebo groups, respectively, during Study A4250-012. The median duration of each clinically significant diarrhoea episode was 5.0 days in the Pooled Phase 3 group, and in Study A4250-012 was 4.5 days in the odevixibat group and 24.0 in the placebo group. The median time to onset of a clinically significant diarrhoea event was 30.0 days in the Pooled Phase 3 group, with median times to onset of 29.5 and 2.0 days in the odevixibat and placebo groups, respectively, in Study A4250-012. Dosing was interrupted in 2 patients.

OLE update:

Overall, 12 (24.0%) of the 50 patients met the criteria for clinically significant diarrhoea, including 6 (35.3%) patients who had received placebo and 6 (18.2%) who had received odevixibat in Study A4250-012. Most patients (11 of 12) met the criteria due to duration of diarrhoea of ≥3 days. All reports of clinically significant diarrhoea were non-serious and Grade 1 or 2 in severity. The events were considered treatment-related in 5 of the 12 patients. No dose modification was required for 10 of the 12 patients. Two patients had a temporary treatment interruption; in 1 of these patients the odevixibat dose was reduced to 40 µg/kg/day.

Fat-soluble Vitamin Deficiency Refractory to Clinically Recommended Vitamin Supplementation and Potential Sequelae of Vitamin Deficiency

Overall, 6 (11.5%) patients in the Pooled Phase 3 group had TEAEs related to levels of fat-soluble vitamins reported by the Investigators (Table 27). For 1 patient, the TEAE related to levels of fat-soluble vitamins was serious, and Grade 3 INR increased, with this event considered by the Investigator to be study drug-related; all other such events were Grade 1 or 2 in severity, non-serious,

and unrelated to study drug. In Study A4250-012, the incidence of TEAEs related to levels of fat-soluble vitamins was 8.6% and 17.6% in the odevixibat and placebo groups, respectively.

Table 27: Overall summary of treatment-emergent incidence of fat-soluble vitamin deficiency adverse events (Safety analysis set)

	STUDY A4250-012 (BY TREATMENT)		**STUDIES A4250-012/ A4250-015 POOLED**
AE CATEGORY:	**PLACEBO (N=17) N (%)**	**ODEVIXIBAT (N=35) N (%)**	**ODEVIXIBAT[A] (N=52) N (%)**
Patients with any Fat-soluble Vitamin Deficiency TEAE	***3 (17.6)***	***3 (8.6)***	***6 (11.5)***
International normalised ratio increased	2 (11.8)	1 (2.9)	3 (5.8)
Vitamin D deficiency	1 (5.9)	1 (2.9)	2 (3.8)
Vitamin A decreased	0	1 (2.9)	1 (1.9)
Vitamin E decreased	0	1 (2.9)	1 (1.9)
Vitamin K deficiency	0	0	1 (1.9)

[a] One patient (01003-102) had both vitamin A and vitamin E decreased reported. Source: ALGS ISS Table 14.3.1.3, CSR A4250-012 Listing 16.2.7.1.

A review of fat-soluble vitamin levels over time on treatment was also conducted. Review of these data indicates small mean changes in fat-soluble vitamin levels and INR with some variability in the data over time during treatment with odevixibat; however, these variations are not considered to be clinically significant.

Possible Sequelae of Fat-soluble Vitamin Deficiency

Treatment-emergent AEs that represent possible clinical sequelae of fat-soluble vitamin deficiency were also evaluated across the Phase 3 studies; results are summarised in **Table 28**.

Among the 52 patients in the Pooled Phase 3 group, 9 (17.3%) patients had TEAEs that were possible sequelae of fat-soluble vitamin deficiency, most commonly haematoma and INR increased (each 3 patients; 5.8%) and coagulopathy (2 patients; 3.8%). All other such events were reported in 1 (1.9%) patient only and included haematemesis, contusion, and forearm fracture. Note that 2 of these 9 patients had INR increased during placebo treatment in Study A4250-012 and during odevixibat treatment in Study A4250-015.

In 2 patients, the possible sequelae were considered Grade 3 and serious, including haematemesis and INR increase experienced by a patient in Study A4250-012 and forearm fracture experienced by a patient in Study A4250-015. The events of haematemesis and INR increased were assessed as treatment-related.

Table 28: Treatment-emergent Adverse Events of Potential Sequelae of Fat-Soluble Vitamin Deficiency (Safety Analysis Set, Integrated Data)

MEDDRA SOC PREFERRED TERM	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17) N (%)	ODEVIXIBAT (N=35) N (%)	ODEVIXIBAT[A] (N=52) N (%)
Patients with any Potential Sequelae Events[b]	***3 (17.6)***	***5 (14.3)***	***9 (17.3)***
International normalised ratio increased	2 (11.8)	1 (2.9)	3 (5.8)
Haematoma	0	3 (8.6)	3 (5.8)
Coagulopathy	0	1 (2.9)	2 (3.8)
Haematemesis	0	1 (2.9)	1 (1.9)
Contusion	0	1 (2.9)	1 (1.9)
Forearm fracture	0	0	1 (1.9)
Epistaxis	2 (11.8)	0	0

[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015.

[b] See Appendix F of the ALGS ISS SAP for specific preferred terms searched for this analysis. Source: ALGS ISS Table 14.3.1.18.

OLE update:

Three cases of fat-soluble vitamin deficiency, refractory to clinically recommended vitamin supplementation, were reported by the Investigators through the 07FEB2024 data cutoff; all 3 patients had received placebo in Study A4250-012. Two of the 3 patients had vitamin D deficiency and 1 had vitamin A deficiency reported. All 3 patients had baseline vitamin levels below or in the low normal range. Review of the cases indicated that supplementation was not adjusted based on the observed decrease in vitamin level in 2 of the patients; treatment with odevixibat continued unchanged in these 2 patients. For 1 patient the low vitamin level was reported at the last assessment as of the data cutoff.

Overall, 12 (24.0%) of the 50 patients had TEAEs that were possible sequelae of fat-soluble vitamin deficiency. Most of these events were reported in a single patient. The only possible sequelae of fat-soluble vitamin deficiency reported in >1 patient was international normalised ratio (INR) increased (3 patients, 6.0%) and coagulopathy (2 patients, 4.0%). The majority of the possible sequelae of fat-soluble vitamin deficiency were assessed as unrelated to study treatment, Grade 1 or 2 in severity and non-serious. One report each of Grade 1 haematochezia and Grade 2 INR increased were assessed as treatment-related. Three patients had possible sequelae that were reported as SAEs, including Henoch-Schonlein purpura, haematemesis, and forearm fracture; all 3 of these events were assessed as unrelated to odevixibat.

Hepatic Adverse Events

There were no liver decompensation events reported during Study A4250-012 or Study A4250-015 as of the data cut-off date and no TEAE reports of ascites, hepatic encephalopathy, portal hypertension, hepatic cirrhosis, or variceal haemorrhage in either Phase 3 study.

A summary of liver-related events is provided in **Table 29**.

Table 29: Treatment-emergent liver-related adverse events (Safety analysis set, integrated data)

	STUDY A4250-012 (BY TREATMENT)		**STUDIES A4250-012/ A4250-015 POOLED**
MEDDRA SOC PREFERRED TERM	**PLACEBO (N=17) N (%)**	**ODEVIXIBAT (N=35) N (%)**	**ODEVIXIBAT[A] (N=52) N (%)**
Patients with Any Liver-Related TEAE[b]	***2 (11.8)***	***4 (11.4)***	***6 (11.5)***
Investigations	**2 (11.8)**	**3 (8.6)**	**5 (9.6)**
International normalised ratio increased	2 (11.8)	1 (2.9)	3 (5.8)
Alanine aminotransferase increased	0	1 (2.9)	1 (1.9)
Blood bilirubin increased	0	0	1 (1.9)
Gamma-glutamyltransferase increased	0	1 (2.9)	1 (1.9)
Hepatic enzyme increased	1 (5.9)	1 (2.9)	1 (1.9)
Hepatobiliary disorders	**0**	**1 (2.9)**	**1 (1.9)**
Jaundice	0	1 (2.9)	1 (1.9)

[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015. [b] Based on SMQs of Drug related hepatic disorders – comprehensive search, Biliary tract disorders, Gallbladder related disorders and Gallstone related disorders. Source: ALGS ISS Table 14.3.1.16.

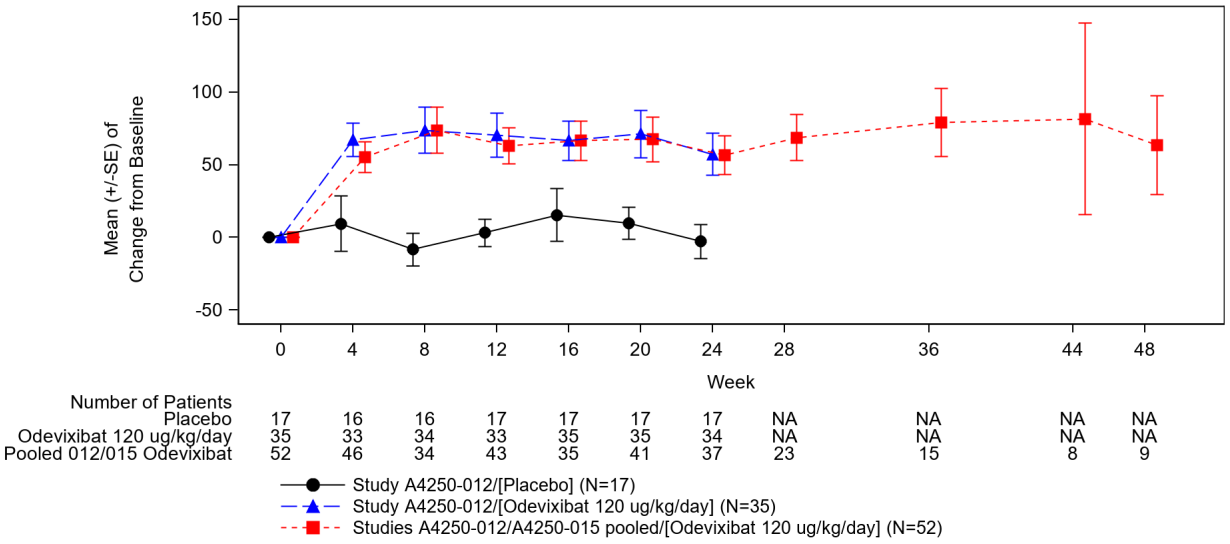
As of the data cut-off of 09SEP2022, 4 cases had undergone review and adjudication by the HSAC, an independent group of expert hepatologists, for suspected DILI (HSAC Adjudication Forms), including 2 patients during Study A4250-012, who both received odevixibat, and 2 patients in Study A4250-015, both of whom had received odevixibat in Study A4250-012. One of the cases was considered by the HSAC to be likely related to the study drug, although the natural history of the disease with severe cholestasis could not be ruled out; the remaining 3 cases were considered related to the patient's underlying disease and unrelated to odevixibat. Case narratives can be found in the CSR.

Hepatic Biochemical Laboratory Data

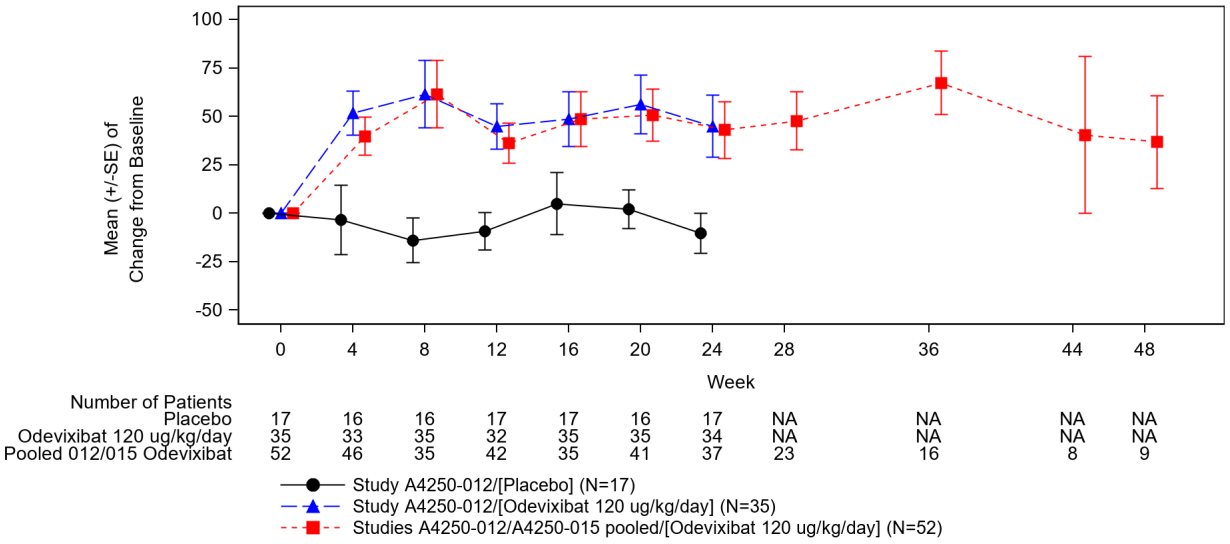
A review of Figure 7 shows an early increase in mean transaminase levels during treatment with odevixibat to Week 4 with a relative plateau thereafter. For total bilirubin, mean changes from baseline varied around zero with similar results through Week 24 for the odevixibat and placebo groups; thereafter the plateau continues with the exception of Week 36 where there is an outlier value.

In study A4250-012, mean and median baseline ALT levels were higher in the odevixibat group (185.6 and 173 U/L, respectively) compared to the placebo group (149.1 and 114.0 U/L, respectively). Consistent with this, the percent of patients with baseline ALT >3 × ULN also was nearly 2-times higher in the odevixibat group compared to the placebo group (65.7% vs 35.3%). It is also clear from the data that ALT levels at baseline were highly variable across the 52 patients ranging from 39 to 403 U/L. This was also observed for AST, which ranged from 57 to 427 U/L, and for GGT, which ranged from 46 to 1275 U/L. For the Pooled Phase 3 group, ALT levels were > 3 × ULN at baseline in 27 (56.3%) of 48 patients and total bilirubin was > 2 × ULN in 29 (60.4%) of 48 patients.

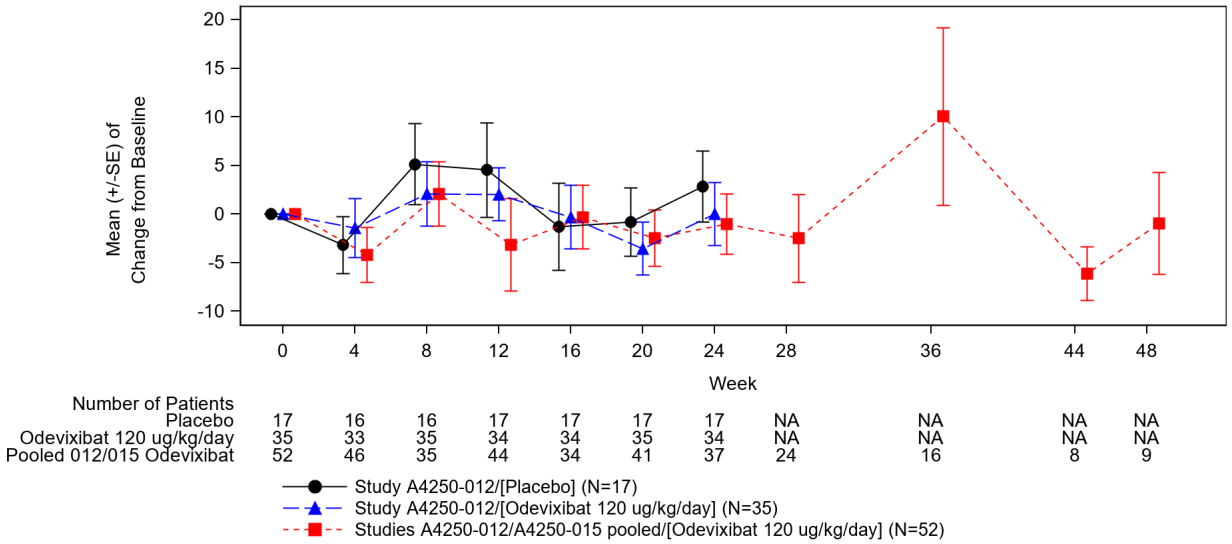
Alanine Aminotransferase



Aspartate Aminotransferase



Total Bilirubin

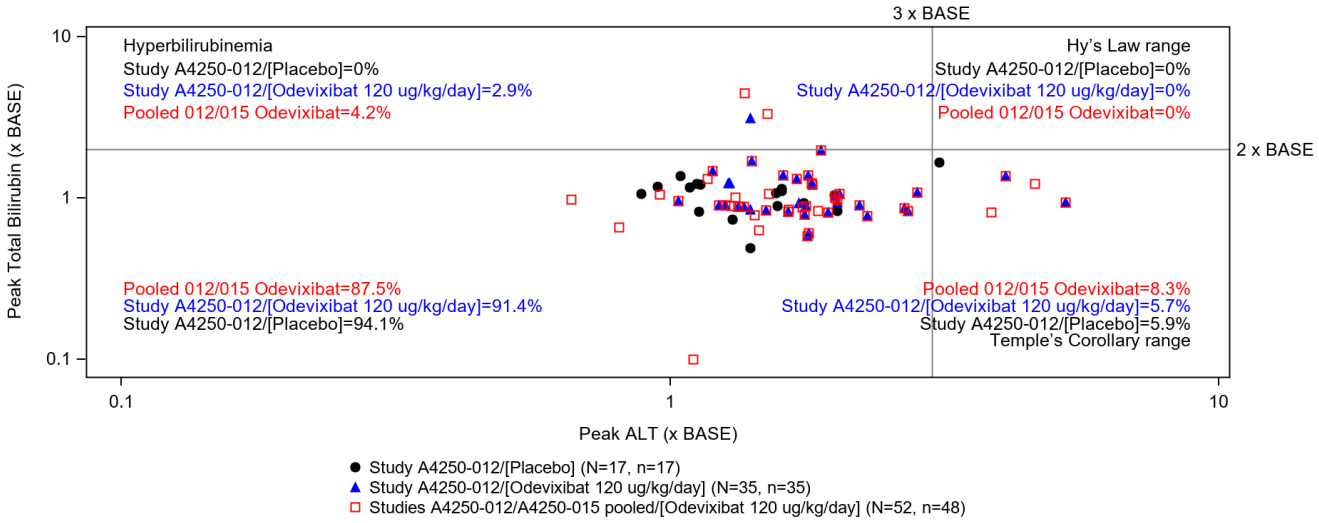


Source: ALGS ISS Figure 14.3.1.1, Figure 14.3.1.2, and Figure 14.3.1.3.

Figure 7: Mean (±se) levels of hepatic biochemical parameters overtime on treatment (safety analysis set, integrated data)

In order to further evaluate the clinical significance of shifts from baseline in hepatic enzymes, post-hoc analyses using eDISH plots were performed. As a further refinement of the standard eDISH plot, the post-baseline analysis used "concurrent" peak total bilirubin measured within 30 days of the peak ALT since increased total bilirubin is a normal feature of ALGS, and the second component of Hy's law specifies that the aminotransferase elevation is concurrent with the elevation of serum total bilirubin.

Figure 8 presents a modified eDISH plot with on-treatment elevations in ALT and concurrent total bilirubin relative to baseline. Review of the figure shows that none of the patients had on-treatment elevations in the upper right quadrant representing potential Hy's law cases. As displayed in the lower right quadrant, elevations to > 3× baseline in ALT without a concurrent (i.e. within 30 days) peak elevation in total bilirubin to > 2× baseline were reported in 4 (8.3%) of 48 patients assessed in the Pooled Phase 3 group; note that 1 of these patients also had ALT > 3× baseline during treatment with placebo in Study A4250-012 (also shown as the black dot in the lower right quadrant of Figure 8.



Source: ALGS ISS Figure 14.3.4.3

Figure 8: Modified edish plot of peak alt vs concurrent peak (within 30 days of peak alt) total bilirubin relative to baseline (full analysis set)

A review of the pertinent clinical and diagnostic information for the 4 patients with transaminase elevations > 3× baseline suggests that the occurrence of DILI is unlikely. The patients had no signs or symptoms associated with the elevation in transaminase levels. All 4 patients remain on treatment in Study A4250-015 as of the data cut-off.

In summary, a detailed review of the pooled data from Study A4250-012 and A4250-015 revealed that following the initial increase in ALT, AST, and GGT, levels plateaued or improved, while total and direct bilirubin either remain stable or improved, and that these changes were not indicative of worsening of liver function.

OLE update:

At baseline, median alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels across the 50 patients were elevated at 206.3 U/L, 187.7 U/L, and 58.71 µmol/L, respectively (**Table 30**). Mean and median levels of ALT and AST at baseline were higher and total bilirubin levels were lower for patients who received odevixibat compared to those who received placebo in Study A4250-012.

Following 72 weeks of treatment in Study A4250-015, mean changes from baseline in ALT and AST across all 50 patients were 47.9 U/L and 35.8 U/L, respectively; the mean increases were higher among patients who had received placebo in Study A4250-012 (56.5 U/L and 50.2 U/L, respectively) compared to patients who had received odevixibat (44.1 U/L and 29.3 U/L, respectively). Small mean decreases were observed to Week 72 in total bilirubin across all 50 patients (-2.51 µmol/L) and within each of the study groups.

Table 30: Hepatic biochemical parameters: mean (+/- SD) baseline values and change from baseline to week 72 (FAS, week 72 analysis).

VARIABLE	PLACEBO[A]/ODEVIXIBAT N=17		ODEVIXIBAT[A]/ODEVIXIBAT N=33		TOTAL N=50	
TIME POINT	N	MEAN (SD)	N	MEAN (SD)	N	MEAN (SD)
ALT U/L						
Baseline	17	146.3 (65.74)	33	237.2 (109.55)	50	206.3 (105.56)
Change to Week 24	14	47.5 (95.21)	31	32.9 (82.41)	45	37.4 (85.76)
Change to Week 48	13	60.1 (75.80)	31	28.6 (89.90)	44	37.9 (86.33)
Change to Week 72	13	56.5 (94.04)	30	44.1 (96.63)	43	47.9 (94.90)
AST U/L						
Baseline	17	150.5 (66.27)	33	206.9 (114.43)	30	187.7 (103.51)
Change to Week 24	14	33.6 (74.47)	32	27.0 (64.60)	46	29.0 (66.98)
Change to Week 48	13	43.8 (53.31)	31	18.1 (86.25)	44	25.7 (78.25)
Change to Week 72	13	50.2 (89.78)	29	29.3 (94.03)	42	35.8 (92.16)
Total Bilirubin µmol/L						
Baseline	17	64.44 (59.701)	33	55.76 (46.314)	50	58.71 (50.812)
Change to Week 24	14	-3.04 (14.214)	32	-2.46 (19.216)	46	-2.64 (17.687)
Change to Week 48	13	-6.02 (12.471)	31	-3.75 (19.683)	44	-4.42 (17.742)
Change to Week 72	13	-0.66 (18.773)	30	-3.31 (15.842)	43	-2.51 (16.598)

As of the current data cutoff of 07FEB2024 for the Week 72 report, 1 additional patient was reviewed by the HSAC for elevated bilirubin; the event was considered unrelated to odevixibat.

There were no TEAEs of new onset or worsening portal hypertension, hepatic cirrhosis, hepatic encephalopathy, or variceal haemorrhage in the study. One patient who was discontinued from treatment to undergo liver transplant developed ascites assessed as unrelated to odevixibat 9 days post-treatment that was reported as a liver decompensation event; the ascites occurred 4 days following liver transplant.

The modified evaluation of drug-induced serious hepatotoxicity (eDISH) plot showed that none of the patients had on treatment elevations in the upper right quadrant representing- potential Hy's law cases. The majority of patients had post-baseline ALT levels < 3× baseline, including 93.9% of patients who had received odevixibat in Study A4250-012 and 82.4% of patients who had received placebo in that study.

2.6.8.4. Laboratory findings

See relevant other chapters of this assessment report.

2.6.8.5. Safety in special populations

Age

The number of patients in the Pooled Phase 3 group across age categories was as follows: < 10 years (n=42), 10 to < 18 years (n=10), < 2 years (n=7), 2 to < 12 years (n=39), and 12 to < 18 years (n=6). In general, age did not appear to affect the overall observed safety and tolerability profile of odevixibat.

Sex

There was a similar number of males and females included in the Pooled Phase 3 group (27 and 25, respectively). The overall incidence of TEAEs by sex in the Pooled Phase 3 group was similar among male and female patients (85.2% and 80.0%, respectively), as was the incidence of SAEs (11.1% and 12.0%, respectively).

Race and Ethnicity

The incidence of TEAEs in the Pooled Phase 3 group was higher among non-white patients than white patients (100.0% vs 79.1%). The incidence of SAEs was similar in these 2 race subgroups (11.1% and 11.6%, respectively). However, the number of non-white patients was notably lower than that of white patients (9 vs 43, respectively), with a 4.8-fold difference. The low number of individual TEAEs and SAEs and of patients in the non-white subgroup precludes meaningful comparisons across race at the preferred term level for TEAEs and SAEs.

ALGS Mutation

Study A4250-012 included 4 patients with the NOTCH2 mutation, including 3 patients who received odevixibat and 1 who received placebo. None of the 3 odevixibat-treated patients experienced an SAE, a TEAE leading to dose interruption, clinically significant diarrhoea, or liver-related TEAEs. One patient experienced possible sequelae of fat-soluble vitamin deficiency and coagulopathy.

Hepatic Impairment by NCI ODWG

Although not directly relevant to this patient population, the NCI-ODWG criteria were used as an additional method of grading hepatic impairment for patients in the Pooled Phase 3 group.

In the Pooled Phase 3 group, 14, 15, and 23 patients had a mild, moderate, and severe hepatic impairment, respectively, based on the NCI ODWG. The overall incidence of TEAEs was relatively similar among patients with mild, moderate, and severe hepatic impairment based on NCI-ODWG at baseline, with an incidence of 71.4%, 80.0%, and 69.2%, respectively. No clear trend was seen regarding the incidence of commonly reported TEAEs or SAEs by baseline hepatic status, as determined by NCI-ODWG criteria.

Baseline Alanine Aminotransferase Level

The incidence of TEAEs by baseline ALT level was similar among patients with baseline ALT levels ≤ 3 × ULN, > 3 and ≤ 5 × ULN, and > 5 × ULN (87.0%, 77.8%, and 81.8%, respectively). No clear trend was seen regarding the incidence of commonly reported TEAEs or SAEs by baseline hepatic status, as determined by baseline ALT level.

Baseline Total and Direct Bilirubin Levels

In the Pooled Phase 3 group, most patients (n=20) had a baseline total bilirubin ≤ 2 × ULN; baseline total bilirubin was > 2 × ULN in 32 odevixibat-treated patients. The overall incidence of TEAEs was 80.0% and 84.4% among patients with baseline total bilirubin levels of ≤ 2 × ULN and > 2 × ULN,

respectively. No apparent trend was seen concerning the incidence of commonly reported TEAEs or SAEs by baseline total bilirubin levels.

Findings were similar when TEAEs and SAEs were analysed for patients with a baseline direct bilirubin ≤ 3 × ULN and > 3 × ULN (N=34 and N=18, respectively). The overall incidence of TEAEs was similar (82.4% and 83.3%) among patients with baseline total bilirubin levels of ≤ 3 mg/dL and > 3 mg/dL, respectively. The incidence of commonly reported TEAEs also was relatively similar when analysed by baseline direct bilirubin levels.

Baseline Serum Bile Acid Levels

In the Pooled Phase 3 group, 28 patients had a baseline serum bile acid level greater than or equal to the median in Study A4250-012 and 24 had values below the median. The overall incidence of TEAEs was 78.6% and 87.5% among patients with baseline serum bile acid levels greater than or equal to and below the median in Study A4250-012, respectively. No meaningful differences were seen with regard to the incidence of commonly reported TEAEs or SAEs by baseline serum bile acid levels.

2.6.8.6. 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 limited, therefore an immunologic response is not to be expected.

2.6.8.7. 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.

2.6.8.8. Discontinuation due to adverse events

The dose reduction of study treatment from 120 to 40 µg/kg/day was reported in 1 (1.9%) of 52 patients in the Pooled Phase 3 group. On Day 2 of treatment with odevixibat in Study A4250-012, one patient experienced non-serious, Grade 1 TEAEs of nausea and vomiting. The dose was reduced to 40 µg/kg/day. On Day 57, the odevixibat dose was increased to 120 µg/kg/day; the patient remains on this dose in Study A4250-015 as of the data cut-off without recurrence of the events.

Treatment-emergent AEs leading to interruption of study drug were reported in 7 (13.5%) of 52 patients in the Pooled Phase 3 group.

The only TEAE leading to study drug interruption for > 1 patient was diarrhoea (2 patients; 3.8%). Other TEAEs leading to dose interruption, each reported for 1 (1.9%) patient included abdominal pain, blood bilirubin increased, dysuria, gastroenteritis, rotavirus gastroenteritis, hepatic enzyme increased, anaemia macrocytic, platelet count decreased, and rhinovirus infection. TEAEs leading to study drug interruption that the Investigator considered to be study drug-related included 1 report each of abdominal pain, hepatic enzyme increased, and blood bilirubin increased.

In Study A4250-012, the incidence of TEAEs leading to interruption of the study drug was 8.6% (3 patients) in the odevixibat group; none of the patients who received placebo had a TEAE leading to study drug interruption. All 3 patients who had odevixibat interrupted due to a TEAE resumed odevixibat at 120 µg/kg/day after the resolution of the TEAE.

Most TEAEs leading to interruption of study drug were Grade 1 or 2 in severity. Grade 3 TEAEs leading to study drug interruption included rhinovirus infection in 1 patient during treatment with odevixibat in Study A4250-012 and diarrhoea in 1 patient during treatment in Study A4250-015; both events were considered unrelated to the study drug.

None of the 52 patients in the Pooled Phase 3 group discontinued study drug because of a TEAE.

OLE update:

One patient (2.0%) discontinued treatment due to TEAEs as of the 07Feb2024 data cutoff. This patient received placebo in Study A4250-012 discontinued odevixibat due in increased blood bilirubin, Grade 2 in severity and assessed as possibly related to study treatment.

2.6.8.9. Post-marketing experience

Odevixibat was authorised for marketing in the US in 2021 for the treatment of pruritus in patients 3 months of age and older with PFIC, and in the EU and GB in 2021 and in Israel and Brazil in 2023 for the treatment of PFIC in patients aged 6 months or older. Odevixibat was also authorised in the US in 2023 for the treatment of pruritus in patients 12 months of age and older with ALGS.

Since the first launch of Bylvay, the estimated cumulative post-marketing exposure through 15 July 2023, the latest data cutoff date for the Periodic Benefit Risk Evaluation Report, was 484 patients (252 in the European Economic Area (EEA) and 232 in non-EEA countries). Estimation was based on drug unit volume supplied. The estimated numbers also include patients who transitioned from Study A4250-008, PFIC-EAP A4250-014, ALGS CUP A4250-023, and Managed Access Programmes in PFIC and ALGS onto commercial product.

Cumulatively, a total of 311 spontaneous adverse drug reactions (ADRs) have been received across 115 patients, of which 39 were serious occurring in 20 patients. The only spontaneous serious ADRs reported in more than 1 patient were blood bilirubin increased, hepatic cirrhosis, and haemorrhage, each reported in 2 patients.

Based on review of the data, there is no evidence of any new significant safety issues with odevixibat when administered according to the recommendations given in the reference safety information and within the approved indications.

2.6.9. Discussion on clinical safety

The assessment of the safety is primarily based on the pooled phase 3 data set, including patients that received odevixibat in the pivotal study 012 and the extension study 015. Exposure to odevixibat in the pivotal study was around 24 weeks in line with the study duration, and all patients had finished their assigned treatment. In the pooled phase 3 data, exposure varies from 0.1-74.4 weeks, reflective of the patients who switched from placebo to odevixibat in the long-term extension study. Exposure to odevixibat is considered limited in ALGS patients, especially regarding long-term treatment. This is understandable, given the rarity of the disease.

Most common TEAEs were reported in the SOCs infections and infestations and in gastrointestinal disorders. The most common TEAE's were diarrhoea (15 patients, 28.8%), pyrexia (11 patients, 21.2%), nasopharyngitis (8 patients, 15.4%), COVID-19 infection (7 patients, 13.5%), and abdominal pain (6 patients; 11.5%). Causality to treatment is considered unlikely in the SOC of infections and infestations given the similar incidence in the placebo and odevixibat group and the commonness of these AEs in children.

Diarrhoea and abdominal pain are known side effects of odevixibat, although they can also be seen as a symptom of the disease. However, given the disbalance in gastrointestinal AEs between the placebo and odevixibat groups, at least part of these AEs can be attributed to treatment. In the pooled phase 3 analysis, 15 (28.8%) of the patients experienced diarrhoea. For 11 patients, this event qualified as clinically significant diarrhoea. Overall, these events were manageable, and no discontinuation of the study drug was necessary. Diarrhoea is labelled as a common adverse drug reaction in 4.8 of the SmPC. As diarrhoea may lead to dehydration section 4.4. of the SmPC advises to monitor patients with diarrhoea regularly to ensure adequate hydration.

Three haematoma events were reported in the odevixibat arm, compared to none in the placebo arm. Of the three events, one was related to accidental trauma. Of the other two, causality is not discussed. Haematoma events could be regarded as sequelae of fat-soluble vitamin deficiency, which is commonly observed in ALGS. The provided data indicated that the incidences of haematoma were due to trauma and likely not related to treatment. No cases of haematoma were reported in the PFIC studies for odevixibat.

A relatively high number of patients in the odevixibat group experienced shifts in vitamin E from normal to low or high. Fat-soluble vitamin deficiencies are a known issue for patients with ALGS, making it difficult to differentiate between disease-associated symptoms and odevixibat-related side effects. In the SmPC, a warning is included that "Assessment of fat-soluble vitamin levels (Vitamins A, D, E) and international normalised ratio (INR) are recommended for all patients prior to initiating odevixibat, with monitoring per standard clinical practice." This is considered sufficient to manage potential fluctuations in fat-soluble vitamins.

As for deficiencies in fat-soluble vitamins, ALGS patients regularly show increased ALT/AST/GGT and bilirubin, which was visible at baseline. Contrary to what would be expected based on the PFIC studies, no improvements in liver function parameters were observed. Increased ALT and AST levels were observed within weeks after the start of odevixibat treatment, while bilirubin levels were constant. Four cases were referred to the adjudication committee for assessment of possible DILI. All but one case of possibly related increased INR were judged as unrelated to the study drug. After a review of the case narratives, this conclusion can be supported. In addition, the eDISH analysis revealed no cases of combined increases in both ALT and bilirubin compared to baseline after the start of odevixibat treatment.

The data do not indicate an increase of acute liver problems under odevixibat treatment. Nevertheless, the increase in ALT and AST remains unexplained and long-term consequences cannot be ruled out. Hepatotoxicity is already included as important potential risk in the safety specifications and the applicant plans to follow-up on this risk in the long-term study 015. However, the follow-up time of this study is not considered sufficient to address the long-term risk. The MAH will further monitor the potential risk of hepatotoxicity in a registry-based safety study which is a specific obligation to this marketing authorisation under exceptional circumstances. The possible increase of liver parameters is raised in 4.4 of the SmPC for the attention of the prescriber. Monitoring of liver function is recommended prior to initiating odevixibat and 6 weeks after initiation.

In the Pooled Phase 3 group, 6 (11.5%) of 52 patients experienced a treatment-emergent SAE. The majority of the SAEs were reported in the SOC infections and were assessed as unrelated to the study drug. For gastrointestinal SAEs, causality cannot be ruled out. The occurrence of grade 3 diarrhoea was assessed as unrelated to the study drug; however, diarrhoea and abdominal pain are known ADRs of odevixibat. Of note, this patient did not continue odevixibat treatment in the follow-up study for an unknown reason.

The only reported drug-related SAE was increased INR and haematemesis in one patient, which led to hospitalisation, and which was successfully treated with vitamin K. This event was assessed as possibly

related to the study drug. A review of the case narratives revealed a potential relationship between an enterovirus infection which led to a vitamin K deficiency, and prolonged INR. INR increase was also observed in the placebo group. In addition, INR is often observed in patients with ALGS, although INR was normal at baseline for this patient. It is, therefore, not considered possible to conclusively establish causality for this AE. SmPC 4.4. recommends assessing fat-soluble vitamin (FSV) levels (Vitamins A, D, E) and international normalised ratio (INR) for all patients prior to initiating odevixibat, with monitoring per standard clinical practice. If FSV deficiency is diagnosed, supplemental therapy should be prescribed.

Subgroup analysis of the safety profile for various intrinsic and extrinsic factors was conducted. Conclusions are hampered by the small number of patients for certain subgroups (for example with respect to ethnicity/race and ALGS mutation) and by the relatively small number of TEAEs. From the limited data, no notable differences were observed for any of the subgroups based on age, sex, race, and ethnicity.

As the majority of patients had moderate hepatic impairment as per the Child-Pugh classification, no conclusions can be drawn about the impact of hepatic impairment on the safety profile. No notable differences were observed for the different subgroups of "Baseline ALT" patients.

No patients discontinued odevixibat due to TEAEs. However, there were 7/52 patients in the pooled group for whom TEAEs led to temporary discontinuation or dose reduction (1/52).

A comparison has been made between the pooled phase 3 safety data in the PFIC studies and the ALGS studies. Overall, the incidence of AE's was slightly lower in the ALGS population compared to the PFIC population, and there were fewer temporary discontinuations or dose reductions. The types of AE's were comparable except for the understandable difference in covid infections. The safety profile of odevixibat in PFIC and ALGS is dominated by gastrointestinal disorders. From this comparison, it can be concluded that although patients with ALGS had a worse hepatic function at baseline, this does not seem to translate to a worse safety profile. Second, the received dose in the ALGS studies was 120 mg/kg/day while in the PFIC studies a considerable number of patients received the lower dose of 40 mg/kg/day. This higher dose did not lead to a worse safety profile.

As requested, the applicant has provided up to date safety information from OLE Study A4250-015 with a cut-off date of 7th Feb 2024. Overall, 44 (88%) of the 50 patients completed the 72-week treatment period compared to just n=2 (3.8%) completing between 60 and 72 weeks of treatment as of the cut-off date in the initial application. Median duration of exposure was 81 weeks, maximum exposure was 2 years.

The incidence of AEs in the OLE was 94% which was higher than in the odevixibat-treated patients in the placebo-controlled study A4250-012, 74%. This may be due to the longer duration of exposure to odevixibat in the OLE. The percentage of drug related TEAEs was similar in the OLE, compared to study A4250-012, 26% v 23%. However, drug related TEAEs were more than double for patients that had switched from placebo to odevixibat treatment at 41% compared to patients that remained on odevixibat across the 2 studies, 18%. The percentage of serious TEAEs was 22% in the OLE, compared to 14% in study A4250-012. The number of serious TEAEs was considerably higher for patients that had switched from placebo to odevixibat treatment at 41% compared to patients that remained on odevixibat across the 2 studies, 12%.

The number of study discontinuations and dose reductions was low in both studies, while the number of drug interruptions in the OLE was consistent compared to study A4250-012 (10 v 8.6%). There were no fatalities in the OLE and no drug related SAEs in the OLE.

Similar to odevixibat-treated patients in the placebo-controlled study A4250-012, the most commonly related AE in the OLE was diarrhoea (11% versus 10%). Clinically significant diarrhoea was observed

in 17% of odevixibat-treated patients in the placebo-controlled study compared to 24% of patients in the OLE. Again, a larger percentage of patients that switched from placebo to odevixibat experienced clinically significant diarrhoea compared to patients that remained on odevixibat across the 2 studies (35% v 18%) and also drug related diarrhoea (17.6 v 6%).

Fat-soluble vitamin deficiency occurred in 8.6% of odevixibat-treated patients in the placebo-controlled study compared with n=3 (6%) patients in the OLE with possible sequelae of 14.3% versus 24%. However, most of these latter sequalae were reported in a single patient skewing the data.

Across the 2 trials, the trend in LFTs was consistent with similar increases in ALT and AST observed with no increase in total bilirubin levels by the end of the 72-week period in the OLE. One additional patient was reviewed by the Hepatic Safety Adjudication Committee (HSAC) but was not considered to be related to odevixibat. Again, levels of ALT and AST were higher in patients that switched from placebo to odevixibat.

The additional data presented for the OLE study following queries is substantial and provides support to the previously submitted safety data especially given the small patient numbers involved due to the rarity of the disease. Interestingly, however, it appears that patients who switched from placebo to odevixibat for study A4250-015 experienced higher levels of drug related TEAEs, serious TEAEs, drug related diarrhoea, clinically significant diarrhoea, and higher levels of ALT and AST compared to patients that remained on odevixibat across the two studies. The applicant does not discuss potential reasons for this; however, this may potentially be due to patients tolerating the treatment better with longer exposure, but it may also be a random result due to the small numbers of patients involved. Overall, however, the safety trends are similar across the two studies with a similar safety profile and no new safety signals observed.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

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

An increase in levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) has been observed on treatment with odevixibat. Clinical relevance and long-term impact of these events is currently not known. The current SmPC advises on monitoring of liver function prior to initiating odevixibat and 6 weeks after initiation. The safety database in particular on long-term safety was not considered comprehensive by the CHMP and it can currently not be ruled out that there is an increased risk of hepatotoxicity associated with long-term use of odevixibat. Taking into account that ALGS is a very rare disease and that development of the sequalae of cholestasis takes a long time, the generation of comprehensive data is not considered possible.

Hepatotoxicity has been included as an important potential risk in the safety concerns and the marketing authorisation holder will perform a registry to provide more data on long-term safety. This commitment is made SOB to this MA under exceptional circumstances. The protocol for the registry-based PASS should be submitted within 6 months after commission decision.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of odevixibat in ALGS patients is in line with the known safety profile of odevixibat and is mainly characterised by gastrointestinal AE's. However, the safety database in ALGS is limited in particular with regards to long term safety. Increased ALT and AST levels were observed within weeks after the start of odevixibat treatment, while bilirubin levels were constant. Four cases were referred to the adjudication committee for assessment of possible DILI. All but one case of possibly related increased INR were judged as unrelated to the study drug. eDISH analysis revealed no

cases of combined increases in both ALT and bilirubin compared to baseline after the start of odevixibat treatment. Hepatotoxicity is an important potential risk in the RMP. The clinical relevance and potential impact on the long-term of the increased ALT/AST at a group level is unclear but appropriate precautionary statements have been included in 4.4 of the SmPC and monitoring of liver enzymes is recommended 6 weeks after start of the treatment with re-assessment of the individual benefit risk of the patient.

Taking into account that ALGS is a very rare disease and that development of the sequalae of cholestasis takes a long time, the generation of comprehensive data is not considered possible but further data on long term safety and efficacy will be provided by means of the final data of the long term safety and efficacy study A4250-015 (category 3 in the RMP) and a prospective registry monitoring hepatotoxicity and the time to liver transplantation in odevixibat-treated and untreated patients that is made specific obligation to the marketing authorisation. Furthermore, the applicant agreed to provide yearly updates on any new information concerning the safety and efficacy of Kayfanda withing annual reassessment.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

Description	**Due data**
Non-interventional Post authorisation safety study (PASS): In order to further investigate the long-term safety of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older, the MAH shall conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with Alagille syndrome (ALGS) treated with odevixibat.	Annual interim reports are to be submitted along with the annual reassessments.
In order to ensure adequate monitoring of safety and efficacy of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of odevixibat.	Annual (within annual reassessment)

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 31: Summary of safety concerns

SUMMARY OF 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

SUMMARY OF SAFETY CONCERNS	
	Use during pregnancy and use in breastfeeding women

2.7.2. Pharmacovigilance plan

Table 32: On-going and planned additional pharmacovigilance activities

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				
PROSPECTIVE REGISTRY-BASED STUDY OF THE LONG-TERM SAFETY OF ODEVIXIBAT IN PATIENTS WITH ALAGILLE SYNDROME (ALGS) PLANNED	THE AIM OF THIS STUDY IS TO ASSESS THE LONG-TERM, REAL-WORLD SAFETY PROFILE OF ODEVIXIBAT TREATMENT IN PATIENTS WITH ALGS USING THE DATA COLLECTED PROSPECTIVELY	HEPATOTOXICITY CLINICALLY SIGNIFICANT OR SEVERE DIARRHOEA LEADING TO DEHYDRATION AND ELECTROLYTE IMBALANCE LONG-TERM USE INTERACTIONS WITH FAT-SOLUBLE DRUGS EMBRYOFETAL TOXICITY USE DURING PREGNANCY AND BREASTFEEDING WOMEN	1.FEASIBILITY ASSESSMENT 2.PROTOCOL SUBMISSION 3. INTERIM RESULTS 4. INTERIM REPORT	1. WITHIN 3 MONTHS OF EC DECISION 2. WITHIN 6 MONTHS OF EC DECISION 3. YEARLY REPORTING WITH ANNUAL REASSESSMENT 4. WITHIN 5 YEARS FROM STUDY START
Category 3 - Required 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) 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 biliary diversion and/or liver transplantation • To evaluate the effect of A4250 on biochemical markers of cholestasis and liver disease	Long-term use Interactions with fat-soluble drugs Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance Hepatotoxicity	Final study report	30-Sep-2024
A4250-019 Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC Ongoing	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	Final study report	31-Dec-2028
A4250-015 An Open Label Study to Evaluate the Long-term Safety and Efficacy of Odevixibat (A4250) in Patients with Alagille Syndrome Ongoing	The primary objective is to demonstrate a sustained effect of odevixibat on pruritus in patients with ALGS who have completed Study A4250-012. The secondary objective is to demonstrate a sustained effect of odevixibat on serum bile acids in patients with ALGS who have completed Study A4250-012; evaluate an effect of odevixibat on parameters related to QoL; and evaluate the long-term safety and tolerability of repeated	Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance Hepatotoxicity Long-term use Interactions with fat-soluble drugs	Final study report	31-Dec-2024

	daily doses of odevixibat in patients with ALGS.			

2.7.3. Risk minimisation measures

Table 33: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	Routine risk communication: SmPC section 4.4 and 4.8 Package leaflet (PL) section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation regarding monitoring for events of diarrhoea 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 odevixibat and recommendation for drinking sufficient liquid in patients with diarrhoea in PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Hepatotoxicity	Routine risk communication: SmPC section 4.4 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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 odevixibat, 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 with PFIC to notify their doctor or pharmacist before taking Bylvay if they have been diagnosed with a complete absence or lack of function of bile salt export pump protein and if they have severely reduced liver function in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Embryofoetal toxicity	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.6 and PL section 2 notes that odevixibat is not recommended for use during pregnancy and in women of childbearing potential not using contraception. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Interactions with fat-soluble drugs	Routine risk communication: SmPC section 4.4, 4.5 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.5 notes that based on the completed interaction study with a lipophilic combination oral contraceptive containing ethinyl estradiol (EE) (0.03 mg) and levonorgestrel (LVN) (0.15 mg) conducted in adult healthy females, concomitant use of odevixibat had no impact on the area under the curve (AUC) of LVN and decreased the AUC of EE by 17%, which is not considered clinically relevant. Interaction studies with other lipophilic medicinal products have not been performed, therefore, effect on the absorption of other fat-soluble medicinal products cannot be excluded. 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 odevixibat, 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. 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, E and K, and some medicines. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Long-term use	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Use during pregnancy and use in breastfeeding women	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.6 and PL section 2 notes that odevixibat is not recommended for use during pregnancy and in women of childbearing potential not using contraception. 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 the patient that the doctor will help the patient to decide whether to stop breastfeeding or to avoid odevixibat treatment considering the benefit of breastfeeding to the baby and odevixibat to the mother. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 5.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the Package leaflet of Bylvay 200, 400, 600 and 1200 micrograms hard capsules for the PFIC indication only. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kayfanda (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

Alagille syndrome is a rare, life-threatening, autosomal dominant genetic disorder with a wide variety of clinical manifestations affecting the liver, heart, skeleton, eyes, skin, central nervous system, kidneys, and facial features. In the majority of patients, the symptoms present early, often within the first 3 months of life, with chronic cholestasis and jaundice and/or with cardiac symptoms. Cholestasis is one of the most common features of ALGS, with approximately 95% of patients initially presenting with cholestasis within the first 3 months of life. The cholestasis manifests with jaundice, pruritus, elevations in hepatic biochemical parameters, and potentially disfiguring or disabling xanthomas due to cholestasis-induced dyslipidaemia. The progressive liver damage due to cholestasis can lead to cirrhosis with an end-stage liver disease requiring transplantation before adulthood. Bile duct paucity is present in about 65% of patients before they are 3 months old.

Intractable pruritus associated with ALGS occurs in 45% to 88% of patients, ranging from mild scratching when undistracted to cutaneous mutilation with bleeding and scarring; severe pruritus has been reported in up to 45% of patients. The impact of pruritus for patients with ALGS occurs early in childhood with a median age at onset of 12 months. The precise mechanism of cholestatic pruritus remains unclear, but elevated serum bile acid levels, present in patients with ALGS, are most commonly considered as direct or indirect pruritic mediators. The pruritus is associated with skin lesions, difficulty with sleep, and mood disturbances.

The incidence is estimated to be 1/30,000 or a birth prevalence of 0.33/10,000 live births.

ALGS is caused by defects in components of the NOTCH signalling pathway, one of the basic signalling pathways during foetal development, involved in both cell-type specification and organogenesis. In about 90% of patients, the disease is caused by mutations in JAG1, which is one of 5 NOTCH signalling ligands. A smaller number of patients (< 5%) have mutations in the gene for the NOTCH2 receptor. Human embryological studies reveal that JAG1 is highly expressed in the heart, kidneys, blood vessels, skeleton, and eyes. It is also clear in studies in mice that JAG1-NOTCH2 interactions are critical for intrahepatic bile duct development. Consequently, mutations in JAG1 and NOTCH2 affect multiple organs, though the clinical manifestations can vary.

The diagnosis of the disease has traditionally been difficult. With the availability of genetic testing, the clinical diagnosis of ALGS is confirmed, or the diagnosis itself is made by the determination of a mutation within the sequence analysis of JAG1 or NOTCH2.

3.1.2. Available therapies and unmet medical need

There is no authorised pharmacological therapy aimed at correcting the underlying genetic defect in ALGS. In 2021, maralixibat, an IBAT inhibitor, was approved for "the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older". Other (off-label) treatment options are anti-pruritic agents such as UDCA, cholestyramine, rifampicin, ondansetron, and/or naltrexone; these agents are only partially effective.

Many patients undergo surgical options as liver disease progresses and symptoms do not respond to medical management. Therefore, liver transplant rates are high with 60% to 76% of ALGS patients

undergoing liver transplant by approximately 18 years of age due to complications of persistent cholestasis, and/or primarily persisting pruritus.

3.1.3. Main clinical studies

This application is based on the final results from Study A4250-012 and interim results from Study A4250-015. Study A4250-012 is a 24-week, randomised, double-blind, placebo-controlled Phase III study conducted in 52 patients (age range from 0.5 to 15.5 years) with a genetically confirmed diagnosis of ALGS and presence of pruritus and high serum bile acid levels at baseline. Patients were randomised to receive placebo or 120 ug/kg/day odevixibat. The primary endpoint was changed from baseline to week 24 in scratching score as measured by the ObsRO, an observer reported outcome to assess pruritus. Results of the ObsRO were supported by the results of the PRO, administered to patients of 8 years and older. The key secondary endpoint was the change from baseline in serum bile acids. Study A4250-015 is an ongoing 72-week open-label extension trial for patients who completed Study A4250-012. Patients receiving placebo in study 012 could change to odevixibat in this study.

3.2. Favourable effects

After 24 weeks, there was a greater decrease (i.e., improvement) in scratching score (primary endpoint) in the odevixibat group (-1.66) than in the placebo group (-0.79), with an LS mean difference -0.88, 95% CI -1.44, -0.33, one-sided p-value 0.0012.

After 24 weeks of treatment, 54% of odevixibat-treated patients reported a >1.5-point decrease in pruritus score, compared with 18% of the placebo patients. A post-hoc sensitivity analysis with a >2 and >2.5-point reduction was supportive of an effect.

A decrease in pruritus score based on the Albireo PRO (secondary endpoint) was observed in patients above 8 years of age. The mean change from baseline to week 21-24 in the placebo group was -0.78 (0.318) versus 1.63 (0.975) in the odevixibat group.

After 24 weeks, serum bile acids (key secondary endpoints) decreased by 88.4 µmol/L in the odevixibat group compared with an increase of 24.6 µmol/L in the placebo group, with an LS mean difference of -112.74 (-178.78, -46.69) µmol/L, one-sided p-value 0.0006.

Improvements in sleep parameters were observed in the ObsRO, especially for the percentage of days the patient needed soothing (LS mean difference (95% CI) of -33.35 (-54.86, -11.85)) or help to fall asleep (LS mean difference (95% CI) of -40.37 (-58.77, -21.96)).

Numerical changes in favour of odevixibat were reported for the improvement of hypercholesterolaemia. No clear difference was observed in the improvement of hypertriglyceridemia between the odevixibat and the placebo group.

No positive effects on liver values were observed under odevixibat treatment. AST, ALT, and bilirubin were all elevated at baseline and stayed elevated after 24 weeks of treatment

3.3. Uncertainties and limitations about favourable effects

No long-term efficacy data has been submitted, as the long-term extension study is still ongoing. Only 10 patients (19%) have been treated for >48 weeks.

Dose modification to a reduced dose level of 40 µg/kg/day is included in the SmPC in order to manage any potential AEs. Dose reductions were permitted in the study protocol of the pivotal trial. While there

is a lack of efficacy data on the lower dose, a dose reduction is acceptable based on safety grounds. The SmPC outlines in section 4.2 that alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat which is acceptable.

3.4. Unfavourable effects

Overall, the safety profile of odevixibat in ALGS patients was mainly characterised by gastrointestinal AEs. The more commonly reported drug-related TEAE's were diarrhoea, abdominal pain, and vomiting. They are labelled in 4.8 of the SmPC as common.

Adverse reactions of diarrhoea occurred at a frequency of 11.5% in ALGS patients treated with odevixibat. Median time to onset of diarrhoea was 14.5 days and median duration was 4 days.

Clinically significant diarrhoea that persisted for 3 or more days without any other aetiology was reported in 5.8% of patients (see section 4.4). Treatment interruption was reported for diarrhoea in 3.8% of patients and no discontinuation of odevixibat due to diarrhoea was reported.

Adverse reactions of abdominal pain and vomiting were reported in 7.7% and 3.8% of patients, respectively; none were concurrent with adverse reactions of diarrhoea. Median time to onset of abdominal pain was 1.5 days and median duration was 6 days. For vomiting, median time to onset was 2.5 days and median duration was 13.5 days.

Increased ALT and AST levels were observed within weeks after the start of odevixibat treatment, while bilirubin levels were constant. Four cases were referred to the adjudication committee for assessment of possible DILI. All but one case of possibly related increased INR were judged as unrelated to the study drug. eDISH analysis revealed no cases of combined increases in both ALT and bilirubin compared to baseline after the start of odevixibat treatment.

The applicant also submitted up-to-date safety information available from the ongoing OLE study to provide further support for the application. Overall, the safety trends were similar no new safety signals identified in the OLE.

3.5. Uncertainties and limitations about unfavourable effects

The safety database in ALGS patients is relatively limited, i.e. too small to reliably identify rare AE's. Median duration of exposure was 81 weeks, maximum exposure was 2 years, long-term safety data is lacking.

Increased ALT and AST levels were observed within weeks after the start of odevixibat treatment, while bilirubin levels were constant. Four cases were referred to the adjudication committee for assessment of possible DILI. All but one case of possibly related increased INR were judged as unrelated to the study drug. eDISH analysis revealed no cases of combined increases in both ALT and bilirubin compared to baseline after the start of odevixibat treatment. Hepatotoxicity is an important potential risk in the RMP. The clinical relevance and potential impact on the long-term of the increased ALT/AST at a group level is unclear but appropriate precautionary statements have been included in 4.4 of the SmPC and monitoring of liver enzymes is recommended 6 weeks after start of the treatment with re-assessment of the individual benefit risk of the patient.

Further information on long term safety and efficacy will be provided by means of the final data of the long-term safety and efficacy study A4250-015 (category 3 in the RMP) and a prospective registry monitoring hepatotoxicity and the time to liver transplantation in odevixibat-treated and untreated

patients that is made specific obligation to the marketing authorisation will complement the long-term safety database.

3.6. Effects Table

Table 34: Effects table for Kayfanda

Effect	Short description	Unit	Treatment	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Pruritus	Change from baseline to week 24 in ObsRO score.	mean (SD)	-1.66 (0.966)	-0.76 (0.820)	LS mean difference -0.88, 95% CI -1.44, -0.33, one sided p-value 0.0012 Supported by responder analysis: 54% of odevixibat treated patients reported a >1.5-point decrease in pruritus score, compared to 18% of the placebo patients	Study A4250-012
sBA	Change from baseline in serum bile acids	µmol/L	-88.4	24.6	LS mean difference 112.74 (-78.78, -46.69) µmol/L, one sided p-value 0.0006	Study A4250-012
Unfavourable Effects						
Diarrhoea		n/N (%)	15/52 (28.8)	1/17 (5.9)		Pooled phase III data
Abdominal pain		n/N (%)	6/52 (11.5)	1/17 (5.9)		Pooled phase III data
Haematoma		n/N (%)	3/52 (5.8)	0 (0)		Pooled phase III data
ALT (U/L)	Change from baseline to week 4	Mean (SD)	67.2 (66.91)	9.6 (75.99)	Plateau is reached after week 4.	Study A4250-012
AST (U/L)	Change from baseline to week 4	Mean (SD)	51.8 (64.59)	-3.4 (71.41)	Plateau is reached after week 4.	Study A4250-012

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with odevixibat led to improvements in pruritus. This endpoint is considered important and clinically relevant, as pruritus is one of the most debilitating symptoms of Alagille syndrome. However, this endpoint was measured as a continuous outcome with the change from baseline to 24 weeks reported on a group level. It is difficult to interpret the clinical relevance of this finding at the group level. Therefore, the responder analysis conducted as a secondary outcome is considered important to support the effect on relieving pruritus.

A threshold for a clinically meaningful change in pruritus score was determined using a blinding interim analysis of the same study. This approach has been agreed upon before by CHMP during scientific advice. Based on the blinded interim data a psychometric analysis was performed to assess the reliability, validity, and sensitivity to change of the Albireo PRO and ObsRO instruments and to estimate a threshold of clinically meaningful change for the pruritus item scores. It can be concluded that the threshold of >1.5-point improvement was based on a relatively modest treatment effect in the CaGIC, which was used as an anchor. Sufficient argumentation has been provided that the effect is not much dependent on baseline value. In addition, supplementary responder analyses with >2 and >2.5-point improvements as responder criteria showed the conclusion of efficacy was not sensitive to the responder definition used. It is thus considered that a robust and clinically relevant effect on pruritus is established.

Given the observed effects and the associated improvements in sleep and caregiver impression of change, it is acknowledged that a positive treatment effect on pruritus is shown. Improvements in sleep are considered a benefit for both the patient and caregiver.

Improvements in serum bile acid levels were observed for the odevixibat-treated arm compared to the placebo arm. Elevated serum bile acids are a hallmark of ALGS and are generally considered to be the major pruritic agent in ALGS. In addition, the MoA of odevixibat is to enhance the clearance of bile acids from the circulation. Serum bile acid levels are therefore a logical efficacy (and pharmacodynamic) outcome. However, it is not known what levels of sBA should be aimed for, and treatment targets are not defined. This complicates the interpretation of the changes from baseline in sBA levels in terms of clinical relevance.

The long-term extension study sustained the positive effects on pruritus and sBA, showing maintenance of the effect. This is important as treatment with odevixibat is expected to be a long-term treatment.

No positive effects of treatment were observed though for ALT, AST, GGT or bilirubin. These markers are indications of the liver damage associated with cholestasis in ALGS, which eventually leads to the need for a liver transplant in around 60% of patients before the age of 18. However, considering that the claimed indication is on cholestatic pruritus, the absence of improvements in liver function parameters is not critical for efficacy assessment.

No adult patients were included in the studies. However, considering the mechanism of action there is no reason to assume a different efficacy and safety profile in adult patients. Nevertheless, some patients are expected to turn 18 in the long-term extension study A4250-015, which is a category 3 study in the RMP, and the final study report will be submitted post-authorisation. Furthermore, further safety and effectiveness data of those patients will become available from the planned registry-based study in ALGS in annual reassessments.

From the clinical studies, no signs indicating acute hepatotoxicity were identified. Normalised levels of p-C4 indicated normalised bile acid synthesis. No increases in bilirubin were observed. Nevertheless, the impact of the increases in transaminases on the long-term hepatic safety are not known. Therefore, following up on this safety concern (hepatotoxicity is specified in the RMP as important potential risk) is necessary post-marketing. The applicant has committed to a registry-based safety study, which is included as SOB to a MA under exceptional circumstances.

3.7.2. Balance of benefits and risks

Odevixibat treatment led to positive and clinically relevant effects on pruritus and associated sleep disturbances in ALGS patients. In addition, decreases in serum bile acids were observed, in line with the pharmacodynamic effect of odevixibat.

Overall, the safety profile is mainly characterised by mild to moderate gastrointestinal adverse reactions. They are adequately described in the product information and considered manageable.

No beneficial effects were observed on liver function parameters. On the contrary, increases in ALT and AST of uncertain clinical relevance were observed but they are considered balanced with precautionary statements as included in 4.4 of the SmPC. The safety database in ALGS patients is limited and comprehensive long-term safety data is lacking, in particular in the younger paediatric population. While the rarity of the disease is acknowledged, further information on long term use on safety will be generated by means of a prospective registry, which is a specific obligation to this marketing authorisation under exceptional circumstances. Furthermore, the applicant will provide yearly updates on all new emerging data on safety and effectiveness with annual reassessments.

The positive effects on pruritus and sBA, outweigh the relatively mild safety profile and the potential risks of long-term hepatotoxicity.

3.7.3. Additional considerations on the benefit-risk balance

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 and safety 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.

Alagille syndrome (ALGS) is a rare, life-threatening, autosomal dominant genetic disorder. There are scarce epidemiological data on ALGS. Many sources give an estimated incidence of 1/70,000 births. Better diagnostic tools, including the advent of molecular testing, have indicated that a more accurate incidence is closer to 1/30,000 or a prevalence of 0.33/10,000 live births (Kamath 2003; Kamath 2010). At a population of approximately 447.7 million (EU-27), this corresponds to ca. 14,800 people affected with the disease in the EU. This number does not take into account the reduced life-expectancy of these patients.

The applicant has been able to conduct a randomised, placebo-controlled trial in 52 patients, showing relevant improvements in pruritus, associated improvement in sleep, and decreased serum bile acid levels. The data in support of the symptomatic treatment of cholestatic pruritus can be considered of good quality.

However, the CHMP did not consider the safety dataset with regards to long term exposure with odevixibat as comprehensive in particular with regards to hepatic safety and long-term safety. Increases in ALT and AST were observed in the study program and, although there were no signs of acute liver toxicity, it cannot be ruled out that there is an increased risk of hepatotoxicity associated with long-term use of odevixibat. The CHMP agreed with the applicant that it may be impossible to establish a comprehensive database based on clinical trial data to determine the long-term hepatic safety in ALGS. Given that ALGS is a rare disease and that robust confirmation of development of the

sequalae of cholestasis takes a long time to develop, it is not expected that these concerns can be addressed within a reasonable timeframe.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate. As an SOB, the applicant committed to conduct a registry-based safety study to further characterise the long-term liver safety. Furthermore, the applicant agreed to a second SOB to provide yearly updates on any new information concerning the safety and effectiveness of Kayfanda within annual reassessment.

3.8. Conclusions

The overall benefit/risk balance of Kayfanda is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kayfanda is not similar to Livmarli within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kayfanda is favourable in the following indication:

Kayfanda is indicated for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older

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 restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

- **Obligation to conduct post-authorisation measures**

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 data**
Non-interventional Post authorisation safety study (PASS): In order to further investigate the long-term safety of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older, the MAH shall conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with Alagille syndrome (ALGS) treated with odevixibat.	Annual interim reports are to be submitted along with the annual reassessments.
In order to ensure adequate monitoring of safety and efficacy of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of odevixibat.	Annual (within annual reassessment)

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0515/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.