20 July 2023
EMA/371338/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bylvay

International non-proprietary name: odevixibat

Procedure No. EMEA/H/C/004691/II/0011

Note

Variation 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
AASLD	American Association for the Study of Liver Diseases
ADR	adverse drug reaction
AE	adverse event
ALGS	Alagille syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CaGIC	caregiver Global Impression of Change
CaGIS	caregiver Global Impression of Symptoms
CI	confidence interval
CL/F	Apparent clearance
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
COA	Clinical Outcomes Assessments (instrument)
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
EAIR	exposure-adjusted incidence rates
EAP	expanded access programme
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19

ABBREVIATION	DEFINITION
GALA	Global Alagille Alliance
GB	Great Britain
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GIC	Global Impression of Change (instrument)
GIS	Global Impression of Symptoms (instrument)
IBAT	ileal bile acid transporter
ICE	intercurrent event
ICH	International Council for Harmonisation
INR	international normalised ratio
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measure
NCI ODWG	National Cancer Institute Organ Dysfunction Working Group
ObsRO	observer-reported outcome
p-C4	plasma-7α-hydroxy-4-cholesten-3-one
PedsQL	Pediatric Quality of Life Inventory
P-gp	P-glycoprotein
PFIC	progressive familial intrahepatic cholestasis
PK	pharmacokinetic
PPY	per patient year
PRO	patient-reported outcome
QoL	quality of life
RoW	rest of the world
SAE	serious adverse event

ABBREVIATION	DEFINITION
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQs	standardised MedDRA queries
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
US	United States
V/F	volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Albireo submitted to the European Medicines Agency on 29 November 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of cholestasis and pruritus in Alagille syndrome (ALGS) in patients from birth and older for BYLVAY, based on 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 with a genetically confirmed diagnosis of ALGS and presence of pruritus and high serum bile acid levels at baseline. Study A4250-015 is an ongoing 72-week open-label extension trial for patients who completed Study A4250-012 and evaluates the long-term safety and efficacy of Bylvay in patients with ALGS. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Bylvay was designated as an orphan medicinal product EU/3/12/1040 on 09/08/2012. Bylvay was designated as an orphan medicinal product for the following indication:

Treatment of Alagille syndrome

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) (EMA/PDCO/687161/2022) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0515/2022) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The Applicant received Protocol Assistance on the development of odevixibat for treatment of Alagille syndrome from the CHMP on 25 June 2020 (EMEA/H/SA/2645/7/2020/PA/SME/II). Hans Ovelgönne and Andreas Kirisits were appointed as coordinators. The Protocol Assistance pertained to the following clinical aspects:

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. For further details please refer to 2.1.3. The development programme/compliance with CHMP guidance/scientific advice.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	31 Dec 2022	31 Dec 2022	☐
☐	CHMP Rapporteur Assessment Report	24 Feb 2023	23 Feb 2023	☐
☐	PRAC Rapporteur Assessment Report	03 Mar 2023	01 Mar 2023	☐
☐	PRAC members comments	08 Mar 2023	08 Mar 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	09 Mar 2023	09 Mar 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	16 Mar 2023	16 Mar 2023	☐
☐	CHMP members comments	20 Mar 2023	20 Mar 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 Mar 2023	23 Mar 2023	☐
☐	RSI	30 Mar 2023	30 Mar 2023	☐
☐	CHMP Rapporteur Assessment Report	23 May 2023	25 May 2023	☐
☐	PRAC Rapporteur Assessment Report	26 May 2023	29 May 2023	☐
☐	PRAC members comments	31 May 2023	31 May 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	01 Jun 2023	01 Jun 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	08 Jun 2023	08 Jun 2023	☐

Status of this report and steps taken for the assessment				
☐	CHMP members comments	12 Jun 2023	12 Jun 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 Jun 2023	16 Jun 2023 20 Jun 2023	☐
☐	2nd RSI	22 Jun 2023	22 Jun 2023	☐
☐	Submission	27 Jun 2023	27 Jun 2023	☐
☐	CHMP Rapporteur Assessment Report	05 Jul 2023	07 Jul 2023	☐
☐	PRAC Rapporteur Assessment Report	n/a	n/a	☐
☐	PRAC/CHMP members comments	10 Jul 2023	10 Jul 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	n/a	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	13 Jul 2023	11 Jul 2023	☐
☐	An Oral explanation took place on	20 Jul 2023	20 Jul 2023	☐
☒	Opinion	20 Jul 2023	20 Jul 2023	☐
☒	The CHMP adopted a report on similarity of Bylvay with Livmarli	20 Jul 2023	20 Jul 2023	☐
☒	The CHMP adopted a report on the significant clinical benefit for Bylvay's new indication in comparison with existing therapies	20 Jul 2023	20 Jul 2023	☐

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

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.

Claimed therapeutic indication

Bylvay 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).

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.

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.

Clinical presentation and diagnosis

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

Table 1: Clinical Manifestations of Alagille Syndrome

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

ORGAN SYSTEM	MEAN FREQUENCIES	CLINICAL PRESENTATION
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
Skin	NR	Disfiguring xanthomas, excoriation and scarring due to pruritus
Other	NR	Failure to thrive, growth impairment, fat-soluble vitamin deficiency, immunodeficiency with recurrent infections, pancreatic insufficiency, steatorrhea, delayed puberty, developmental delays, thrombocytopenia, splenomegaly

NR: not reported.

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. In a knock-out mouse model with cholestasis showing elevated levels of hepatic bile acids, the serum levels of bile acids, alanine, and aspartate aminotransferases (ALT and AST), and alkaline phosphatase were also markedly elevated. The increase in both hepatic bile acids and of these liver injury markers, including serum bile acids, was successfully reduced with IBAT inhibition leading to an improvement in cholangiopathy and hepatic 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.

Management

There is no authorised pharmacological therapy aimed at correcting the underlying genetic defect in ALGS. In 2021, maralixibat, an IBAT inhibitor, was approved in the US for the treatment of cholestatic pruritus in patients with ALGS ≥ 1 year of age [Livmarli 2021]. In the EU, maralixibat was approved under the tradename Livmarli, and is "indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older". Other current treatments, both within and outside the US, 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.

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. Liver transplant rates are higher than surgical biliary diversion rates, with 60% to 76% of ALGS patients undergoing liver transplant by approximately 18 years of age. The most common reasons cited for liver transplant were complications of persistent cholestasis, primarily refractory pruritus in 69% of patients, as well as growth failure (54%), and xanthomas (49%). Other factors reported as leading to liver transplant include bone fractures, refractory fat-soluble vitamin deficiency, liver failure, and the manifestation of portal hypertension. In additions, liver transplantation is associated with post-operative mortality and the requirement for lifelong immunosuppression.

2.1.2. About the product

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

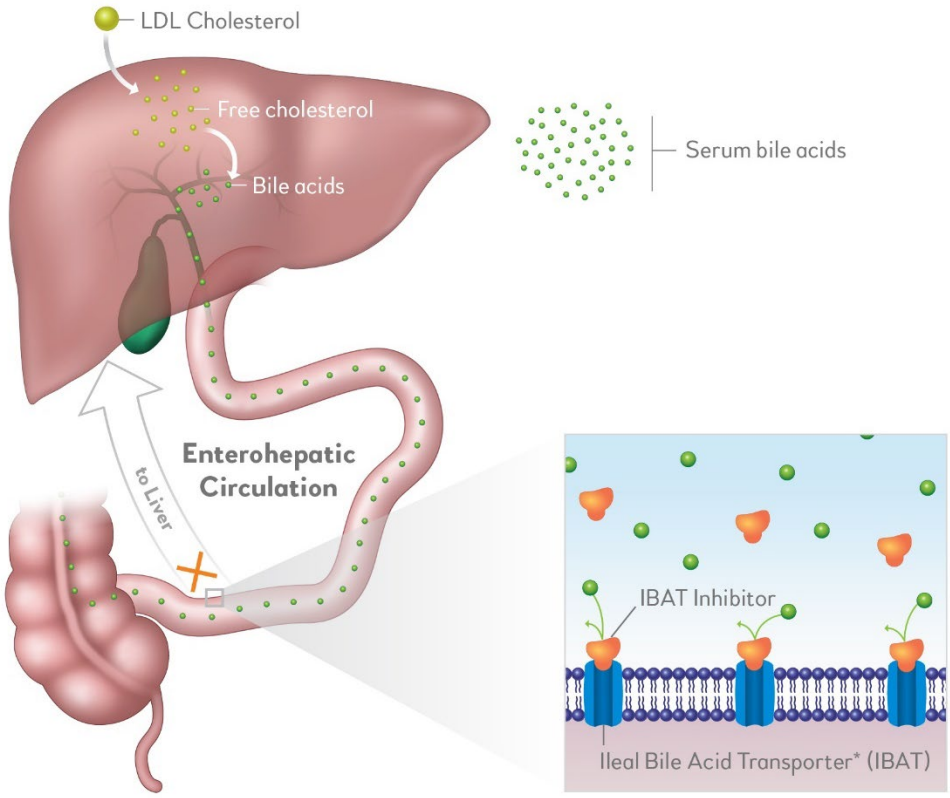
In 2021, odevixibat (tradename BYLVAY) was authorised for marketing by the US Food and Drug Administration (FDA) for the treatment of pruritus in patients 3 months of age and older with PFIC and by the European Commission and the United Kingdom (UK) Medicines and Health Care Products Regulatory Agency 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 a daily basis. Therefore, IBAT is a key regulator of the bile acid pool and a key 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



2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Key regulatory interactions with the EMA related to the clinical development of odevixibat in patients with ALGS are provided below.

Table 2: Summary of Key Regulatory Interactions with EMA Related to Odevixibat Clinical Development in ALGS

TYPE OF MEETING/ CORRESPONDENCE	PURPOSE OF CORRESPONDENCE	NOTABLE OUTCOMES
OD in the treatment of ALGS. Granted: 09AUG2012	To request OD for odevixibat in the treatment of ALGS	OD granted for odevixibat in the treatment of ALGS. EU/3/12/1040
2013 Protocol Assistance Meeting Meeting date: 28NOV2013 Final Advice Letter: 19DEC2013	To obtain input from EMA on the pre-clinical and clinical development of odevixibat.	EMA agreed that non-clinical studies were sufficient for MAA filing.
2018 Protocol Assistance Meeting Meeting date: 29OCT2018 Final Advice Letter: 15NOV2018	To obtain input from EMA on the analyses of the ObsRO/PRO data used to evaluate the pruritus endpoints, as well as the handling of missing data and patients undergoing surgery.	EMA agreed to using interim data in a blinded way to estimate a threshold for clinically meaningful change to use in the responder analysis of pruritus endpoints. EMA recommended including a justification as to whether a 1-point drop has the same meaning across the scale, i.e. that going from 4 to 3, and from 3 to 2 are all considered clinically relevant.
2020 Protocol Assistance Requested 17APR2020 Final Advice Letter: 25JUN2020	To obtain input from EMA on the endpoints and overall design of a Phase 3 programme for the use of odevixibat (A4250) in the treatment of ALGS and the overall development expectations for an MAA.	General outline, duration and design of study agreed to, but advised to increase sample size (from initial target of 36 patients). Advised to discuss the expected effects in patients > 18 years of age and consider including them in the primary efficacy population in order not to restrict labelling. The used dose should be thoroughly substantiated at the time of an MAA. Use of ObsRO for the primary endpoint may be acceptable but particular weight would rest on additionally collected PRO data in patients 8 years and older and very good concordance between ObsRO and PRO is expected for these patients.

TYPE OF MEETING/ CORRESPONDENCE	PURPOSE OF CORRESPONDENCE	NOTABLE OUTCOMES
		Treatment effect on the primary endpoint established as difference between average pruritus of Weeks 21 to 24 and average pruritus calculated for the 14 days preceding start of treatment may create some scale inconsistency as it can be expected that the two-week average will be more variable than the four-week average. If a chronic label is intended, the major clinical and laboratory outcomes should be operationalised as important secondary endpoints after 1 year. Previous advice (from 2018) given as regards ObsRO/PRO validation is reiterated. Establishing the clinical meaningfulness of varying degrees of change on the proposed scale(s) in an independent study and confirm these assumptions exploratorily in the proposed study (both via anchoring) can be supported. Request to provide details on how missing data and intercurrent events will be handled. Similarly, it should be prespecified how outcomes following intercurrent events (e.g. treatment withdrawal, rescue treatment) will be considered in the analysis. In general, the data package envisaged to substantiate the B/R in ALGS patients might be sufficient, especially if the ALGS indication is applied for as a type II variation. It is agreed that data generated in other, related conditions can lend support to the ALGS indication. A comprehensive pharmacology package is expected at the time of MAA, complying with the usual regulatory standards. Assessment will take into account degree of pruritus control achieved, consistency of effect across endpoints and (potential) subgroups, AE pattern and manageability of those.
Pre-submission interaction Requested 13JUN2022	To obtain agreement of submission plan (e.g. Type II variation application) for marketing	The EMA agreed to proposed Type II variation and the high-level content plan but pointed out that the Applicant should discuss the comprehensiveness of the data package and propose post-authorisation studies that could

TYPE OF MEETING/ CORRESPONDENCE	PURPOSE OF CORRESPONDENCE	NOTABLE OUTCOMES
Written responses received: 01JUL2022	authorisation, including high-level content plan.	gather further efficacy/safety data, as appropriate, in Module 1.5.4.

2.2. Non-clinical aspects

Apart from clarification on the environmental risk assessment submitted at the time of the initial Marketing Authorisation no new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

During the initial Marketing Authorisation application (EMEA/H/C/004691/0000), a full ERA of odevixibat was submitted, which included the determination of physical-chemical properties and Phase I (PBT and PECsw) assessment. As the PECsw threshold limit of 0.01 µg/L was not exceeded, no further Phase II environmental fate studies were needed.

In the previous ERA of odevixibat, in addition to the indication 'treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older', also the treatment of biliary atresia (BA) and alagille syndrome (ALGS) were taken into account.

Due the refined Fpen used, based on the prevalences of the three diseases, which were 0.00008 µg/L, 0.001 µg/L and 0.003 µg/L for PFIC, ALGS and BA, respectively, the combined PECsw (PFIC + ALGS) remains below the threshold limit of 0.01 µg/L. The previous ERA reported prevalence for ALGS of 0.33 in 10 000, which was used to calculate the PECsw, is in line with the opinion on orphan designation for Bylvay (EMA/COMP/526568/2012).

Therefore, the current ERA is also valid for the inclusion of the ALGS indication. The Applicant updated the ERA summary table as per below including the current ALGS indication.

Substance (INN/Invented Name): Odevixibat			
CAS-number (if available): 501692-44-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	log K_{ow} = 5.2 (at pH for neutral molecule)	Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.2 (at pH for neutral molecule)	potentially B
	BCF	P.M.	B/not B
Persistence	ready biodegradability	P.M.	P/not P
	DegT50	P.M.	P/not P
Toxicity	NOEC algae NOEC crustacea NOEC fish	P.M.	T/not T
	CMR	not investigated	potentially T

PBT-statement:	P.M.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, refined on the basis of public literature	0.00008 (PFIC) 0.0001 (ALGS) 0.00018 (Total)	µg/L	< 0.01 threshold

The PEC_{sw} for PFIC (0.00008 µg/L) and ALGS (0.0001 µg/L) together result in a total PEC_{sw} of 0.00018 µg/L, which is well below the action limit of 0.01 µg/L, a further assessment is not deemed necessary.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, odevixibat is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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

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
A4250-015 03SEP2021 - Ongoing	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.

2.3.2. Pharmacokinetics

Odevixibat acts as a potent, selective inhibitor of the ileal bile acid transporter (IBAT). Odevixibat 40 and 120 µg/kg/day is currently approved for progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. In this type II variation, an extension of the indication is proposed, the addition of a new therapeutic indication into include treatment of cholestasis and pruritus in Alagille syndrome (ALGS) in patients from birth and older. The recommended odevixibat dose for ALGS is 120 µg /kg/ day. Dose reduction to 40 mcg/kg/day may be considered if tolerability issues occur, so the dose range for ALGS and PFIC are the same.

The clinical pharmacology data of odevixibat are based on previously submitted in the PFIC dossier, as well as new information based on the primary study conducted in patients with ALGS, A4250-012. For the ALGS programme, the initial population pharmacokinetic (PK) model conducted in support of dosing in patients with PFIC was updated to include results of sparse PK samples collected in Study A4250-012.

Methodology

Bioanalytical methods

In study A4250-012A, the plasma concentration of odevixibat has been determined using a validated LC-MS/MS assay by Drug Development Solutions (DDS), Fordham, Cambridgeshire, United Kingdom. The final bioanalytical report for the determination of odevixibat in human plasma (LGC336789QB21) has been submitted.

The method was validated at DDS under analytical projects QBR111522QB02 and LGC278335QB01 with an updated calibration range of 0.0500-500 ng/mL partially validated under LGC308183QB21. A change of business took place during the course of this analytical project, the business name was changed from LGC to DDS.

A total of 120 human plasma samples from study A4250-012 were received and stored at -20°C for a maximum of 310 days. In total, 94 were analysed across 5 acceptable analytical batches, all within the validated sample storage period of 348 days. In many study samples the odevixibat concentration was below the lower limit of quantification, or very low (below QC Low concentration of 0.150 ng/mL)

Acceptable within-run and between-run accuracy and precision was shown. Back-calculated concentrations of the A4250 calibration standards were within ±15% RE of the nominal value (±20% RE at the LLOQ) for at least 75% of the calibration standards in each accepted analytical batch. As there were less than 20 results that were above QC Low concentration, incurred sample reanalysis (ISR) was not performed under this analytical project.

Table 3 Clinical sample analysis summary

Test compound	**A4250**
Analytical matrix	Human plasma (lithium heparin)
Analyte	A4250
Internal standard	AZ 11639816-002
Validated method	4681
Lower limit of quantification	0.0500 ng/mL
Upper limit of quantification	5.00 ng/mL
Quality Control (QC) summary statistics	Low QC 0.150 ng/mL: 4.0% RE, 5.2% CV Medium QC 1.50 ng/mL: 6.0% RE, 4.7% CV High QC 3.75 ng/mL: 2.4% RE, 5.4% CV Dilution QC (1 in 2) 3.75 ng/mL: 1.1% RE, 5.3% CV Dilution QC (1 in 4) 3.75 ng/mL: 0.3% RE, 2.3% CV
Analytical technique/method of detection	Liquid-liquid extraction with LC-MS/MS detection
Total number of samples analysed	94
Sample storage conditions	In a freezer set at -20°C in polypropylene containers

Population PK modelling

The initial population PK analysis of odevixibat was performed based on Phase 1 studies in healthy adult subjects (A4250-001, A4250-004, and A4250-013) and Phase 2 and Phase 3 studies in paediatric patients (A4250-003 and A4250-005). The updated population PK model also includes data of a study conducted in patients with ALGS, A4250-012.

- ***Initial PopPK model***

The initial population PK model contained data from 158 subjects. The PK of odevixibat was described using a one-compartment model with linear elimination. Concentration-time profiles presented double absorption peak profiles with a secondary peak occurring at approximately 4 hours post-dose which coincided with meal intake. The population PK model included a first- and second-rate constant of absorption to characterise double peak profiles (Ka1 and Ka2, respectively).

The model has been assessed in bylvay-epar. Due to the limited availability of detectable PK samples, the population model is mainly driven by data from studies A4250-004 and A4250-013. Population PK modelling and simulations were performed using NONMEM.

The initial model included a total of 105 adults and 53 paediatric subjects. As the concentration of odevixibat was not detectable in about half of the study samples, the model accounted for the samples BLQ, using the likelihood method M3.

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

The effect of hepatic impairment was assessed based on individual post-hoc PK parameters derived from the initial population PK model. The exposure of odevixibat was calculated for the 40 and 120 µg/kg/day dose levels in 11 patients with mild liver impairment (Child-Pugh A) or no liver impairment and 5 patients with moderate hepatic impairment from study A4250-005A. Hepatic impairment had an effect on the clearance of odevixibat; a 60.6% lower CL/F was observed in patients with moderate liver impairment (Child-Pugh B) relative to patients with mild or no liver impairment.

- ***Updated population PK model with data from ALGS patients***

The initial model was updated by performing a population PK analysis by including data collected in Study A4250-012. The updated population PK model contains data of 191 subjects. The analysis included a total of 105 (55.0%) healthy subjects, 39 (20.4%) patients with ALGS (Studies A4250-003 and A4250-012), 43 (22.5%) patients with PFIC (Studies A4250-003 and A4250-005) and 4 (2.1%) patients with other cholestatic liver diseases (Study A4250-003).

Of a total of 3016 samples collected, 1513 (50.2%) had undetectable concentrations of odevixibat. A total of 25 (39.7%) samples had undetectable concentrations of odevixibat out of a total of 63 samples collected in Study A4250-012. The pop PK model accounted for the samples BLQ, using the likelihood method M3.

The population PK data set included 33 paediatric subjects from study A4250-012. These subjects all received odevixibat 120 µg/kg/day, and all presented with moderate hepatic impairment (Child-Pugh B). The majority of patients were between 2 and 12 years of age (N=283), N=3 were < 2 years old, and N=4 were ≥ 12 to < 18 years. None of the subjects was younger than 0.5 years of age (see section 5.4.2).

In study A4250-012, PK samples were collected at pre-dose on Week 4 and Week 20, and end of treatment (only for children with body weight >10 kg).

The PK of odevixibat was described by a one-compartment model with linear elimination and included a first- and second-rate constant of absorption to characterise double peak profiles. Typical values of PK parameters derived with the final updated population PK model (run2001) of odevixibat are presented in Table 4.

Table 4 Population PK Analysis of Odevixibat: Parameter Estimates (updated model)

Parameter	Estimate	RSE*	BSV	Shrinkage
CL/F (L/h)	**2970**	**5.67%**	**38.6%**	**21.4%**
	× $(WT/70)^{0.75}$	NA	NA	NA
	× (1 - 0.374) if Concomitant Administration of P-gp Inhibitors	12.9%	NA	NA
	× (1 - 0.770) if Child-Pugh B (Moderate Hepatic Impairment)	4.11%	NA	NA
V/F (L)	**3338**	**11.4%**	**33.0%**	**32.3%**
	× $(WT/70)^{1}$	NA	NA	NA
Ka_1 (h^{-1})	**0.329**	**11.4%**	**29.2%**	**35.8%**
	× (1 -0.863) if Formulation A (powder blend in capsule)	20.6%	NA	NA
Ka_2 (h^{-1})	**1.62**	**16.7%**	NA	NA
Lag_1 (h)	**0.581**	**1.87%**	NA	NA
Lag_2 (h)	**3.90**	**0.76%**	NA	NA
F1 (Ka_1 and Ka_2)	**0.869**	**1.34%**	NA	NA
Frel	**1, Fixed**	**NA**	**NA**	**NA**
	× (1 - 0.342) if Sprinkle dosage form	13.0%	**NA**	**NA**
	× (1 - 0.447) if Formulation A (powder blend in capsule)	116%	**NA**	**NA**
Error Model	**Proportional: 0.261**	**6.95%**	**NA**	**NA**
	Additive (ng/mL): 0.0235	**7.69%**	**NA**	**NA**

CL/F = apparent clearance, V/F = apparent volume of distribution; Ka_1 = first (slow) rate of absorption; Ka_2 = second (rapid) rate of absorption; Lag_1 = first absorption lag time; Lag_2 = second absorption lag time; F1 = fraction of drug that is absorbed via the first route (Ka_1, Lag_1); Frel = relative bioavailability; BSV = between-subject variability; RSE = relative standard error derived from the bootstrap analysis.
PK parameter correlation and results derived from the bootstrap resampling analysis are presented in Appendix 1 (Section 11.15 and 11.16).

The effect of disease was formally evaluated using a stepwise covariate analysis. The effect of disease was evaluated using a binary variable (i.e. two categories) whereby PK parameters in patients with ALGS were compared to those observed in all other subjects/patients combined. In addition, the effect of disease was evaluated using the following 3 categories: 1) patients with ALGS, 2) healthy subjects, and 3) patients with PFIC or other cholestatic liver diseases. Results from the covariate analysis evaluating the effect of disease on PK parameters of odevixibat are presented in Table 5.

Table 5: Covariate Analysis – Effect of Disease (ALGS) on PK Parameters (updated population model)

Steps	Covariate	Base OFV	New OFV	OFV Drop (ΔOFV)
1	Effect of Disease - ALGS vs. Others on CL/F	-5315.25	-5316.017	-0.767
2	Effect of Disease - ALGS vs. Others on V/F	-5315.25	-5316.255	-1.005
3	Effect of Disease - ALGS vs. Others on Frel	-5315.25	-5316.372	-1.122
4	Effect of Disease - ALGS vs. Healthy vs. (PFIC or Other Cholestatic Diseases) on CL/F	-5315.25	-5316.098	-0.848
5	Effect of Disease - ALGS vs. Healthy vs. (PFIC or Other Cholestatic Diseases) on V/F	-5315.25	-5318.446	-3.196
6	Effect of Disease - ALGS vs. Healthy vs. (PFIC or Other Cholestatic Diseases) on Frel	-5315.25	-5316.242	-0.992

CL/F = apparent clearance; V/F = apparent volume of distribution; Frel = relative bioavailability; OFV= objective function value.

Note: Inclusion of a covariate tested at a significance level of $p < 0.01$ (ΔOFV drop higher than 6.63490).

ALGS = 6 patients from Study A4250-003 and 33 patients from Study A4250-012

PFIC = 10 patients from Study A4250-003 and 33 patients from Study A4250-005

Other Cholestatic Diseases = 3 patients with biliary atresia and 1 patient with intrahepatic cholestasis from Study A4250-003

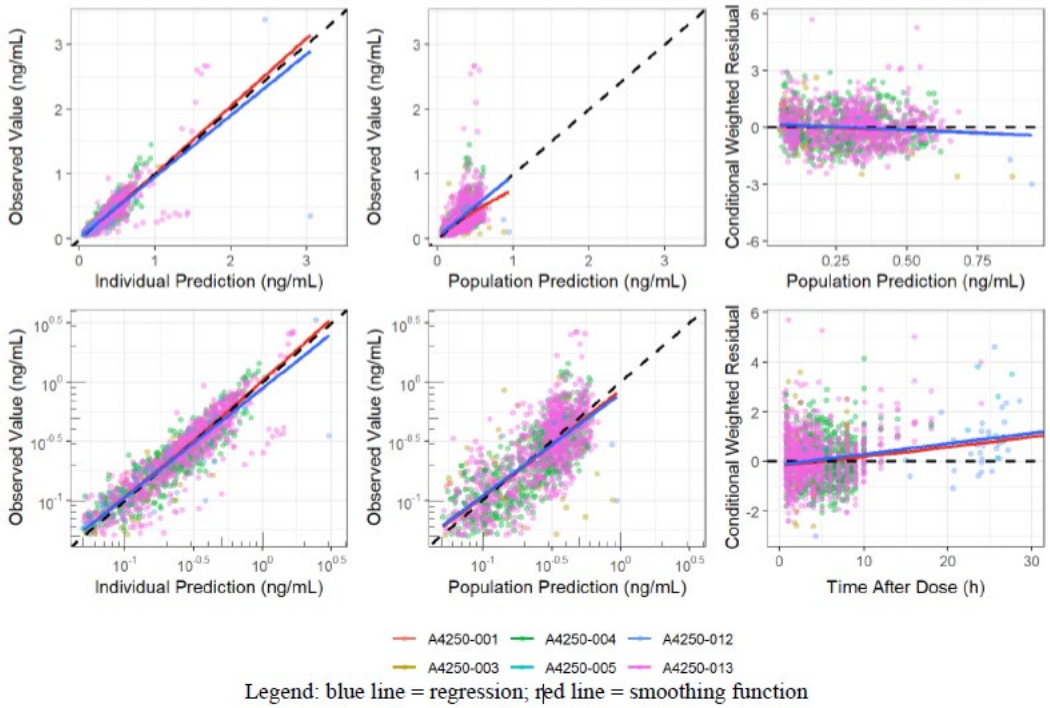
The CL/F, V/F and Frel of odevixibat in patients with ALGS (Steps 1, 2 and 3) were not statistically different than that observed in other subjects (Healthy + PFIC + Other cholestatic diseases). In addition, the CL/F, V/F and Frel in patients with ALGS were not statistically different from that observed in healthy subjects and patients with either PFIC or other cholestatic diseases (Steps 4, 5, and 6). Based on the above results, patients with ALGS presented similar PK parameters as those observed in healthy subjects, patients with PFIC or patients with other cholestatic diseases (i.e. biliary atresia or intrahepatic cholestasis associated with microvillus atrophy).

Hepatic impairment status (Child-Pugh B), drug-drug interaction (concomitant administration of P-gp inhibitors), formulation (formulation A, powder blend in capsule) and formulation presentation (sprinkle dosage form) were already included in the initial model. Age, sex, race, renal impairment, and co-administration of CYP3A substrates were previously shown to have no effect on PK parameters of odevixibat.

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

The goodness-of-fit derived with the final population PK model of odevixibat in the overall population is presented in Figure 2

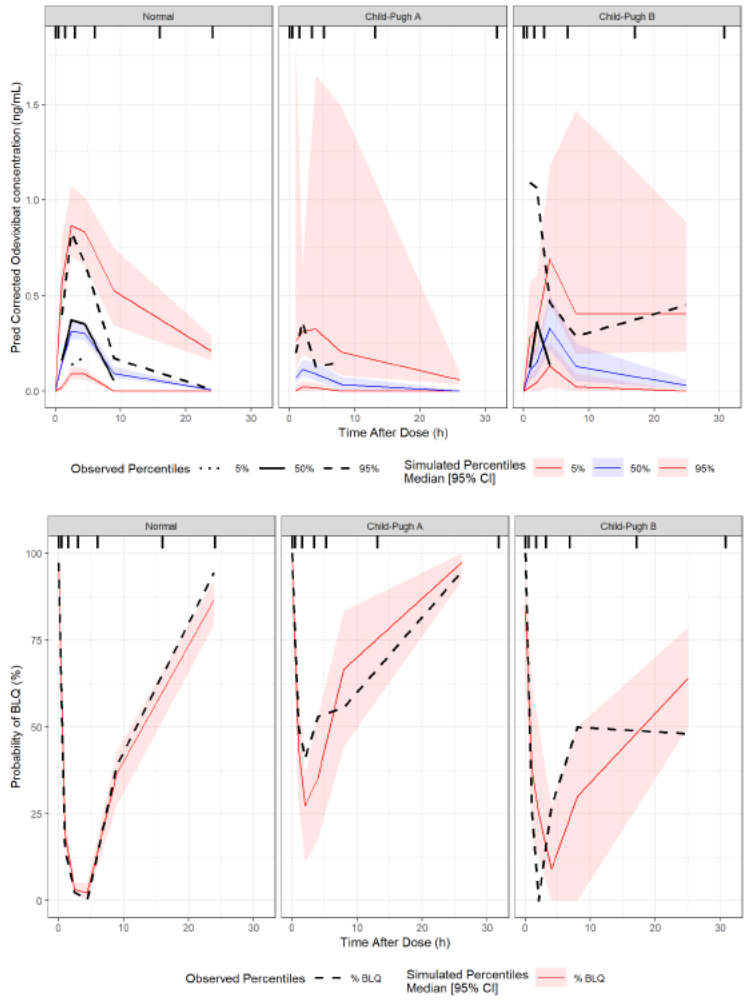
Figure 2 Goodness-of-Fit: Population and Individual Predicted vs. Observed Concentrations of Odevixibat – All Studies



Legend: blue line = regression; red line = smoothing function

Hepatic impairment had an effect on the clearance 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.

Figure 3 Population PK Analysis – Final Model – Visual Predictive Check – By Degree of Hepatic Impairment – Linear Scale



Individual post-hoc PK parameters of odevixibat were derived in patients with ALGS in Study A4250-012 (N=33), and results were summarised with descriptive statistics. All patients on active drug from Study A4250-012 presented with moderate hepatic impairment (Child-Pugh B). Mean CL/F, V/F and Ka1 in patients with ALGS with moderate liver impairment (Child-Pugh B) who received 120 µg/kg/day in Study A4250-012 were 212 L/h, 1160 L and 0.311 h-1, respectively. Mean AUC, Cmax and t½ were 13.2 ng.h/mL, 1.13 ng/mL and 4.75 h, respectively. No accumulation of odevixibat was observed following repeated administration in patients with ALGS (i.e. <10%). Descriptive statistics of exposure parameters of odevixibat in patients with ALGS are presented in Table 6.

Table 6 Descriptive Statistics of PK Parameters of Odevixibat in Patients with ALGS – Study A4250-012 (updated population model)

Parameters	N = 33 Mean (CV%) Median [Min, Max]
	120 µg/k/day, Moderate Hepatic Impairment (Child-Pugh B)
CL/F (L/h)	212 (48.2) 180 [35.1, 528]
V/F (L)	1160 (46.9) 950 [355, 2710]
Ka_1 (h^{-1})	0.311 (13.7) 0.309 [0.166, 0.389]
AUC (ng.h/mL)	13.2 (87.3) 11.3 [5.50, 74.5]
C_{max} (ng/mL)	1.13 (40.8) 1.08 [0.446, 3.53]
T_{max} (h)	5.17 (8.2) 5.20 [4.50, 6.50]
t½ (h)	4.75 (105.9) 4.03 [1.38, 31.1]
Accumulation Ratio	1.09 (25.1) 1.03 [1.00, 2.59]

CL/F = apparent clearance, V/F = apparent volume of distribution; Ka_1 = first (slow) rate of absorption; C_{max} = maximum concentration; t_{max} = time to maximum concentration; AUC = area under the curve; $t_{1/2}$ = elimination half-life; CV = coefficient of variation.

Individual post-hoc PK parameters of odevixibat were derived in patients with PFIC in Study A4250-005 (N=33) using the updated population model.

The mean AUC and Cmax of odevixibat in PFIC patients with mild hepatic impairment (Child-Pugh A) who received the 40 µg/kg/day dose in Study A4250-005 were approximately 88% and 72% lower than those observed in patients with moderate hepatic impairment (Child-Pugh B), respectively. Likewise, the mean AUC and Cmax of odevixibat in PFIC patients with mild hepatic impairment (Child-Pugh A) who received the 120 µg/kg/day dose in Study A4250-005 were approximately 77% and 64% lower than those observed in patients with moderate hepatic impairment (Child-Pugh B), respectively.

Descriptive statistics of exposure parameters of odevixibat in patients with PFIC in Study A4250-005 are presented in Table 7.

Table 7 Descriptive Statistics of PK and Exposure Parameters of Odevixibat in Patients with PFIC – Study A4250-005 - By Dose and Hepatic Impairment Status (updated model)

Parameters	N Mean (CV%) Median [Min, Max]			
	40 µg/kg/day		120 µg/kg/day	
	Mild Hepatic Impairment (Child-Pugh A)	Moderate Hepatic Impairment (Child-Pugh B)	Mild Hepatic Impairment (Child-Pugh A)	Moderate Hepatic Impairment (Child-Pugh B)
CL/F (L/h)	N=11 1030 (43.7) 935 [611, 2170]	N=6 209 (71.9) 184 [37.3, 482]	N=11 1010 (53.7) 791 [115, 1950]	N=5 175 (43.3) 210 [62.1, 241]
V/F (L)	N=11 675 (27.6) 715 [405, 954]	N=6 1090 (61.0) 894 [411, 2330]	N=11 962 (55.7) 739 [399, 1900]	N=5 1210 (114.0) 675 [363, 3670]
Ka_1 (h^{-1})	N=11 0.324 (9.9) 0.329 [0.235, 0.370]	N=6 0.287 (20.1) 0.309 [0.209, 0.342]	N=11 0.323 (10.4) 0.329 [0.226, 0.362]	N=5 0.331 (6.1) 0.339 [0.295, 0.341]
AUC (ng.h/mL)	N=11 0.587 (17.2) 0.601 [0.369, 0.746]	N=6 5.05 (108.3) 2.80 [1.79, 16.1]	N=11 2.77 (92.5) 1.99 [1.52, 10.4]	N=5 12.1 (68.9) 8.56 [7.47, 26.9]
C_{max} (ng/mL)	N=11 0.108 (16.3) 0.112 [0.0692, 0.132]	N=6 0.387 (61.6) 0.341 [0.186, 0.833]	N=11 0.387 (30.5) 0.366 [0.277, 0.705]	N=5 1.07 (18.9) 1.02 [0.869, 1.40]
T_{max} (h)	N=11 2.15 (33.6) 1.90 [1.70, 4.30]	N=6 5.30 (12.2) 5.05 [4.70, 6.30]	N=11 2.58 (51.1) 2.00 [1.90, 5.90]	N=5 5.08 (12.0) 4.70 [4.70, 6.10]
t½ (h)	N=11 0.479 (17.7) 0.494 [0.279, 0.570]	N=6 5.70 (107.6) 2.97 [1.98, 17.8]	N=11 1.10 (161.5) 0.534 [0.458, 6.44]	N=5 5.86 (126.8) 2.08 [2.03, 19.0]
Accumulation Ratio	N=11 1.00 (0.0) 1.00 [1.00, 1.00]	N=6 1.16 (26.6) 1.01 [1.00, 1.78]	N=11 1.01 (4.5) 1.00 [1.00, 1.15]	N=5 1.17 (31.2) 1.00 [1.00, 1.83]

CL/F = apparent clearance, V/F = apparent volume of distribution; Ka_1 = first (slow) rate of absorption; C_{max} = maximum concentration; t_{max} = time to maximum concentration; AUC = area under the curve; $t_{1/2}$ = elimination half-life; CV = coefficient of variation.

PK parameters in patients with PFIC (A4250-005) were compared to those observed in patients with ALGS (A4250-012).

- Patients with PFIC or ALGS with moderate liver impairment (Child-Pugh B) who received 120 µg/kg/day presented similar mean values of CL/F (212 and 175 L/h, respectively), V/F (1160 and 1210 L, respectively) and Ka1 (0.311 and 0.331 h-1, respectively).
- Patients with PFIC with mild liver impairment (Child-Pugh A) or no liver impairment had an approximately higher clearance and a lower Cmax and AUC.

Absorption

Odevixibat is minimally absorbed following oral administration, with an estimated relative bioavailability is < 1%. Simulated C_{max} and AUC values for the 120 mcg/kg/day dose in a paediatric ALGS population were similar to PFIC. There is a minimal accumulation of odevixibat following once-daily dosing.

Distribution

Odevixibat is more than 99% bound to human plasma proteins. The V/F of odevixibat for a typical 70 kg subject was determined to be 2510 L in the initial model and 3388 L in the updated model.

Elimination

Following administration of a single oral dose of 3 000 mcg of radiolabelled odevixibat in healthy adults, the average percent recovery of the administered dose was 82.9% in faeces; less than 0.002% was recovered in the urine. More than 97% of faecal radioactivity was determined to be unchanged odevixibat.

The CL/F of odevixibat for a typical 70 kg subject was determined to be 2180 L/h in the initial model and 2970 L/h in the updated model.

Dose proportionality and time dependencies

The C_{max} and AUC_{0-t} increase with increasing doses in a dose-proportional manner; however due to the high interindividual variability of approximately 40%, it is not possible to estimate the dose proportionality accurately.

Special populations

No clinically significant differences in the pharmacokinetics of odevixibat were observed based on age, sex, or race.

Hepatic impairment

The majority of patients with PFIC and all patients with ALGS presented with some degree of hepatic impairment because of the disease.

Based on population PK analysis, patients with mild hepatic impairment exhibited comparable pharmacokinetics compared to other subjects with a normal hepatic function. 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; no accumulation of odevixibat was observed.

Renal impairment

There are no clinical data in patients with renal impairment, but the impact of renal impairment is expected to be small due to low systemic exposure, and odevixibat is not excreted in the urine.

Pharmacokinetic interaction studies

Odevixibat is a substrate for the efflux transporter P-glycoprotein (P-gp). In healthy adult subjects, co-administration of the strong P-gp inhibitor itraconazole increased the plasma exposure of a single dose of odevixibat 7200 µg by approximately 50-60%. In healthy adult subjects, concomitant use of odevixibat decreased the area under the curve (AUC) of oral midazolam (a CYP3A4 substrate) by 30% and 1-OH-midazolam exposure by less than 20%, which is not considered clinically relevant.

No interaction studies have been conducted with UDCA and rifampicin.

No interaction studies have been conducted with oral hormonal contraceptives or other lipophilic medicinal products. As mentioned in the SmPC it cannot be excluded that the absorption of oral contraceptives is affected by the concomitant use of odevixibat.

In clinical trials, decreased levels of fat-soluble vitamins were observed in some patients receiving odevixibat. Levels of fat-soluble vitamins should be monitored.

Pharmacokinetics using human biomaterials

In vitro studies

In in vitro studies, odevixibat was shown to be an inhibitor of CYP3A4/5, but did not inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at clinically relevant concentrations, but was shown to be an inhibitor of CYP3A4/5.

In vitro, odevixibat did not induce CYP enzymes

Odevixibat does not inhibit the transporters P-gp, breast cancer resistance protein (BCRP), organic anion transporter (OATP1B1, OATP1B3, OAT1, OAT3), organic cation transporter (OCT2), multidrug and toxin extrusion transporter (MATE1 or MATE2-K).

In vitro, odevixibat is a substrate for the gastrointestinal efflux transporter P-gp, but not for BCRP."

2.3.3. 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

Primary pharmacology

The pharmacodynamic effect of odevixibat has been characterised in the initial studies and data has been assessed at the time of the initial MAA.

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.

Secondary pharmacology

A dedicated QT study was not conducted. Non-clinical data indicated a low potential for adverse effects on the cardiovascular system, including cardiac conduction, as assessed by ECG. This was supported by the ECG findings performed in Phase 1 studies conducted in healthy volunteers. Odevixibat did not affect the hERG potassium channel at the tested concentration (1 µM), which is 7700-fold higher than the 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 (Bylvay EPAR).

2.3.4. PK/PD modelling

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.

2.3.5. Discussion on clinical pharmacology

The Applicant proposes an extension of the indication: the addition of a new therapeutic indication to include the treatment of cholestasis and pruritus in Alagille syndrome (ALGS) in patients from birth and older. To support this indication, the additional 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 population PFIC PK model with data from ALGS patients describes 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. This has been reflected in the SmPC section 5.2.

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. Despite this effect on clearance, no significant accumulation has been observed as the bioavailability of odevixibat is low No dose adjustment is required for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) have not been studied, additional monitoring for adverse reactions is recommended for these patients as advised in 4.2 of the SmPC.

The Applicant proposed to indicate odevixibat from birth and older; however, odevixibat has not been studied in paediatric subjects younger than 6 months. It is not clear, if PK data of odevixibat in children aged 6 months or older can be safely extrapolated to paediatric subjects < 6 months. To support full extrapolation, the MAH provided population PK simulations for paediatric patients with ALGS, aged < 6 months. The model predictions assume that the bioavailability of odevixibat is very low in patients ≤ 6 month and that the PK of the absorbed fraction is mainly affected by body weight and hepatic function; the impact of maturation of intestinal permeability, transport by P-gp, and a milk-only diet is assumed to be low. Although these model assumptions appear reasonable, with a very low bioavailability, also small deviations from the assumed values may have a big impact on the simulated exposures and the applicant was requested to provide further substantiation for full extrapolation to patients of this age. However, as the applicant narrowed the indication claim to patients from 6 month of age no further substantiation for full extrapolation is needed.

The MAH may consider to amend the phase 3 study A4250-011 protocol, to collect sparse PK data in patients ≤6 months. This could potentially enable a future indication for the youngest patients (≤6 months).The pharmacodynamic effect of odevixibat has been discussed in the initial MAA. 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 decreases 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.

2.3.6. 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. Despite of this, no dose adjustment is required, due to very low bioavailability of odevixibat no accumulation was observed and the safety profile was also comparable between the patient groups.

It was not considered convincingly demonstrated that the PK data of odevixibat in children aged 6 months or older can be safely extrapolated to paediatric subjects < 6 months. However, as the Applicant revised their indication claim to patients from 6 month of age this issue is not further pursued.

The pharmacodynamic effect of odevixibat has been assessed at the initial MAA. In line with the known PD effect, decreases in serum bile acids and autotaxin were observed. Increased p-C4 levels indicated a normalisation of bile acid synthesis.

2.4. Clinical efficacy

2.4.1. Dose response study A4250-003

The CSR of study A4250-003 was included in the PFIC dossier and was discussed at the initial MAA. Since the study also enrolled patients with ALGS, a summary is included and the results of these patients are discussed.

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 1 was female; 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 8). 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 8: 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 9: 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.

2.4.2. Main study A4250-012

The primary data in support of the efficacy of odevixibat are derived from the Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled Study A4250-012 conducted in 52 patients with a genetically confirmed diagnosis of ALGS.

Additional data are available through 09SEP2022 from the ongoing open-label extension study, A4250-015, which allows continued treatment with odevixibat for patients who completed Study A4250-012. Efficacy data from Studies A4250-012 and A4250-015 have also been integrated and pooled for analysis to allow for a review of the longer-term efficacy of treatment for up to 48 weeks.

A Phase 3 Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients with Alagille Syndrome (ASSERT)

Methods

Study participants

Inclusion criteria

1. A male or female patient (of any age) with a genetically confirmed diagnosis of ALGS. A patient could be randomised based on genetic testing results in the medical record. If genetic testing results were not available, testing was performed at Screening Visit 1, and the patient could not be randomised until the genetic diagnosis was confirmed.

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. For each AM and PM weekly assessment, a minimum of 4 of 7 expected scores was required to be recorded. The mean of the weekly AM and the mean of the weekly PM scores were averaged to determine the pruritus score as measured by ObsRO.

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).

4. Patient and/or legal guardian must have signed informed consent (and assent) as appropriate.

5. Caregivers must have been willing and able to use an eDiary device as required by the study and patients ≥ 8 years of age must have been willing to use an eDiary, if able to do so.

6. Sexually active males and females must have agreed to use a reliable contraceptive method with ≤ 1% failure rate) throughout the duration of the study and 90 days thereafter (from signed informed consent through 90 days after last dose of study drug) (see Appendix 6 of the protocol included in Appendix 16.1.1 for further details).

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.

9. Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period.

10. Patient had a liver transplant, or a liver transplant was planned within 6 months of randomisation.

11. 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 QD 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 may be 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. In addition, if the study drug is interrupted for clinically significant diarrhoea and the patient fails re-challenge at 120 µg/kg/day, the patient may be re-challenged at 40 µg/kg/day. Except for clinically significant diarrhoea, the timing of dose increase/re-challenge at 120 µg/kg/day is at the discretion of the investigator. Two dose reductions are 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 concentration

• Change from baseline to Week 24 in serum AST concentration

• Change from baseline to Week 24 in gamma-glutamyl transferase concentration

• Change from baseline to Week 24 in total 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

9.1.4 Exploratory Cohort Endpoints

• All endpoints assessed for the primary analysis population will be assessed for the

cohort of patients ≥18 years of age at randomisation and are considered exploratory.

Sample size

Forty-five (45) patients <18 years of age will be randomised at an experimental to control the 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, the pooled SD of change from baseline to Week 16 (Weeks 13 to 16 assessments) will be calculated by an independent statistician. Samples size re-estimation is based on non-comparative blinded data for which no alpha adjustment is required. If the pooled SD was underestimated in this original sample size calculation, an adjustment will be made to maintain study power, assuming a 1.2 treatment effect. It is assumed that the Week 16 and Week 24 SDs will be equivalent; however, a multiplication factor (e.g. 1.2) on the calculated SD may be made based on the current understanding of the instrument at the time of sample size re-estimation. If SD was overestimated, in this original sample size calculation, the sample size will not be decreased.

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. Accordingly (based on Table 4 in the SAP; Appendix 16.1.9), 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. A total of 52 patients were enrolled.

Randomisation

After written informed consent was obtained, an 8-digit patient identification number was assigned by the Interactive Web Response System (IWRS). The first 2 digits denoted country, followed by a 3-digit site number, and a 3-digit patient sequence number. 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 had been randomised according to one age stratification factor, i.e. <10, and 10 to <18 years of age. This stratification factor was based on Kamath et al. (2020), showing an increase in the prevalence and severity of pruritus in children <10 years of age.

Patients who withdrew from the study after the randomisation visit were not to be replaced and their randomisation number was not be reused.

Blinding (masking)

A double-blind design is employed so that both the investigators and the patients were unaware of the treatment assignment.

To ensure blinding, the study drug and the matching placebo have 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 and adjustment for multiplicity

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

No interim analyses were planned or performed for the primary endpoint, therefore no adjustment for multiplicity is required.

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 yoa	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

The primary efficacy endpoint was a change in scratching severity score (AM and PM combined) from baseline to Month 6 (Weeks 21-24) based on the worst scratching score (Item 1) of the ObsRO from the AM and ObsRO PM assessments.

For the analysis, the estimand strategy includes 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:

ICE: Treatment discontinuation prior to week 24 (treatment policy): include all data collected after this type of ICEs. This reflects the patients' outcomes in practice if they are unable to continue receiving the investigational drug.

ICE: Undergoes biliary diversion surgery or liver-transplant (hypothetical): As biliary diversion surgery may be viewed as a "rescue" treatment for pruritus, it may be reasonable for the primary analysis of pruritus outcomes to utilise a hypothetical strategy which assumes that the biliary diversion surgery did not occur. A similar strategy may be reasonable for liver transplantation, although transplantation may be indicated for reasons other than pruritus. 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. Only a small number of patients, if any, are expected to have biliary diversion surgery or liver transplant during the placebo-controlled portion of the trial.

ICE: Change in anti-pruritis medication: Although not permitted by the study protocol, a significant change in anti-pruritus medication may also be considered as an ICE as it can affect the patient's scratching score. However, due to large number of various anti-pruritic medications with different pharmacokinetic and pharmacodynamic properties, it would be challenging from a clinical standpoint to define significant changes in anti-pruritus medication based on duration and dose collected in concomitant medication only. Therefore, a change in 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.

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 will be 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 is 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 is calculated as the monthly score minus the baseline score.

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

There will be 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) will be used. Each week, at least 4 of 7 assessments need to be completed for each of the AM and PM assessments. If these minimum assessments are not available, the week is considered missing. Monthly values will only be calculated if at least 3 weeks can 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 key secondary efficacy endpoint is a change in serum bile acid levels from baseline, defined as the average of the last 2 values prior to the first dose of study drug, to the average of values at Weeks 20 and 24. For baseline, if only 1 value was available, that value was used. The same estimand strategy used for the primary endpoint was used in assessing this 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 are displayed in a scatterplot

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

The same estimand strategy used for the primary efficacy endpoint was used for all other efficacy endpoints.

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 will be used to estimate a threshold of clinically meaningful change (i.e. responder definition) in Albireo ObsRO and PRO pruritus scores. The analysis will be performed by a group independent of both the study team and Albireo. Blinded data will be used for this analysis; data will be 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 will be considered primary** in the estimation of the meaningful change threshold. Other analyses will be considered complementary and used to confirm the estimates that will emerge from the anchor-based analyses.

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

Anchor-based analyses will involve examining the degree of change in the Albireo PRO and ObsRO scores from baseline to Week 24 for patients who experience 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 will be selected as a candidate threshold value. Final meaningful change estimates will be 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.

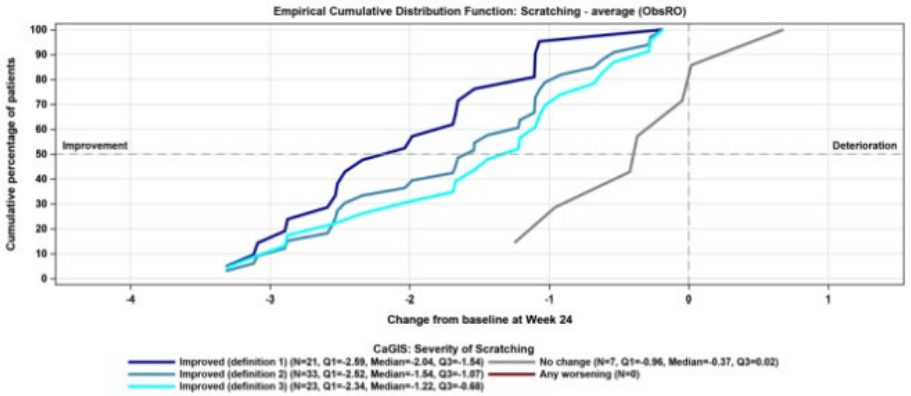
The smallest absolute median Albireo ObsRO scratching average change value for the CaGIS that exceeded the values from the distribution-based analyses and the lower bound of the 95% CI from the stable anchor category was 1.22 and 1.29 at Week 24 for the ObsRO scratching average and worst weekly scores, respectively. 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 40: Summary of Anchor- Based Analyses of Albireo ObsRO Scratching Average Score

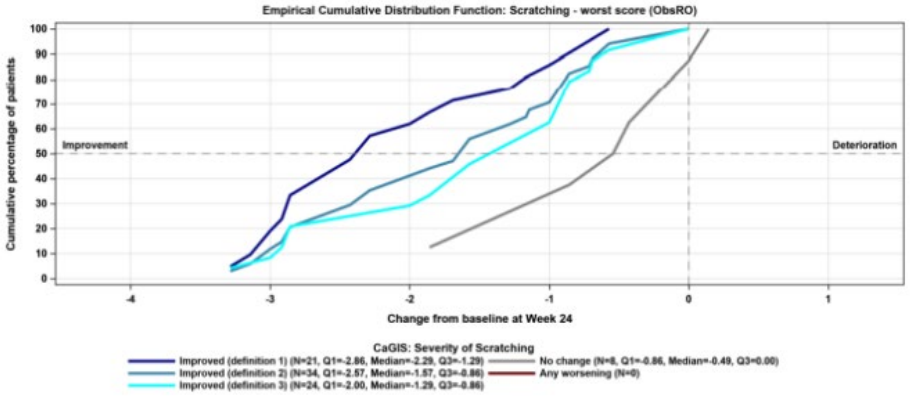
ANCHOR/ANALYSIS	STATISTIC	CHANGE FROM BASELINE TO WEEKS 9-12 (N)		CHANGE FROM BASELINE TO WEEKS 21-24 (N)
CaGIS: Improved - Definition 1	Mean, Median	-1.89,-1.92 (18)		-2.04,-2.04 (21)
CaGIS: Improved - Definition 2	Mean, Median	-1.60,-1.65 (34)		-1.67,-1.54 (33)
CaGIS: Improved - Definition 3	Mean, 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

Figure 10: eCDF for Albireo ObsRO Scratching Score Using CaGIS as Anchor (Week 24; Monthly Score)

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.

In summary, according to the Applicant, the blinded psychometric analysis results (Psychometric report Appendix G) 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.

Subgroup analyses

The following subgroup analyses will be 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 will follow 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)

A forest plot of the subgroup analyses will be provided for the key secondary endpoint.

Statistical analysis will be performed only when the sample size is ≥5 in each treatment group. If the sample size is <5 in either treatment group, only summary statistics will be provided; the p-value will not be reported.

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 (3 in France, 3 in Germany, 3 in Italy, 2 in the Netherlands, 1 in Belgium, and 1 in Poland), 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: 26FEB2021

Date last patient completed: 09SEP2022

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. Key revisions based on the country-specific amendments are outlined below.

Amendment	**Key changes**
United Kingdom, V2.1 29JAN2021	Further details and clarifications were added regarding study discontinuation and requirements for study restart.
Italy, V2.2 12FEB2021	Two exclusion criteria were added: o Known hypersensitivity to any components of odevixibat o Body weight < 4 kg • Definitions of end of study by country and globally were included. • Included text that the clinical work-up of the aetiology of diarrhoea should follow institutional/local guidelines and that electrolyte levels could be determined as part of this evaluation.
Netherlands, V2.4 11MAY2021	Clarification was added to distinguish pruritus scoring based on the PRO (as itching) and ObsRO (as scratching). • Removed the allowance for dose modification to 40 µg/kg unless related to clinically significant diarrhoea. • Included additional details on the patient assignment, randomisation, the IWRS, and drug dispensing, labelling, and unblinding. • Included blood urea nitrogen and triglycerides as part of the clinical chemistry assessment.
Germany, V2.5 16JUN2021	Details were added to the risk-benefit section to provide information on prior study results in paediatric patients, including patients with PFIC, treated with odevixibat. • Definitions of end of study by country and globally were included.
United Kingdom, V2.6 01JUL2021	A section was added on the risk/benefit of receiving the COVID-19 vaccine during study participation.

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, 1 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, Patient 03001-102 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 another 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 the important deviations detailed in Table 14, 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 groups with an overall treatment compliance documented as < 80% per final drug accountability.

Table 10: 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.

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 11). 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 11: 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.

All patients had hepatic impairment at baseline based on both the Child-Pugh and NCI ODWG 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 above.

Outcomes and estimation

Primary endpoint

As described above, the estimand strategy for the primary analysis of all efficacy endpoints was to include all data collected except those following the ICEs of biliary diversion surgery and liver transplant. As these ICEs did not occur in Study A4250-012, no data were excluded from the analysis of efficacy.

Treatment with odevixibat 120 µg/kg/day for 6 months led to a statistically significant improvement in pruritus severity compared to placebo (Table 12).

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.

Table 12: 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)

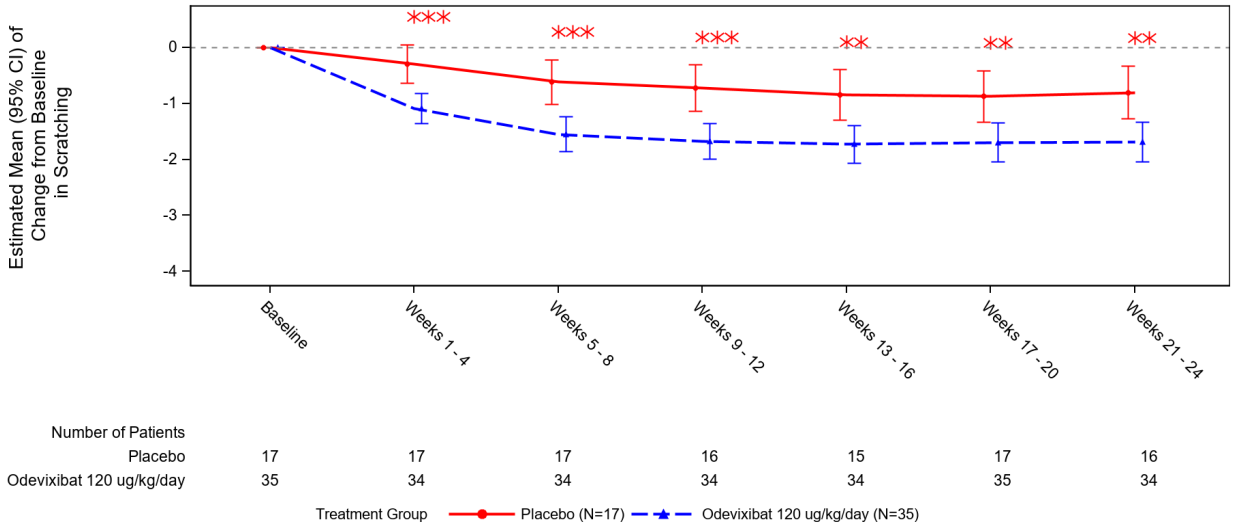
Visit **Statistic**	**Placebo** **n=17**	**Odevixibat** **n=35**
Baseline		
N	17	35
Mean (SD)	3.01 (0.636)	2.80 (0.520)
Median	3.18	2.71
Minimum, maximum	2.1, 4.0	1.9, 4.0

Visit **Statistic**	**Placebo** **n=17**	**Odevixibat** **n=35**
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	

Source: CSR A4250-012, Table 14.2.1.1.1.

The improvement in scratching severity was observed early after the initiation of treatment with odevixibat (**Figure 2**). 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.

Figure 4: Estimated Mean (±95% CI) Change from Baseline in Monthly Scratching Severity Score (AM and PM Scores Combined) – Albireo ObsRO Instrument (MMRM) (Full Analysis Set; Study A4250-012)



Source: CSR A4250-012 Figure 14.2.1.2.1.

Sensitivity and Supplementary Analyses

Results of the sensitivity analyses for the primary efficacy endpoint were consistent with the main analysis confirming the robustness of the results:

Sensitivity analysis	LS mean difference (95% CI) (odevixibat-placebo)
1: MMRM with control-based MI	-0.89 (-1.44, -0.34)
2. Tipping point analysis	No plausible tipping point
3: MMRM based on the worst weekly scratching score for a month	-0.84 (-1.40, -0.29)
4: MMRM with control-based MI based on worst weekly scratching score for a month	Not performed, no missings
5: MMRM with baseline score using 4 weekly average AM and PM scores in the 28 days prior to treatment start	-0.90 (-1.45, -0.35)
6: MMRM of observed scratching at Month 6	-0.88 (-1.44, -0.33)
Supplementary analyses	
Per protocol analysis	-0.98 (-1.56, -0.40)

*For the tipping point analysis of change from baseline in scratching severity score to Weeks 21-24 based on the MMRM with MI, data from only 2 patients, 1 in each treatment group, required imputation due to missing scratching severity scores at Weeks 21-24. For this analysis, the imputed change from baseline for the placebo patient was decreased by 0.5-point increments to -4 points and for the odevixibat patient was increased by 0.5-point increments to +4 points at Weeks 21-24 and missing data at other visits were imputed assuming MAR. The tipping points to non-significant results only occurred with 3 shift combinations (-3.5, +4), (-4, 3.5), and (-4, 4) (Table 14.2.1.2.2). These

scenarios are implausible as patients in the odevixibat group could not enter the study with a baseline score of 0.5.

As no plausible tipping point was identified, an additional worst-case scenario was conducted where missing scores at Month 6 were imputed as 0 for placebo and 4 for odevixibat. Even in this worst-case scenario, the results for the difference in change in scratching score to Weeks 21-24 between the groups was statistically significant in favour of odevixibat (one-sided p = 0.0092).

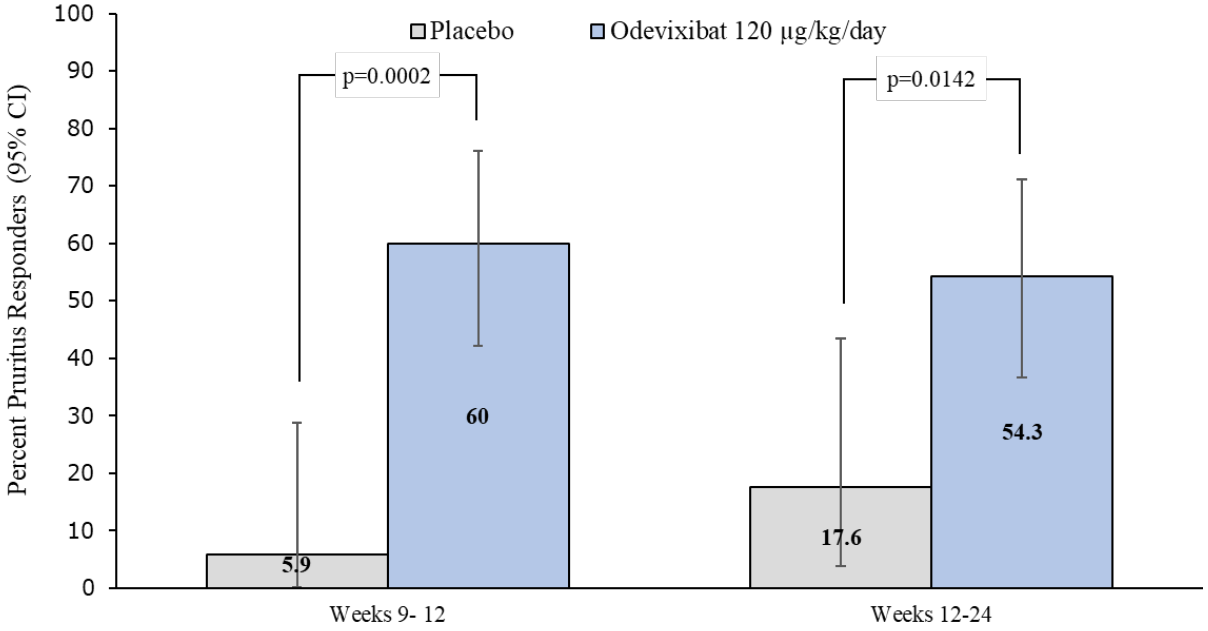
Results of the supplementary analysis conducted in the PPS also were consistent, showing a LS mean difference (95% CI) (odevixibat-placebo) of -0.98 (-1.56, -0.40).

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 5). 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.

Figure 5: 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)



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.

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.

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 13).

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

Table 13: 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)

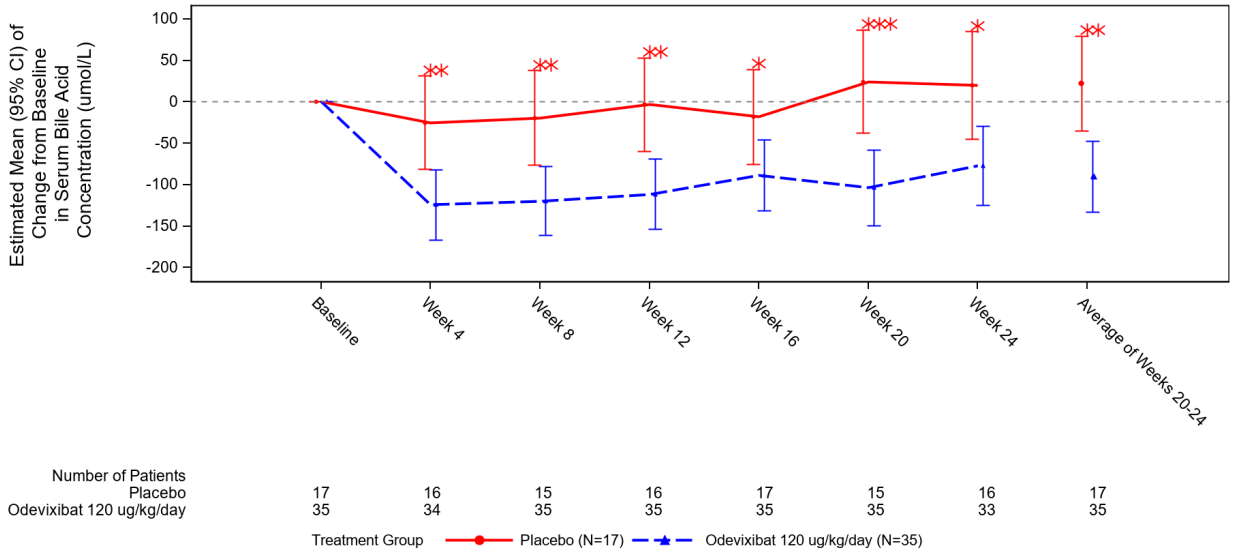
Visit Statistic	Serum Bile Acids (µmol/L)	
	Placebo N=17	Odevixibat N=35
95% CI	(-34.75, 79.52)	(-133.14, -47.56)
LS mean difference (SE) (odevixibat-placebo)[a]	-112.74 (32.864)	
95% CI	(-178.78, -46.69)	
One-sided p-value	0.0006	

Source: CSR A4250-012 Table 14.2.2.1.1 and Table 14.2.2.1.1a

Following initiation of treatment with odevixibat, an early improvement was observed in serum bile acid levels (

Figure 6). 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.

Figure 6: Estimated Mean (±95% CI) Change from Baseline in Serum Bile Acid Concentration (µmol/L) by Visit Through Week 24 (Full Analysis Set; Study A4250-012)



Source: CSR A4250-012 Figure 14.2.2.1.1.

Sensitivity and Supplementary Analyses

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

Results of the supplementary analyses conducted in the PPS and the rank transformed ANCOVA also were consistent with the results in the FAS.

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.

Table 14: Descriptive Statistics for Actual Values and Change in Itching Severity Score (AM and PM Scores Combined) from Baseline to Month 6 (Weeks 21-24) Based on the PRO (FAS)

VISIT STATISTIC	PLACEBO N=5	ODEVIXIBAT N=11
Baseline		
n	5	11
Mean (SD)	2.14 (0.309)	2.66 (0.553)
Median	2.07	2.52
Minimum, maximum	1.7, 2.5	1.9, 3.8
Average of Weeks 21-24		
n	5	11
Mean (SD)	1.36 (0.594)	1.11 (0.774)
Median	1.02	1.30
Minimum, maximum	0.8, 2.0	0.0, 2.1
Change from Baseline to Month 6 (Weeks 21- 24)		
n	5	10
Mean (SD)	-0.78 (0.318)	-1.63 (0.975)
Median	-0.96	-1.67
Minimum, maximum	-1.1, -0.4	-3.2, -0.1

PRO: patient-reported outcomes; SD: standard deviation.

Source: Table 14.2.3.1.

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.

Evaluations of the relationship between caregiver- and patient-reported changes in monthly scratching scores (ObsRO) and itching scores (PRO) indicated consistent results across these outcome assessments with strong correlations between the 2 scores for both night-time (r = 0.87) and daytime (r = 0.87) monthly pruritus scores.

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 15).

Table 15: 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.

Sleep Parameters Based on the PRO

At Weeks 21-24, larger mean (SD) reductions from baseline were observed for odevixibat-treated patients compared to patients who received placebo for percent of days with difficulty falling asleep (-1.29 [1.218] vs -0.83 [0.539]) difficulty staying asleep (-1.33 [1.185] vs -0.77 [0.494]), and for tiredness in the morning (-1.06 [1.364] vs -0.50 [0.619]) and in the evening (-1.09 [1.225] vs -0.33 [0.853]). Results for change from baseline to Weeks 21-24 in percent of nights waking up were similar in the 2 groups (-29.54 [38.782] and -30.24 [38.203] in the odevixibat and placebo groups, respectively).

Global Impression of Symptoms

Results for changes in global symptom relief based on the GIC as completed by caregivers (CaGIC) indicated improvements during treatment with odevixibat for scratching and sleep compared to placebo, consistent with the reported changes based on the ObsRO.

At baseline, caregivers reported that a high proportion of patients had severe or very severe scratching (79.6%) and sleep disturbance (61.2%).

By Week 4, the proportions of patients reported to have improvements in scratching and sleep based on the CaGIC were higher for patients who received odevixibat (85.7% and 74.3%, respectively) compared to patients who received placebo (37.5% and 12.5%, respectively). By Week 24, the proportions of patients reported to have improvements in scratching and sleep also were higher for the odevixibat group (87.5% and 78.1%, respectively) compared to placebo (35.3% and 29.4%, respectively).

The clinicians also indicated that a higher proportion of patients who received odevixibat had improved by Week 24 with regard to pruritus (80.0%) and sleep (74.3%) compared to patients who received placebo (41.2% and 35.3%, respectively).

For the patient-reported information (PGIC), data at Week 24 were available for 10 and 5 patients in the odevixibat and placebo groups, respectively. In this analysis, results for changes to Week 24 for sleep were similar to caregiver reports with 70.0% of patients in the odevixibat group reporting improvement compared to 40.0% of patients receiving placebo. However, for itching, the proportions of patients indicating improvement at Week 24 was high for both treatment groups (80.0%).

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 16: 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.

	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%)	

Quality of Life Assessment: Paediatric Quality of Life Inventory

Caregiver-reported total scores on the PedsQL increased from baseline to Week 24 for patients ≥ 2 years of age in both the odevixibat and placebo groups indicating improvement in QoL independent of treatment. Based on the MMRM, the LS mean (SE) changes to Week 24 were 13.50 (2.541) and 10.72 (3.957) for the odevixibat and placebo groups, respectively with an LS mean difference (95% CI) between groups of 2.78 (-6.31, 11.87).

Improvement between baseline and Week 24 also was observed in the QoL of the family in both treatment groups. Based on the MMRM, the LS mean (SE) changes in the total score were 14.04 (3.342) and 8.52 (4.850) in the odevixibat and placebo groups, respectively with an LS mean difference (95% CI) between groups of 5.52 (-5.81, 16.86).

Patient and Caregiver Impression of Treatment Effect at Week 24 Based on the Exit Survey

A higher proportion of caregivers of patients who received odevixibat reported meaningful change in the patient since the start of treatment (78.1%) compared to caregivers of patients who received placebo (26.7%).

Exploratory Efficacy Analysis: Changes from Baseline Over Time in Growth Parameters

Both treatment groups entered the study with z-scores well below 0, with patients in the odevixibat group having greater growth deficits for both mean height and weight z-scores (-1.80 and -1.83,

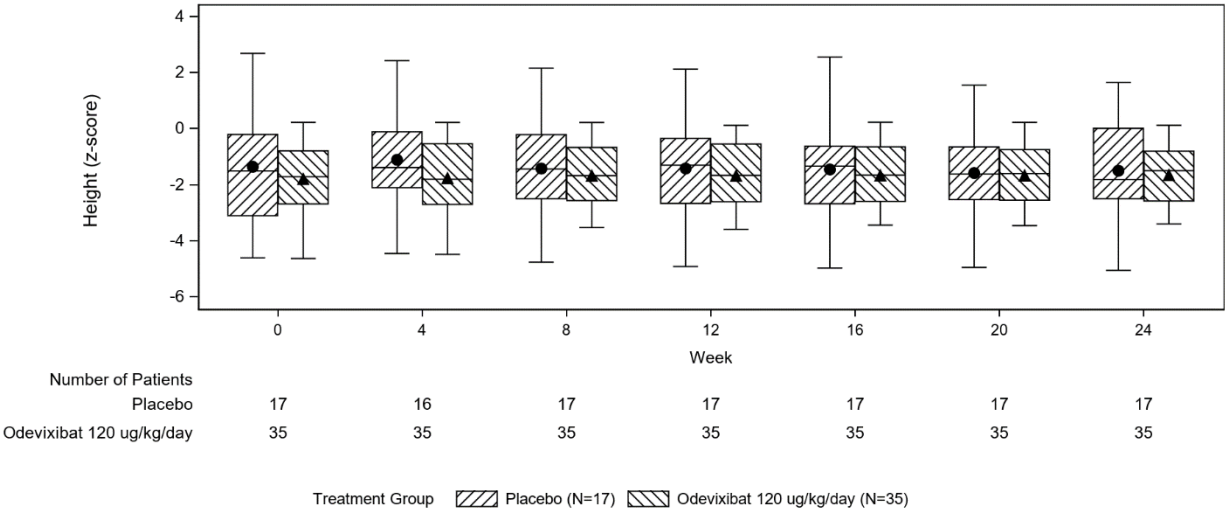
respectively) compared to the placebo group (-1.36 and -1.50, respectively). There was also an imbalance across age groups at baseline, with a higher proportion of patients in the placebo group who were < 2 years of age (29.4%) compared to the odevixibat group (8.6%). This is relevant as patients in this age group tend to exhibit greater growth velocity during this early stage of development. Based on the growth curves for these younger patients, small changes in height or weight can lead to relatively large changes in z-scores.

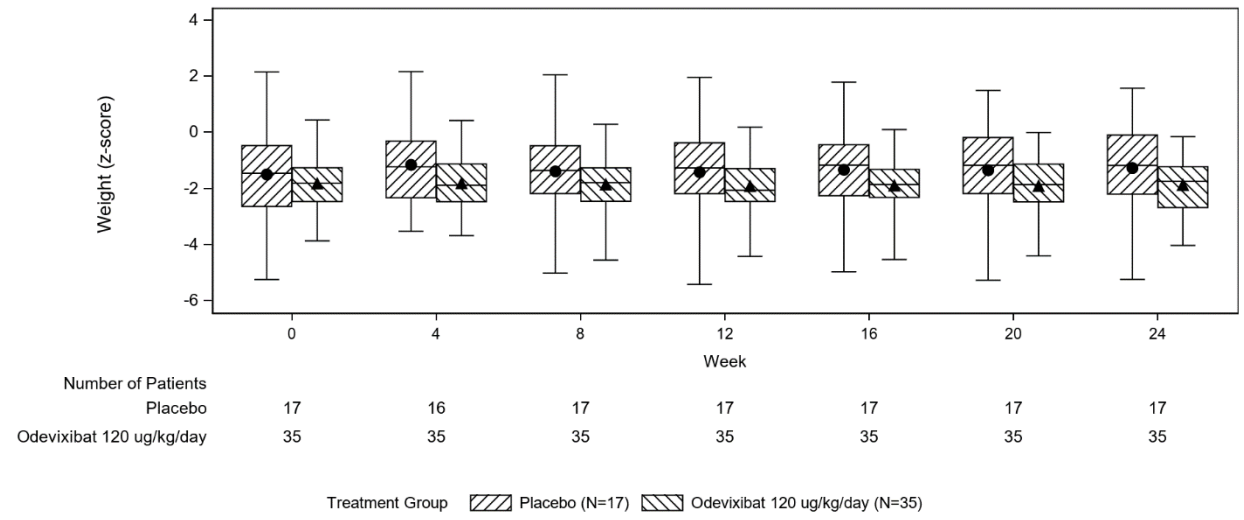
A review of the box and whisker plots of height and weight z-scores (Figure 7) shows the variability in the data over time for these parameters in both treatment groups; however, the 25th and 75th percentiles for the 2 groups are largely overlapping, as are the maximum and minimum values within 1.5 × the interquartile range at each visit.

After 24-weeks of treatment, small mean changes were noted in height and weight z-scores in both treatment groups. LS mean (SE) changes from baseline to Week 24 in height z-scores were 0.12 (0.081) in the odevixibat group and -0.15 (0.112) in the placebo group. For weight z-scores, LS mean (SE) changes from baseline to Week 24 were small in the odevixibat group indicating little change from baseline over 24 weeks (-0.05 [0.073]); in the placebo group, a small increase was noted (0.23 [0.103]). Results for BMI z-score were consistent with the changes in height and weight.

Review of actual changes in height/length (cm) and weight (kg) indicated that patients in both the odevixibat and placebo groups grew with mean (SD) changes of 3.04 (1.789) and 3.03 (2.091) cm, respectively, and gained weight with mean changes to Week 24 of 0.86 (0.782) and 1.31 kg (0.739), respectively.

Figure 7: Box and Whisker Plot of Height and Weight Z-scores (Full Analysis Set, Study A4250-012)





Source: Figure 14.2.11.2.

Endpoints: markers of liver function

Note: Markers of liver function were not presented by the MAH 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.

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 17: 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)

Summary of main study(ies)

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 1. Summary of Efficacy for trial A4250-012

Title: A4250-012		
Study identifier	EudraCT: 2020-004011-28	
Design	Double blind, randomised, placebo controlled phase 3 study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable 72 weeks, in study A4250-015
Hypothesis	Superiority to placebo	
Treatments groups	Control group	Placebo, 24 weeks, n=17
	Active treatment	Odevixibat 120 ug/kg/day, 24 weeks, n=35

Endpoints and definitions	Primary endpoint	Pruritus	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
	Key Secondary endpoint	sBA	Change in serum bile acid levels from baseline through Week 24
	Secondary endpoint	Pruritus responder analysis	Percentage of patients achieving a clinically meaningful decrease in pruritus (pruritus responders) of >1.5 points as measured by the Albireo ObsRO/PRO instruments
Database lock	09 SEP 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT		
Descriptive statistics and estimate variability	Treatment group	Placebo	Odevixibat
	Number of subject	16	34
	Pruritus Mean	-0.76	-1.66
	SD	0.820	0.966
	sBA Mean	24.6	-88.4
	SD	131.63	120.27
	Pruritus responder n/N (%)	3/17 (18)	19/35 (54)
Effect estimate per comparison	Primary endpoint, pruritus	Comparison groups	Odevixibat versus placebo
		LS mean difference	-0.88
		95% CI	-1.44, -0.33
		P-value	0.0012

	Key Secondary, sBA	Comparison groups	Odevixibat versus placebo
		LS mean difference	-112.74
		95% CI	-178.78, -46.69
		P-value	0.0006

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 09SEP2022, 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.

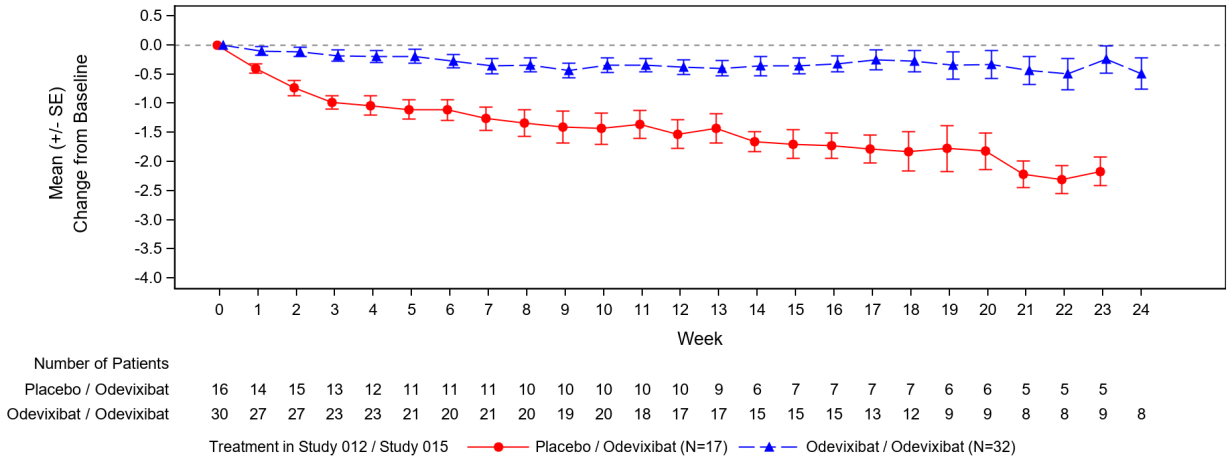
Changes from Baseline in Scratching Severity Score Based on the ObsRO

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 6). 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 8: Mean (SE) Change from Study A4250-015 Baseline in Weekly Scratching Severity Score (AM and PM Scores Combined) – Albireo ObsRO Instrument (FAS)



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

Changes from Baseline in Patient-Reported Itching Severity Based on the PRO

A total of 14 patients ≥ 8 years of age had sufficient data available for assessment of itching score at baseline of Study A4250-015. The mean (SD) baseline itching score was 0.98 (0.835) for patients who received odevixibat in Study A4250-012 and 1.36 (0.571) for patients who received placebo. Data were limited for the PRO at Weeks 9-12 and Weeks 21-24. The mean (SD) change from baseline in itching severity score to Weeks 9-12 was -0.27 (0.386) for the 5 patients who had received odevixibat and was -0.24 (0.249) for the 3 patients who had received placebo. For the 2 patients who had received odevixibat, mean (SD) change from baseline in itching severity score to Weeks 21-24 was -0.40 (0.700).

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.

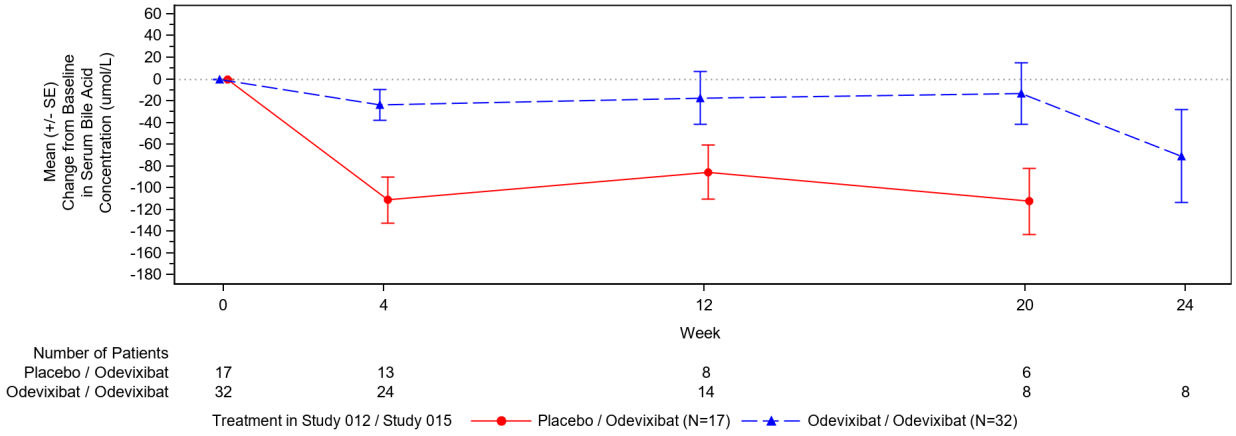
Changes from Baseline Over Time in Serum Bile Acid Assessments

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 9).

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 9: 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.

2.4.3. Discussion on clinical efficacy

Justification of the dose

Dose finding study 003 was included in the PFIC dossier and was discussed at the initial MAA. The study also enrolled patients with ALGS. In the described study 003, doses were tested from 30 to 200 mg/kg/day. Lowering of serum bile acids was observed across this dose range in PFIC patients. For each dose level, 4 patients were planned to be included in an open-label fashion, without control, but only 6 ALGS patients participated. Meaningful changes from baseline in serum bile acids were observed in 5/6 patients on doses ranging from 10-200 ug/kg/day. In the phase 3 study for PFIC, 2 doses were tested: 40 and 120 ug/kg/day. In the label, for PFIC 40 ug/kg/day has been approved as a starting dose since no improved efficacy was observed with 120 ug/kg/day. As the PFIC trial was not concluded at the initiation of the ALGS trial, the data from the PFIC trial could not be used to inform on the dose for ALGS patients. Hence, the dose selection was mainly based on preclinical studies, as the proposed dose of 120 ug/kg/day resembles the ED90 dose.

However, 120 mg/kg/day is the maximum recommended dose for PFIC in the approved label for odevixibat and thus the proposed dose for ALGS does not exceed the maximum dose currently included in the label which is considered acceptable.

In the study, a dose decrease to 40 ug/kg/day was possible per protocol to manage gastrointestinal AE's. This option is also included in the SmPC, which is considered appropriate.

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 studies 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 PFIC. A 40 ug/kg/day dose is included in the label for the treatment of PFIC, with the possibility to escalate up to 120 ug/kg/day in case of insufficient response. In the pivotal ALGS study, all patients were treated with 120 ug/kg/day.

Medicines 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 MAH for use in PFIC in earlier PFIC trials and is also considered acceptable to measure pruritis in ALGS patients. The results of the ObsRO are supported by the patient-reported instrument (PRO).

Based on a blinded interim analysis, the MAH aimed to establish a threshold for a clinically meaningful change in ALGS patients. To use the interim analysis from the same study to estimate a clinically meaningful change is not considered optimal, but due to the rarity of the disease, it is agreed to use interim data in a blinded way. 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. Drop-outs 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 modelled 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 were prohibited (but it could still have taken place) and argues that 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 is included in the analyses. The CHMP did not agree with the decision that it will not be considered an intercurrent event because it is difficult to account for, but view it as a potentially relevant intercurrent event that (implicitly) will be handled with a treatment policy strategy, meaning outcomes are included regardless of the use of anti-pruritic medication.

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 (see results), and the planned sensitivity and supportive analysis, this is 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 were hierarchically tested; the results of all other secondary endpoints were not included in the testing strategy and were considered supportive and only descriptive analysis was used.

The planned subgroup analyses are 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 can be collected with this study. Final results are expected in 2024 as described in the RMP (category 3 study).

As this is an open-label study, the results are 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. In Italy, patients below 4 kg body weight were excluded. Although ALGS diagnosis is enhanced with genetics diagnosis, pruritus becomes apparent around the age of 6 months. Therefore, it is not likely that patients below 4 kg would have been included in the study population. The Netherlands removed the allowance for dose modification to 40 µg/kg unless related to clinically significant diarrhoea. This amendment has not impacted the results as dose reductions for other causes were rare.

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 AE's 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, with the exception of ALT which was slightly higher in the odevixibat group. Contradictory, 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 points 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 MAH has provided argumentation that a 1 point reduction is likely to be perceived the same across the scale, independent of baseline value.

In the responses to the CHMP questions, to assess the impact of the choice of the responder definition, the MAH 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 ≥ 2.0-point 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 ≥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. In the responses to the CHMP questions, the MAH 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. In contrast with the results observed in the PFIC studies, 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. Interestingly, in the initial MAA, positive effects were observed for ALT, GGT and total bilirubin upon odevixibat treatment in patients with PFIC, indicative of a positive effect on hepatic pathology. 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. In the absence of improvements in liver function, the MAH was requested to provide adequate substantiation on their indication claim that the cholestasis is improved but the applicant adjusted the indication to “treatment of cholestatic pruritus”. Therefore this issues was not further pursued.

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.

Overall, the data from the long-term extension study are in agreement with and supportive to the pivotal study.

2.4.4. 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. Therefore, it is considered that the indication "treatment of cholestasis and pruritus" is not sufficiently supported by the provided data. In response to this objection, the MAH has however dropped their claim on the treatment of cholestasis and narrowed the claimed indication to "treatment of cholestatic pruritus" which is accepted.

In addition, no patients were included in the studies below 6 months of age and thus, no efficacy data is available in this population (see also the discussion on pharmacokinetics). In the absence of PK data in this age group the applicant used population PK modelling to extrapolate the pharmacokinetics.

Altogether it was assumed for the modelling that the bioavailability of odevixibat is very low in patients < 6 month and that the PK of the absorbed fraction is mainly affected by body weight and hepatic function. Although these assumptions were acknowledged by the CHMP it was considered that extrapolation should be done with caution to patients < 6 months and due to the uncertainties of missing data in these youngest patients the CHMP requested further substantiation. However, as the Applicant amended the claimed indication to patients from 6 months and older, this issue was not further pursued.

2.5. Clinical safety

Introduction

The known safety profile of odevixibat is based on studies in PFIC patients and is mainly characterised by Grade 1 or 2 gastrointestinal disturbances, primarily reports of diarrhoea.

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.

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 18).

Table 18: Duration of Study Treatment (Safety Analysis Set)

	Study A4250-012 (By Treatment)		Studies A4250-012/ A4250-015 pooled
Exposure Parameter	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)

Exposure Parameter	Study A4250-012 (By Treatment)		Studies A4250-012/ A4250-015 pooled
	Placebo (N=17)	Odevixibat (N=35)	Odevixibat[a] (N=52)
> 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.

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 19).

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 21.

Table 19: Overall Summary of Treatment-emergent Adverse Events (Safety Analysis Set, Integrated Data)

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	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
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 20.

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%).

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 20: 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)
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)

MedDRA SOC Preferred Term	Study A4250-012 (By Treatment) Placebo (N=17) n (%)	 Odevixibat (N=35) n (%)	Studies A4250-012/ A4250-015 pooled Odevixibat[a] (N=52) n (%)
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 other infections occurred in 1 or 2 patients. Most infections among patients in the Pooled Phase 3 group were Grade 1 or 2 in severity. Three (5.8%) patients experienced a severe infection, including otitis media, rhinovirus infection, and tonsillitis (each 1 patient; 1.9%). All infections were assessed by the Investigator as unrelated to study drug.

In 3 (5.8%) patients in the Pooled Phase 3 group, an infection was reported as an SAE during treatment with odevixibat (see section on the SAE's).

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.

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.

Drug-related Adverse Events

Drug-related TEAEs reported in > 1 patient in the Pooled Phase 3 group are presented in Table 21.

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 21: 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)

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 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).

Source: ALGS ISS Table 14.3.1.9.

Adverse Events of Grade 3 Severity

Treatment-emergent AEs of Grade 3 severity were presented; no Grade 4 or Grade 5 events were reported in either Study A4250-012 or Study A4250-015.

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.

Treatment-emergent Adverse Events of Interest

Diarrhoea Events, including Clinically Significant Diarrhoea

Based on review of TEAEs reported in the Gastrointestinal disorders SOC, events of diarrhoea were the most common TEAEs in patients treated with odevixibat.

In the Pooled Phase 3 group, the incidence of diarrhoea was 28.8% (15 patients), with at least 1 case of diarrhoea being considered by the Investigator to be study drug-related for 6 (11.5%) patients. For 14 of these 15 patients, diarrhoea events were Grade 1 or 2 in severity and non-serious. For 1 patient who received odevixibat in Study A4250-012, diarrhoea was Grade 3 in severity and was reported as an SAE in Study A4250-015. This event, which occurred concurrently with gastroenteritis due to rotavirus infection and led to the interruption of study treatment, was considered by the Investigator to be unrelated to study treatment. One other patient who had received placebo in Study A4250-012 had study treatment interrupted due to Grade 1 diarrhoea during treatment with odevixibat in the extension study.

Most patients in the Pooled Phase 3 group who experienced diarrhoea had only 1 or 2 episodes of diarrhoea of short duration.

Table 22: Overall Summary of Treatment-emergent Diarrhoea Adverse Events (Safety Analysis Set, Integrated Data)

	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 (%)**
Any Diarrhoea TEAE	1 (5.9)	10 (28.6)	15 (28.8)
Drug-Related Diarrhoea TEAE	1 (5.9)	4 (11.4)	6 (11.5)
Severe Diarrhoea TEAE	0	0	1 (1.9)
Serious Diarrhoea TEAE	0	0	1 (1.9)
Interruption of study drug due to Diarrhoea TEAE	0	0	2 (3.8)
Discontinued due to Diarrhoea TEAE	0	0	0

[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015. Note: diarrhoea TEAEs include preferred terms of diarrhoea and diarrhoea haemorrhagic.

Source: ALGS ISS Table 14.3.1.3, Table 14.3.1.5, Table 14.3.1.6, Table 14.3.1.8, Table 14.3.1.9, and Table 14.3.1.12.

A review of the EAIR for diarrhoea did not indicate an increase in incidence rate with longer-term exposure to odevixibat, with an incidence of 0.63 PPY across all odevixibat treatment in the Pooled Phase 3 group and 0.76 for the odevixibat group during 24 weeks of treatment in Study 4250-012; this is likely related to the patients who transitioned from placebo to odevixibat.

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.

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 23). 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 23: 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)

AE CATEGORY:	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17) N (%)	ODEVIXIBAT (N=35) N (%)	ODEVIXIBAT[A] (N=52) N (%)
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.

A shift analysis of the highest and lowest post-baseline vitamin A, D, and E levels and INR relative to the normal range is presented in Table 24.

Most (37 of 48 patients with data available) patients had normal INR values at baseline, with 9 having high values. Shifts to both high and low INR levels were observed. Shifts from normal or high INR at baseline to low on study were observed for 3 (6.5%) of 46 patients. Of the 39 patients with low or normal INR values at baseline, 13 (33.3%) experienced a shift to high on study. Four of the 13 patients who shifted to high INR had values in the protocol recommended range of ≤ 1.2 but were flagged for shifts to high INR due to the laboratory reference range of 0.9-1.1. Of the 13 that shifted to high INR, 3 were on the protocol-recommended supplementation strategy.

Table 24: Shift Analysis of Vitamin Levels and INR to the Lowest or Highest Post-Baseline Value for the Pooled Phase 3 Groups (Safety Analysis Set, Integrated Data)

SHIFT FOR:	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17) N/N (%)	ODEVIXIBAT (N=35) N/N (%)	ODEVIXIBAT[A] (N=52) N/N (%)
Vitamin A			
Normal or Low to High	2/7 (28.6)	4/14 (28.6)	5/17 (29.4)
Normal or High to Low	0	0	1/44 (2.3)
Vitamin D			
Normal or Low to High	0	1/34 (2.9)	2/45 (4.4)
Normal or High to Low	0	8/16 (50.0)	11/27 (40.7)
Vitamin E			
Normal or Low to High	2/5 (40.0)	4/16 (25.0)	6/18 (33.3)

SHIFT FOR:	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17) N/N (%)	ODEVIXIBAT (N=35) N/N (%)	ODEVIXIBAT[A] (N=52) N/N (%)
Normal or High to Low	0	4/29 (13.8)	5/38 (13.2)
INR			
Normal or Low to High	3/14 (21.4)	12/30 (40.0)	13/39 (33.3)
Normal or High to Low	5/16 (31.3)	2/34 (5.9)	3/46 (6.5)

[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015. Note: Percentages were calculated based on the number of patients with non-missing values at both the baseline and post-baseline visit. The categories (low/normal/high) were defined based on the normal reference ranges of laboratory tests. Source: ALGS ISS Table 14.3.5.6.3.1 and Table 14.3.5.6.3.2.

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 25.

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 one patient (Study A4250-012) and forearm fracture experienced by another patient (Study A4250-015). The events of haematemesis and INR increased were assessed as treatment-related.

Table 25: 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)

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 (%)
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.

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 26. Overall, 6 (11.5%) of the 52 patients in the Pooled Phase 3 group experienced liver-related TEAEs across the 4 SMQs. All but 1 liver-related event were Grade 1 or 2 in severity and non-serious. As detailed above, 1 patient had Grade 3 increased INR concurrent with haematemesis that was considered by the Investigator to be study drug related.

In Study A4250-012, liver-related events were reported in 4 (11.4%) of 35 patients in the odevixibat group and in 2 (11.8%) of 17 patients in the placebo group. Overall, the profile of these hepatic events in Study A4250-012 was consistent with that in the Pooled Phase 3 group.

Table 26: Treatment-emergent Liver-Related Adverse Events (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 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)

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 (%)
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.

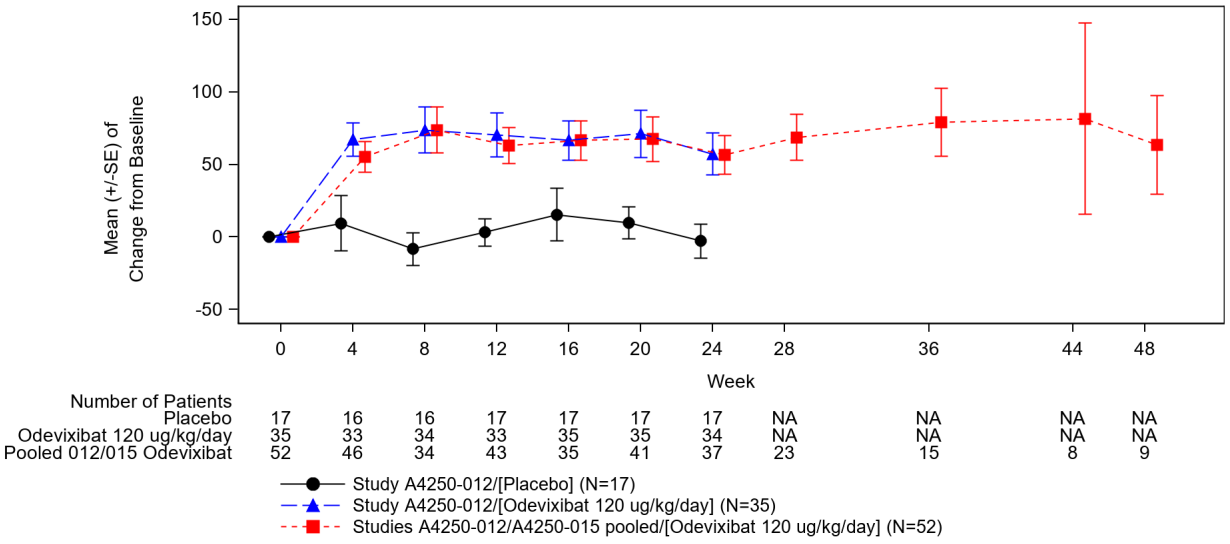
As of the data cut-off of 09SEP2022, 4 cases had undergone review and adjudication by the HSAC, an independent group of expert hepatologists, for suspected DILI (HSAC Adjudication Forms), including 2 patients during Study A4250-012, both received odevixibat, and 2 patients in Study A4250-015 both of 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

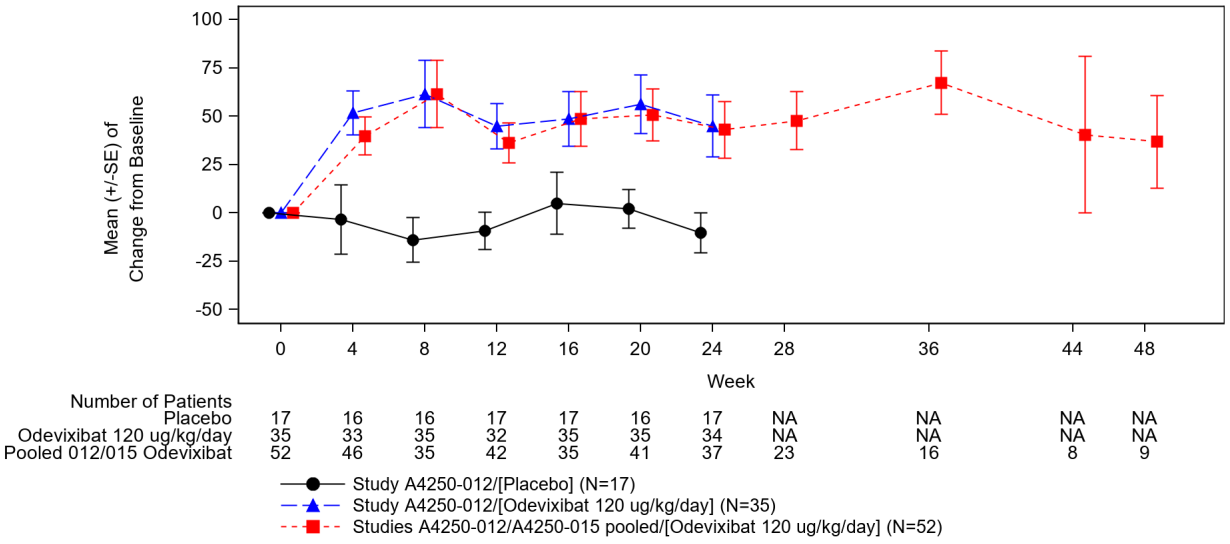
A review of Figure 3 shows an early increase in mean transaminase levels during treatment with odevixibat to Week 4 with a relative plateau thereafter. For total bilirubin, mean changes from baseline varied around zero with similar results through Week 24 for the odevixibat and placebo groups; thereafter the plateau continues with the exception of Week 36 where there is an outlier value (see description above).

Figure 10: Mean (±SE) Levels of Hepatic Biochemical Parameters Overtime on Treatment (Safety Analysis Set, Integrated Data)

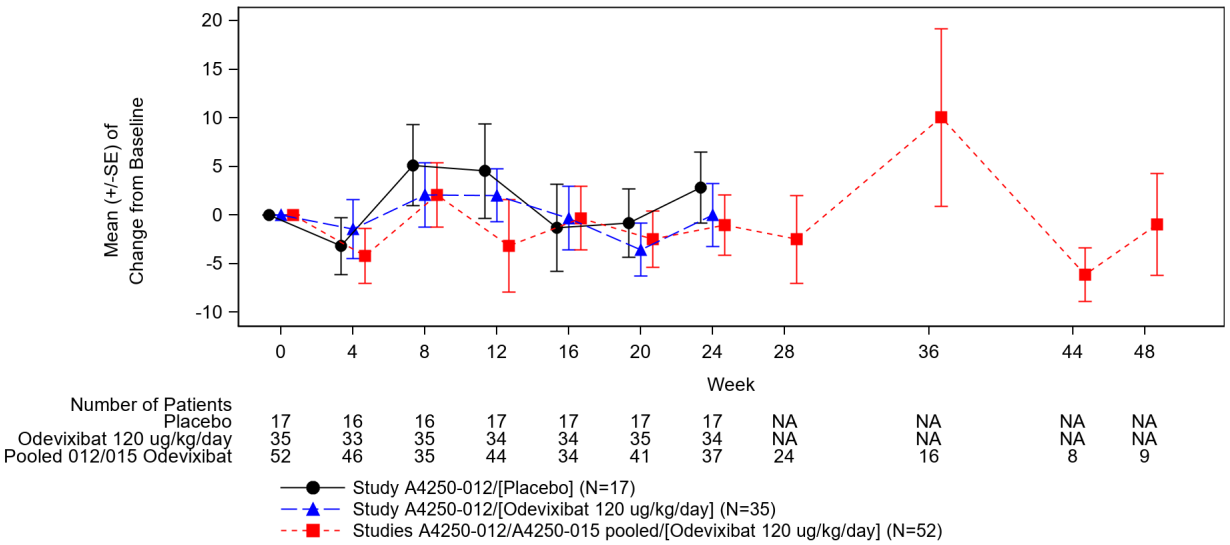
Alanine Aminotransferase



Aspartate Aminotransferase



Total Bilirubin



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

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.

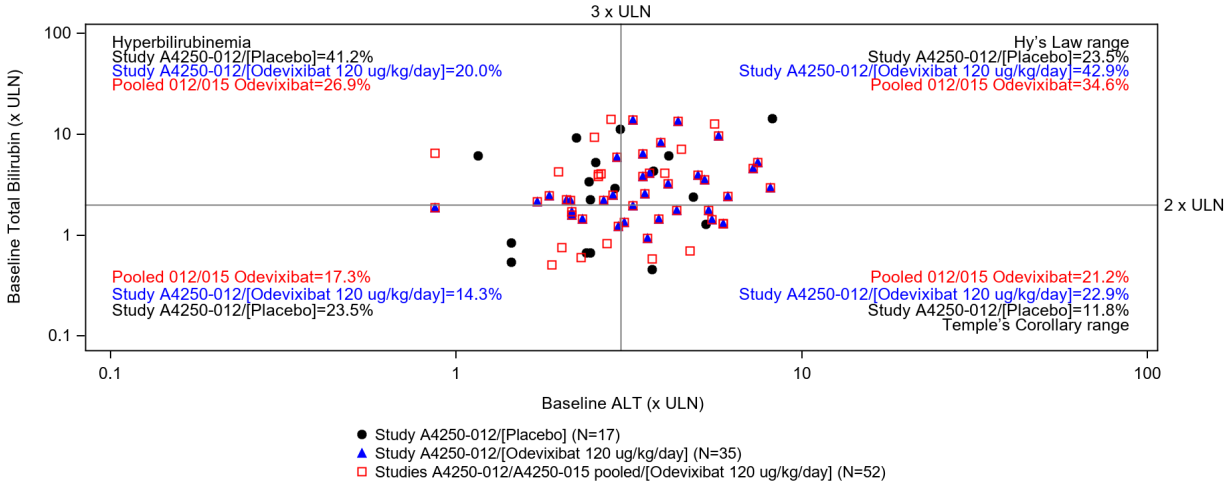
In the standard application of the eDISH plot [Merz 2014], study participants with on-treatment peak ALT and total bilirubin in the upper right quadrant ("Hy's Law Quadrant") or the lower right quadrant ("Temple's Corollary Quadrant") suggest a potential for severe DILI. However, in patient populations with underlying liver disease such as ALGS where many study participants have baseline ALT and total bilirubin that already places them in these quadrants, the standard application is of limited utility. In these populations, it has been proposed to plot peak ALT and total bilirubin levels as multiples of each individual patient's baseline values commonly called the modified eDISH plot [Parks 2013]. Therefore, in addition to an analysis of peak ALT vs peak concurrent total bilirubin as multiples of ULN (on-treatment eDISH), analyses of baseline ALT and total bilirubin as multiples of ULN (baseline eDISH), and peak ALT vs peak concurrent total bilirubin as multiples of individual patient baseline values (modified eDISH) were performed.

Figure 4 presents eDISH plots of baseline ALT vs total bilirubin and post-baseline peak ALT vs peak concurrent total bilirubin reported for the odevixibat and placebo groups in Study A4250-012 and for the Pooled Phase 3 group; for the latter group, baseline is prior to the first dose of odevixibat. As shown in the figure, at baseline in Study A4250-012, the proportion of patients in the Hy's law quadrant of the plot was higher in the odevixibat group than in the placebo group (42.9% vs 23.5%, respectively). The proportion of patients in the Temple's corollary quadrant also was higher in the odevixibat group than in the placebo group (22.9% vs 11.8%). On treatment, the baseline imbalance of patients in Hy's law quadrant persisted, with both groups increasing by approximately 20% (to 62.9% in the odevixibat group and 47.1% in the placebo group). In contrast, the imbalance of patients in Temple's corollary quadrant at baseline appeared to resolve on treatment, with odevixibat and placebo groups having similar proportions (31.4% and 29.4%, respectively) in this quadrant due to a larger increase in the placebo group.

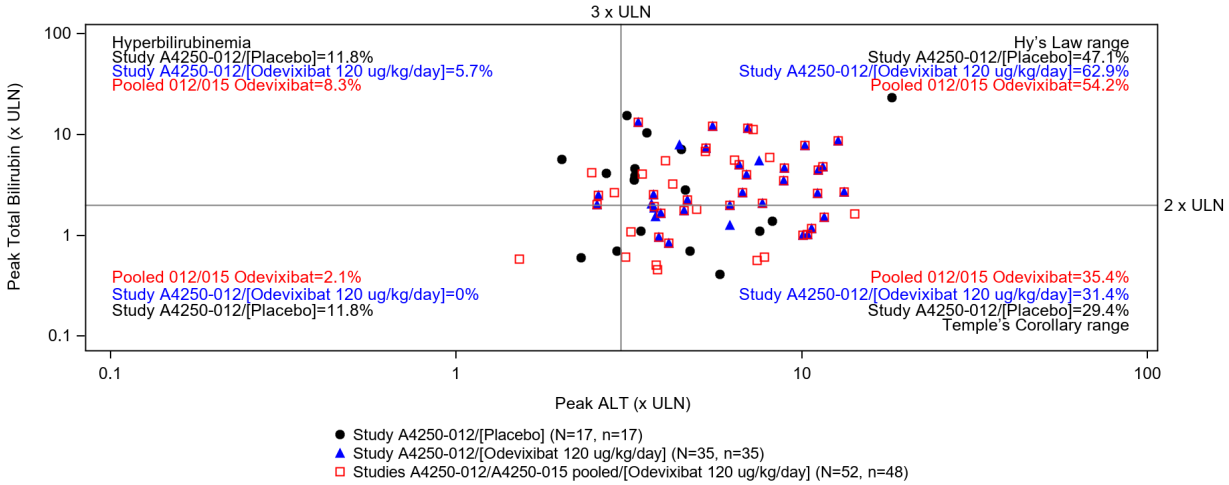
In the Pooled Phase 3 group, results were similar, with 34.6% of patients in the Hy's law quadrant of the plot prior to the first dose of odevixibat increased by ~20% to 54.2% post-baseline. At the time of initiation of odevixibat, the proportion of patients in the Temple's corollary quadrant was 21.2%; post-baseline, the proportion was 35.4%.

Figure 11: eDISH Plots of ALT and Total Bilirubin Relative to Upper Limit of Normal, Baseline and Post-Baseline (Full Analysis Set)

Baseline



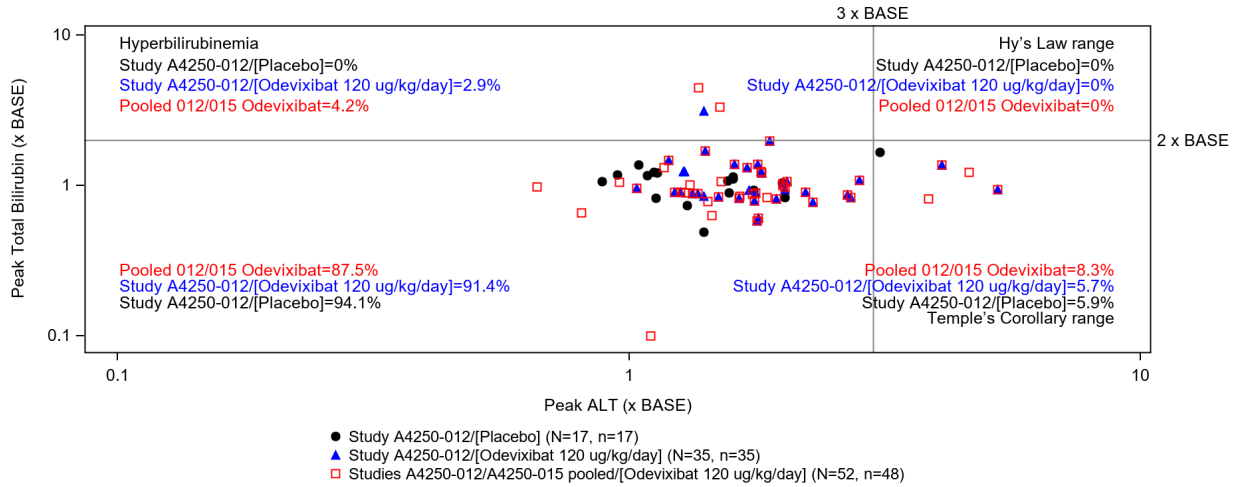
Post-Baseline



Note: baseline plot presents concurrent levels of ALT and total bilirubin; post-baseline plot presents peak ALT on treatment with peak total bilirubin within 30 days of peak ALT; small 'n' representing number of patients with post-baseline results used to calculate proportions post-baseline. Source: ALGS ISS Figure 14.3.4.1 and Figure 14.3.4.2

Figure 12 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 12. Brief narratives for these 4 patients are provided below.

Figure 12: Modified eDISH Plot of Peak ALT vs Concurrent Peak (within 30 days of Peak ALT) Total Bilirubin Relative to Baseline (Full Analysis Set)



Source: ALGS ISS Figure 14.3.4.3

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.

Serious adverse event/deaths/other significant events

In the Pooled Phase 3 group, there were no deaths. Six (11.5%) of 52 patients experienced a treatment-emergent SAE (Table 30). The incidence of treatment-emergent SAEs in Study A4250-012 was similar in the odevixibat group (5 patients, 14.3%) and in the placebo group (2 patients, 11.8%). One event of fatigue in a patient who had previously received placebo was re-classified as a treatment-emergent SAE after the data cut-off. All treatment-emergent SAEs by preferred term were reported in only 1 patient each amongst patients in the Pooled Phase 3 studies.

For all but 1 patient, treatment-emergent SAEs were assessed as unrelated to study drug. One patient experienced study drug-related SAEs of INR increased and haematemesis during treatment with odevixibat in Study A4250-012.

Table 27: Listing of Patients with Treatment-Emergent Serious Adverse Events (Safety Analysis Set, Integrated Data)

	Age/Sex	Treatment -Emergent SAE (Preferred Term)	Start/ Stop Day	Relationship	Severity	Action with Study Drug
Study A4250-012						
Odevixibat Group						
	9.1 years/Female	Rhinovirus infection	D100-D102	Not related	Grade 3	Drug interrupted
	3.8 years/Male	Pneumonia	D52-D57	Not related	Grade 2	Dose not changed

	Age/Sex	Treatment -Emergent SAE (Preferred Term)	Start/ Stop Day	Relationship	Severity	Action with Study Drug
	11.4 years/Male	Abdominal pain Constipation Abdominal pain	D140-D142 D128-D130 D156-D161	Not related Not related Not related	Grade 3 Grade 3 Grade 3	Dose not changed Dose not changed Dose not changed
	3.2 years/Female	Haematemesis International normalised ratio increased	D102-D103 D102-D103	Related Related	Grade 3 Grade 3	Dose not changed Dose not changed
	3.1 years/Female	Tonsillitis	D87-D89	Not related	Grade 3	Dose not changed
Placebo Group						
	0.7 years/Male	Pyrexia	D136-D138	Not related	Grade 3	Dose not changed
	3.6 years/Female	Subcutaneous abscess Cerumen impaction Otitis media chronic Adenoidal hypertrophy	D38-D39 D38-D39 D126-D128 D126-D128	Not related Not related Not related Not related	Grade 3 Grade 3 Grade 2 Grade 1	Dose not changed Dose not changed Dose not changed Dose not changed
Study A4250-015						
Placebo to Odevixibat						
	11.0 years/Female	Fatigue	D11-ongoing	Unrelated	Grade 1	Dose not changed
	9.7 years/Male	Forearm fracture	D31-ongoing	Unrelated	Grade 3	Dose not changed
Odevixibat to Odevixibat						
	3.1 years/Female	Diarrhoea	D176-D177	Unrelated	Grade 3	Dose interrupted
		Gastroenteritis	D178-D182	Unrelated	Grade 2	Not applicable

ID: identification; INR: international normalised ratio.

Note: For the placebo/odevixibat group and odevixibat/odevixibat group, age and start and stop day of the event are based on the date of the first dose of odevixibat.

* Patient had SAEs in both Study A4250-012 and Study A4250-015

[a] This event was determined to be treatment-emergent after database lock. Since this update occurred after database lock, tabulated safety summaries were not modified:

Source: ALGS ISS Table 14.3.2.1

Laboratory findings

In the Pooled Phase 3 group, no clinically meaningful changes from baseline were observed in haematology parameters during treatment with odevixibat. Mean changes from baseline to Weeks 24, 36, and 48 of treatment for the Pooled Phase 3 group were small, including haemoglobin (0.6, -1.8, and -2.8 g/L, respectively), leukocyte count (-0.749, -1.057, and -0.138× 10^9/L, respectively), and neutrophil count (-0.127, −0.443 and −0.059 × 10^9/L, respectively). Larger mean changes from baseline were seen in the platelet count at Weeks 24 and 36 (-31.6, −61.9× 10^9/L), with a smaller mean change at Week 48 (−9.0× 10^9/L); however, mean platelet counts remained above 150 × 10^9/L. In general, the small mean changes observed for the pooled results were comparable to results from Study A4250-012 and were similar in the odevixibat and placebo groups in that study.

In the Pooled Phase 3 group, generally, no clinically meaningful changes in clinical chemistry parameters were observed during treatment with odevixibat. This was also observed in Study A4250-012, where mean changes from baseline to the last assessment for chemistry parameters were small and similar in odevixibat- and placebo-treated patients.

In the Pooled Phase 3 group, no trends over time were observed on the assessment of urinalysis test results. Similarly, in Study A4250-012, no clinically meaningful differences were noted for changes from baseline to the last assessment for urine pH.

There were no TEAEs related to urinalysis test results reported during the Phase 3 studies.

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. The differences in the number of patients aged < 10 years (n=42) vs ≥ 10 years (n=10) and between patients 2 to < 12 years (n=39) vs ≥12 years (n=6) should be considered when reviewing incidences of TEAEs by SOC and preferred term across age groups.

Review of the most common (incidence ≥ 10%) TEAEs overall by age category showed that pyrexia occurred exclusively in patients aged < 12 years. This is related to a higher incidence of infections reported in this age group, with infections reported in 71.4% of patients < 2 years of age and in 61.5% of patients between 2 and < 12; in patients ≥ 12 years, the incidence of infections was 33.3%. The infections reported are common in the paediatric population. No other apparent trend was seen with regard to the incidence of TEAEs overall or commonly reported TEAEs among odevixibat-treated patients by age category (Table 28).

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).

The incidence of pyrexia was higher in females (28.0%) than in males (14.8%); the incidence of other commonly reported TEAEs was similar in each gender group (Table 28).

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.

In the Pooled Phase 3 group, all but 8 patients were not Hispanic or Latino in ethnicity so, as per above, 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 (CSR A4250-012). None of the 3 odevixibat-treated patients experienced an SAE, a TEAE leading to dose interruption, clinically significant diarrhoea, or liver-related TEAEs (CSR A4250-012 Listing 16.2.7.1). One patient experienced possible sequelae of fat-soluble vitamin deficiency and coagulopathy.

Table 28: Common Treatment-Emergent Adverse Events (≥ 10% of Patients in the Pooled Phase 3 Group) by Age and Sex Category, Phase 3 Pool (Safety Analysis Set, Integrated Data)

System Organ Class/ Preferred Term	Study A4250-012 Placebo (N=17) n (%)	Studies A4250-012 / A4250-015 pooled							
			Age (years)					Sex	
		Odevixibat[a] (N=52) n (%)	< 10 (N=42) n (%)	10 to < 18 (N=10) n (%)	< 2 (N=7) n (%)	2 to < 12 (N=39) n (%)	12 to < 18 (N=6) n (%)	Male (N=27) n (%)	Female (N=25) n (%)
Patients with any TEAEs	12 (70.6)	43 (82.7)	34 (81.0)	9 (90.0)	6 (85.7)	32 (82.1)	5 (83.3)	23 (85.2)	20 (80.0)
Gastrointestinal Disorders	2 (11.8)	20 (38.5)	16 (38.1)	4 (40.0)	2 (28.6)	16 (41.0)	2 (33.3)	9 (33.3)	11 (44.0)
Diarrhoea	1 (5.9)	15 (28.8)	13 (31.0)	2 (20.0)	1 (14.3)	13 (33.3)	1 (16.7)	7 (25.9)	8 (32.0)
Abdominal pain	1 (5.9)	6 (11.5)	4 (9.5)	2 (20.0)	1 (14.3)	4 (10.3)	1 (16.7)	4 (14.8)	2 (8.0)
General Disorders and Administration Site Conditions	5 (29.4)	12 (23.1)	11 (26.2)	1 (10.0)	3 (42.9)	9 (23.1)	0	5 (18.5)	7 (28.0)
Pyrexia	4 (23.5)	11 (21.2)	11 (26.2)	0	3 (42.9)	8 (20.5)	0	4 (14.8)	7 (28.0)
Infections and Infestations	10 (58.8)	31 (59.6)	29 (69.0)	2 (20.0)	5 (71.4)	24 (61.5)	2 (33.3)	16 (59.3)	15 (60.0)
Nasopharyngitis	1 (5.9)	8 (15.4)	7 (16.7)	1 (10.0)	2 (28.6)	5 (12.8)	1 (16.7)	4 (14.8)	4 (16.0)
COVID-19	4 (23.5)	7 (13.5)	6 (14.3)	1 (10.0)	0	6 (15.4)	1 (16.7)	3 (11.1)	4 (16.0)

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 Tables 14.3.1.3, 14.3.1.3.1, 14.3.1.3.2, and 14.3.1.3.4.

Hepatic Function

See Table 32.

Child-Pugh Classification

The Child-Pugh classification system was originally developed for adult patients with cirrhosis and is less commonly used in the description of paediatric patients. Although cirrhosis occurs in patients with ALGS, the Applicant did not assess for the presence of cirrhosis as part of the baseline study procedures; the Child-Pugh scores are based on results of the laboratory test results for serum bilirubin, serum albumin, and INR. Therefore, the degree of liver disease underlying the Child-Pugh scores calculated for the patients in the Phase 3 studies may not reflect the same degree of liver disease in adult patients with cirrhosis having equivalent scores.

At baseline, all odevixibat-treated patients and all but 1 placebo-treated patients (51 of 52 patients; 98.1%) had a Child-Pugh classification of "B", indicating moderate hepatic impairment. One patient in the placebo group had Child-Pugh classification of "C", indicating severe hepatic impairment. The low number of individual TEAEs and SAEs occurring in the patient in the severe (N=1) category with no patients in the mild category precludes meaningful comparisons across Child-Pugh classification at the preferred term level for TEAEs and SAEs.

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 ≥ the median in Study A4250-012 and 24 had values < the median. The overall incidence of TEAEs was 78.6% and 87.5% among patients with baseline serum bile acid levels ≥ and < 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.

Table 29 Common Treatment-Emergent Adverse Events (≥ 10% of Patients in the Pooled Phase 3 Group) by Child-Pugh Classification and Selected Baseline Liver Function Tests (Safety Analysis Set, Integrated Data)

System Organ Class Preferred Term	Study A4250-012 Placebo (N=17) n (%)	Studies A4250-012/ A4250-015 pooled								
			Child-Pugh Classification			Baseline ALT			Baseline Total Bilirubin	
		Odevixibat[a] (N=52) n (%)	Mild (N=0) n (%)	Moderate (N=51) n (%)	Severe (N=1) n (%)	≤ 3 × ULN (N=23) n (%)	> 3 and ≤ 5 × ULN (N=18) n (%)	> 5 × ULN (N=11) n (%)	≤ 2 × ULN (N=20) n (%)	> 2 ULN (N=32) n (%)
Patients with any TEAEs	12 (70.6)	43 (82.7)	-	42 (82.4)	1 (100.0)	20 (87.0)	14 (77.8)	9 (81.8)	16 (80.0)	27 (84.4)
Gastrointestinal Disorders	2 (11.8)	20 (38.5)	-	19 (37.3)	1 (100.0)	9 (39.1)	7 (38.9)	4 (36.4)	10 (50.0)	10 (31.3)
Diarrhoea	1 (5.9)	15 (28.8)	-	14 (27.5)	1 (100.0)	7 (30.4)	4 (22.2)	4 (36.4)	7 (35.0)	8 (25.0)
Abdominal pain	1 (5.9)	6 (11.5)	-	6 (11.8)	0	2 (8.7)	3 (16.7)	1 (9.1)	4 (20.0)	2 (6.3)
General Disorders and Administration Site Conditions	5 (29.4)	12 (23.1)	-	12 (23.5)	0	4 (17.4)	4 (22.2)	4 (36.4)	4 (20.0)	8 (25.0)
Pyrexia	4 (23.5)	11 (21.2)	-	11 (21.6)	0	4 (17.4)	4 (22.2)	3 (27.3)	3 (15.0)	8 (25.0)
Infections and Infestations	10 (58.8)	31 (59.6)	-	31 (60.8)	0	13 (56.5)	11 (61.1)	7 (63.6)	12 (60.0)	19 (59.4)
Nasopharyngitis	1 (5.9)	8 (15.4)	-	8 (15.7)	0	4 (17.4)	3 (16.7)	1 (9.1)	2 (10.0)	6 (18.8)
COVID-19	4 (23.5)	7 (13.5)	-	7 (13.7)	0	2 (8.7)	5 (27.8)	0	4 (20.0)	3 (9.4)

ALT: alanine aminotransferase; TEAE: treatment-emergent adverse event; ULN; upper limit of normal.

Source: ALGS ISS Tables 14.3.1.3, 14.3.1.3.7, 14.3.1.3.8, and 14.3.1.3.9.

Safety related to drug-drug interactions and other interactions

The DDI studies have been assessed in the initial MAA. Information on DDI's is sufficiently included in the SmPC, including the warning for the potential for decreased absorption of oral contraceptives. No further amendments of the SmPC are warranted.

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 nonserious, 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.

Comparison of safety of odevixibat in patients with ALGS and with PFIC

The following sections present a comparison of exposure, baseline and safety results reported in the pivotal Phase 3 study that led to the approval of odevixibat in patients with PFIC, A4250-005, with that from the Phase 3 study in patients with ALGS, A4250-012.

An overview of exposure to study treatment in the 2 randomised, placebo-controlled Phase 3 studies in patients with PFIC and with ALGS is provided in Table 33. In both studies, the median duration of exposure in all study groups was approximately 24 weeks consistent with most patients completing the study.

Table 30: Exposure Parameters (Safety Analysis Set, Studies A4250-005 and A4250-012)

	PFIC Study A4250-005			ALGS Study A4250-012	
Category Statistic	Placebo (N=20)	Odevixibat 40 µg/kg/day (N=23)	Odevixibat 120 µg/kg/day (N=19)	Placebo (N=17)	Odevixibat 120 µg/kg/day (N=35)
Duration of treatment (weeks)					
n	20	23	19	17	35
Mean (SD)	21.6 (4.57)	21.7 (4.95)	21.7 (5.83)	24.26 (0.485)	23.94 (0.726)
Median	23.7	23.9	23.9	24.00	24.00
Min, max	11.7, 29.1	10.7, 25.9	4, 27.6	23.7, 25.1	21.1, 26.0

Source: CSR A4250-005 Table 14.1.7.1; CSR A4250-012 Table 14.1.9.1

In the Phase 3 PFIC and ALGS studies, there was generally an equal representation of males and females across the treatment groups. The median age was also similar across treatment groups and in the 2 studies. Most of the patients in both Study A4250-005 and Study A4250-012 were enrolled in Europe.

Table 34 presents hepatic impairment classification and liver function test results at baseline for the two Phase 3 studies. Patients with ALGS in Study A4250-012 were more likely to have moderate hepatic impairment based on the Child-Pugh classification and to have moderate or severe impairment based on NCI-ODWG compared to patients with PFIC in Study A4250-005. Consistent with this, mean and median levels of ALT were higher for patients with ALGS in Study A4250-012 compared to those with PFIC in Study A4250-005.

Table 31: Baseline Hepatic Function (Safety Analysis Set, Studies A4250-005 and A4250-012)

	PFIC Study A4250-005			ALGS Study A4250-012	
Category Statistic	Placebo (N=20)	Odevixibat 40 µg/kg/day (N=23)	Odevixibat 120 µg/kg/day (N=19)	Placebo (N=17)	Odevixibat 120 µg/kg/day (N=35)
Child-Pugh, n (%)					
A (mild)	12 (60.0)	15 (65.2)	14 (73.7)	0	0
B (moderate)	8 (40.0)	8 (34.8)	5 (26.3)	16 (94.1)	35 (100.0)
C (severe)	0	0	0	1 (5.9)	0

Category Statistic	PFIC Study A4250-005			ALGS Study A4250-012	
	Placebo (N=20)	Odevixibat 40 µg/kg/day (N=23)	Odevixibat 120 µg/kg/day (N=19)	Placebo (N=17)	Odevixibat 120 µg/kg/day (N=35)
NCI ODWG					
No impairment	2 (10.0)	0	1 (5.3)	0	0
Mild	8 (40.0)	8 (34.8)	9 (47.4)	6 (35.3)	7 (20.0)
Moderate	4 (20.0)	11 (47.8)	5 (26.3)	3 (17.6)	15 (42.9)
Severe	6 (30.0)	4 (17.4)	4 (21.1)	8 (47.1)	13 (37.1)
ALT (U/L)					
n	20	23	19	17	35
Mean (SD)	76.9 (56.21)	127.7 (165.81)	89.1 (86.94)	149.1 (84.15)	185.6 (83.20)
Median	55.5	83.0	59.0	114.0	173.0
Min, max	19, 236	21, 798	16, 314	52, 403	39, 365
Total bilirubin (µmol/L)					
n	20	23	19	17	35
Mean (SD)	53.3 (57.99)	52.2 (48.57)	57.0 (78.70)	61.62 (57.022)	51.99 (43.380)
Median	30.7	47.3	26.4	40.0	33.9
Min, max	5, 195.1	5.7, 217.7	2.9, 318.2	7.4, 195.1	12.8, 189.6

ALGS: Alagille syndrome; max: maximum; min: minimum; NCI ODWG: National Cancer Institute Organ Dysfunction Working Group; PFIC: progressive familial intrahepatic cholestasis; SD: standard deviation.

Source: CSR A4250-005 Table 14.1.4; CSR A4250-012 Table 14.1.6.1

An overall summary of TEAE incidence is provided for Studies A4250-005 and A4250-012 by treatment group in Table 35. Most patients in both studies reported at least 1 TEAE during the 24-week treatment period. Patients with ALGS who received odevixibat 120 µg/kg/day had a lower incidence of drug-related TEAEs (22.9% vs 36.8%) and TEAEs leading to treatment interruption (8.6% vs 31.6%) compared to patients with PFIC receiving the 120 µg/kg/day dose. There were no deaths in either study, and the incidence of severe TEAEs and SAEs was similar for patients who received odevixibat 120 µg/kg/day in both studies. The incidence of treatment discontinuation was low in both studies, reported in 1 patient in Study A4250-005 and none of the patients in Study A4250-012.

Table 32: Overall Summary of Treatment-emergent Adverse Events (Safety Analysis Set; Studies A4250-005 and A4250-012)

	PFIC Study A4250-005			ALGS Study A4250-012	
Patients with Any:	Placebo (N=20) n (%)	Odevixibat 40 µg/kg/day (N=23) n (%)	Odevixibat 120 µg/kg/day (N=19) n (%)	Placebo (N=17) n (%)	Odevixibat 120 µg/kg/day (N=35) n (%)
TEAEs	17 (85.0)	19 (82.6)	16 (84.2)	12 (70.6)	26 (74.3)
Drug-Related TEAEs	3 (15.0)	7 (30.4)	7 (36.8)	3 (17.6)	8 (22.9)
Severe TEAEs[a]	2 (10.0)	1 (4.3)	2 (10.5)	2 (11.8)	5 (14.3)
Serious TEAEs	5 (25.0)	0	3 (15.8)	2 (11.8)	5 (14.3)
Drug-Related Serious TEAEs	0	0	0	0	1 (2.9)
TEAEs Leading to Death	0	0	0	0	0
TEAEs Leading to Study Treatment Interruption	1 (5.0)	3 (13.0)	6 (31.6)	0	3 (8.6)
TEAEs Leading to Treatment Discontinuation	0	0	1 (5.3)	0	0
Drug-Related TEAEs Leading to Treatment Discontinuation	0	0	1 (5.3)	0	0

Source: CSR A4250-005 Table 14.3.1.1 and Table 14.3.2.2 and CSR A4250-012 Table 14.3.1.1

A summary of TEAEs reported in ≥ 5% of patients in Study A4250-005 or Study A4250-012 who received odevixibat 120 µg/kg/day is provided in Table 36. In both studies, the most commonly reported types of events were infections and gastrointestinal disorders. In general, the types and incidence of TEAEs were similar across the 2 studies with a few notable exceptions. There were no reports of COVID-19 infection in Study A4250-005 which was completed in July 2020, whereas in Study A4250-012, which completed in September 2022, 9 of the 52 patients reported this infection, including 14.3% and 23.5% of patients who received odevixibat and placebo, respectively. The overall incidence of TEAEs in the Investigations SOC was higher among PFIC patients in Study A4250-005 who received odevixibat (30.4% and 42.1% for patients who received the 40 and 120 µg/kg/day dose) compared to ALGS patients who received odevixibat 120 µg/kg/day in Study A4250-012 (20.0%); the incidences were similar across the placebo groups in the 2 studies (20.0% and 17.6%, respectively). This difference across the studies was related to a higher reported incidence of TEAEs related to hepatic biochemical parameters in the PFIC study, primarily reports of increased ALT and blood bilirubin.

Table 33: Treatment-emergent Adverse Events (≥ 5% of Patients who Received Odevixibat 120 µg/kg/day) by System Organ Class and Preferred Term (Safety Analysis Set, Studies A4250-005 and A4250-012)

	PFIC Study A4250-005			ALGS Study A4250-012	
MedDRA SOC Preferred Term	Placebo (N=20) n (%)	Odevixibat 40 µg/kg/day (N=23) n (%)	Odevixibat 120 µg/kg/day (N=19) n (%)	Placebo (N=17) n (%)	Odevixibat 120 µg/kg/day (N=35) n (%)
Infections and infestations	**12 (60.0)**	**11 (47.8)**	**11 (57.9)**	**10 (58.8)**	**18 (51.4)**
COVID-19	0	0	0	4 (23.5)	5 (14.3)
Upper respiratory tract infection	3 (15.0)	3 (13.0)	5 (26.3)	2 (11.8)	3 (8.6)
Nasopharyngitis	1 (5.0)	1 (4.3)	2 (10.5)	1 (5.9)	2 (5.7)
Otitis media	0	0	2 (10.5)	0	1 (2.9)
Influenza	2 (10.0)	0	1 (5.3)	1 (5.9)	0
Gastroenteritis	0	1 (4.3)	0	0	2 (5.7)
Bronchitis	0	1 (4.3)	0	0	3 (8.6)
Respiratory tract infection	0	0	1 (5.3)	1 (5.9)	3 (8.6)
Conjunctivitis	0	1 (4.3)	0	0	2 (5.7)
Gastrointestinal disorders	**6 (30.0)**	**14 (60.9)**	**8 (42.1)**	**2 (11.8)**	**12 (34.3)**
Diarrhoea	1 (5.0)	9 (39.1)	4 (21.1)	1 (5.9)	10 (28.6)
Vomiting	0	4 (17.4)	3 (15.8)	1 (5.9)	2 (5.7)
Abdominal pain	0	2 (8.7)	1 (5.3)	1 (5.9)	4 (11.4)
Investigations	**4 (20.0)**	**7 (30.4)**	**8 (42.1)**	**3 (17.6)**	**7 (20.0)**
Blood bilirubin increased	2 (10.0)	3 (13.0)	2 (10.5)	0	0
Alanine aminotransferase increased	1 (5.0)	3 (13.0)	3 (15.8)	0	1 (2.9)
Aspartate aminotransferase increased	1 (5.0)	2 (8.7)	1 (5.3)	0	0
Weight decreased	0	1 (4.3)	0	0	2 (5.7)

MedDRA SOC Preferred Term	PFIC Study A4250-005			ALGS Study A4250-012	
	Placebo (N=20) n (%)	Odevixibat 40 µg/kg/day (N=23) n (%)	Odevixibat 120 µg/kg/day (N=19) n (%)	Placebo (N=17) n (%)	Odevixibat 120 µg/kg/day (N=35) n (%)
General disorders and administration site conditions	**5 (25.0)**	**9 (39.1)**	**5 (26.3)**	**5 (29.4)**	**9 (25.7)**
Pyrexia	5 (25.0)	7 (30.4)	5 (26.3)	4 (23.5)	8 (22.9)
Asthenia	0	0	0	0	2 (5.7)
Respiratory, thoracic and mediastinal disorders	**4 (20.0)**	**3 (13.0)**	**4 (21.1)**	**3 (17.6)**	**6 (17.1)**
Cough	3 (15.0)	0	2 (10.5)	1 (5.9)	3 (8.6)
Epistaxis	1 (5.0)	1 (4.3)	1 (5.3)	2 (11.8)	0
Skin and subcutaneous tissue disorders	**6 (30.0)**	**3 (13.0)**	**2 (10.5)**	**0**	**2 (5.7)**
Pruritus	1 (5.0)	2 (8.7)	1 (5.3)	0	0
Metabolism and nutrition disorders	**3 (15.0)**	**0**	**3 (15.8)**	**1 (5.9)**	**2 (5.7)**
Vitamin D deficiency	1 (5.0)	0	2 (10.5)	1 (5.9)	1 (2.9)
Blood and lymphatic system disorders	**1 (5.0)**	**0**	**2 (10.5)**	**0**	**3 (8.6)**
Splenomegaly	0	0	2 (10.5)	0	0
Vascular disorders	**1 (5.0)**	**0**	**0**	**0**	**3 (8.6)**
Haematoma	0	0	0	0	3 (8.6)

ALGS: Alagille syndrome; MedDRA: Medical Dictionary for Regulatory Activities PFIC: progressive familial intrahepatic cholestasis; SOC: system organ class.

Note that MedDRA version 23.0 was used in Study A4250-005 and version 25.0 was used for Study A4250-012.

Source: CSR A4250-005 Table 14.3.1.2 and CSR A4250-012 Table 14.3.1.3.

The most common types of drug-related TEAEs for patients who received odevixibat in both studies were gastrointestinal disorders and laboratory abnormalities in the Investigations. The incidence of gastrointestinal disorders was similar across the 2 studies, whereas drug-related laboratory abnormalities were reported more commonly in PFIC Study A4250-005. Commonly reported drug-related TEAEs in both studies (> 10% in either 120 µg/kg/day group) were diarrhoea (11.4% in Study A4250-012 vs 8.7% and 10.5% in the 40 and 120 µg/kg/day dose groups, respectively, in Study A4250-005), ALT increased (0% vs 8.7% and 10.5%, respectively), and blood bilirubin increased (0% vs 8.7% and 10.5%, respectively).

In both the PFIC and ALGS studies, most TEAEs were mild to moderate (Grade 1 or 2) in severity.

In Study A4250-012, 7 of the 52 patients experienced treatment-emergent SAEs over the course of the 24-week treatment period, including 5 (14.3%) patients who received odevixibat and 2 patients (11.8%) who received placebo. Similarly, in Study A4250-005, 8 patients experienced treatment-emergent SAEs, including 3 patients (15.8%) who received odevixibat 120 µg/kg/day and 5 patients (25.0%) who received placebo; none of the patients in the 40 µg/kg/day group experienced an SAE. The most commonly reported types of treatment-emergent SAEs in both studies were infections, all of which were reported as unrelated to study treatment. One patient in Study A4250-012 had two treatment-related SAEs; none of the SAEs in Study A4250-005 were reported as related to study treatment.

Post marketing experience

No post-marketing data are available.

2.5.1. 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 TEAE's 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 AE's 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 AE's between the placebo and odevixibat groups, at least part of these AE's 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. This is in line with the known safety profile of odevixibat. Gastrointestinal adverse reactions are described as selected adverse reactions in 4.8 of the SmPC.

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. Nevertheless, given the imbalance in incidence between the placebo and odevixibat arm, the MAH was requested to discuss the causality to treatment. 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.

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 Bylvay, with monitoring per standard clinical practice." This is considered sufficient to manage potential fluctuations in fat-soluble vitamins.

The MAH has thoroughly assessed the hepatic safety profile of odevixibat. 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. 4.4. of the SmPC includes, therefore, a precautionary statement to monitor liver function 6 weeks after start of treatment with re-assessment of the individual benefit-risk ratio.

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, therefore, included as important potential risk in the safety specifications and will be followed up by means of a registry based study that is made specific obligation of this marketing authorisation under exceptional circumstances.

In the Pooled Phase 3 group, 6 (11.5%) of 52 patients experienced a treatment-emergent SAE. The majority of the SAE's were reported in the SOC infections and were assessed as unrelated to the study drug. For gastrointestinal SAE's, 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 ADR's 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 increase 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.

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 TEAE's. 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 TEAE's. However, there were 7/52 patients in the pooled group for whom TEAE's 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-19 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 amount of patents received the lower dose of 40 mg/kg/day. This higher dose did not lead to a worse safety profile.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of odevixibat in ALGS patients is in line with the known safety profile and is mainly characterised by gastrointestinal AE's.

A concern was raised on the worsening of liver function parameters ALT and AST after the start of odevixibat treatment. Even though the clinical data do not indicate acute liver damage, long-term consequences of the increased transaminases cannot be ruled out. Hepatotoxicity has already been included as an important potential risk in the safety concerns and precautionary statements were added to 4.4 of the SmPC recommending the monitoring of liver function 6 weeks after start of the treatment. Furthermore, considering the limitations with regards to safety exposure and long term safety in this rare disease the marketing authorisation holder will provide further data on hepatotoxicity and the time to liver transplantation in odevixibat-treated and untreated patients by means of a registry based study that is specific obligation to this marketing authorisation and within annual reassessments.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 2.4 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.4 is acceptable.

The CHMP endorsed this advice

The CHMP endorsed the Risk Management Plan version 2.4 with the following content:

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 Use during pregnancy and use in breastfeeding women

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study number to be assigned Prospective registry-based safety study on hepatotoxicity and liver outcomes in patients with ALGS Planned	The primary objective is to monitor hepatotoxicity and the time to liver transplantation in odevixibat-treated and untreated patients.	Hepatotoxicity	Feasibility assessment Protocol submission Annual reports	Within 3 months of EC decision Within 6 months of EC decision Submitted with annual reassessments
Category 3 - Required additional pharmacovigilance activities				
A4250-008 An Open-label Extension Study to Evaluate Long-term Efficacy and	Primary Objective (Cohort 1) • To demonstrate a sustained effect of A4250 on serum bile acids and pruritus in children with PFIC Types 1 and 2. Primary Objective (Cohort 2)	Long-term use Interactions with fat-soluble drugs Clinically significant or severe diarrhoea leading to	Final study report	30-Sep-2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2) Ongoing	• 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	dehydration and electrolyte imbalance Hepatotoxicity		
A4250-019 Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC Proposed	Collect safety data on adverse events including, but not limited to: Episodes of diarrhoea lasting more than 3 days, bloody diarrhoea or diarrhoea leading to dehydration or electrolyte imbalance and any treatment Episodes of fat-soluble vitamin deficiencies, including symptoms and treatment Hospitalisations including diagnoses and treatments Collect available specified laboratory data ALT, AST, bilirubin, INR, and fat-soluble vitamin levels Collect data on growth (height and weight z-scores)	Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance Hepatotoxicity Long-term use Interactions with fat-soluble drugs	Protocol Submission Final study report	Within 6 months of EC decision 31-Dec-2026
A4250-022 DDI study with oral contraceptives	To evaluate the effects of odevixibat on the fat-soluble drugs and those with a known entero-hepatic cycle	Interactions with fat-soluble drugs	Final study report	30-Apr-2023

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Ongoing				
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 daily doses of odevixibat in patients with ALGS.	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

Abbreviations: ALT= Alanine aminotransferase; ALGS= Alagille syndrome; AST= Aspartate aminotransferase; DDI= drug-drug interaction; EC= European Commission; INR= International normalised ratio; PFIC= progressive familial intrahepatic cholestasis; QoL= quality of life; s-BA= serum bile acid

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study A4250-008 Study A4250-019 Study A4250-015
Hepatotoxicity	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study A4250-008 Study A4250-019 Study A4250-015 Registry-based safety study (study number to be assigned)
Embryofoetal toxicity	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Interactions with fat-soluble drugs	Routine risk minimisation measures: SmPC section 4.4 and 4.5 PL section 2 and 4 Legal status: Prescription only medicine. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study A4250-008 Study A4250-019 Study A4250-022 Study A4250-015
Long-term use	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Prescription only medicine. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: Study A4250-008 Study A4250-019 Study A4250-015
Use during pregnancy and use in breastfeeding women	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. For further details please refer to the full PI.

2.7.1. 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.

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 as a result of 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 an 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.

In the current procedure, the MAH proposes an extension of the indication to include "treatment of cholestasis and pruritus in Alagille syndrome (ALGS) in patients from birth and older".

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 2022, 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. The most common reasons cited for liver transplant were complications of persistent cholestasis, 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 change 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

A difference in decrease (i.e. improvement) from baseline to week 24 in scratching score (primary endpoint) 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.

After 24 weeks of treatment, 54% of odevixibat-treated patients reported a >1.5 point decrease in pruritus score, compared to 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 PRO 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.

A difference in a decrease from baseline to week 24 in serum bile acids (key secondary endpoint) was observed for the odevixibat (-88.4 µmol/L) group versus the placebo group (24.6 µmol/L), with an LS mean difference -112.74 (-178.78, -46.69) µmol/L, one-sided p-value 0.0006.

Improvements in sleep parameters were observed in the ObsRO, especially on 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.

3.3. Uncertainties and limitations about favourable effects

As no positive effects on dyslipidaemia and liver function parameters were observed, it cannot be concluded that odevixibat is effective in treating cholestasis. This claim was dropped by the MAH in the course or the procedure.

No patients below 6 months of age were included in the clinical studies. Due to uncertainties in the extrapolation solely based on PK modelling the CHMP asked the Applicant for further substantiation of this claim. As the Applicant amended in their response the claimed indication to patients from 6 months of age, this issue was not further pursued.

No long-term efficacy data has been submitted, as the long-term extension study (A4250-015) is still ongoing. Only 10 patients (19%) have been treated for >48 weeks. Results of this category 3 study are planned to be submitted end of 2024 as outlined in the RMP.

3.4. Unfavourable effects

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

Gastrointestinal adverse reactions occurred at a frequency of 21% in ALGS patients treated with Bylvay. Adverse reactions of diarrhoea were mostly mild in severity and non-serious. Three patients experienced an adverse reaction of clinically significant diarrhoea that persisted for 3 or more days without any other aetiology. Treatment interruption was reported for diarrhoea in 3.8% of patients and no discontinuation of Bylvay due to diarrhoea was reported. Adverse reactions of abdominal pain and vomiting were mild to moderate in severity and in most cases of limited duration. Subgroup analysis of the safety profile for various intrinsic and extrinsic factors was conducted. From the limited data, no notable differences were observed for any of the subgroups based on age, sex, race, and ethnicity. No patients discontinued odevixibat due to TEAE's. However, there were 7/52 patients in the pooled group for whom TEAE's let to temporary discontinuation or dose reduction (1/52). These mainly pertained to gastrointestinal AE's.

Increased ALT and AST levels were observed within weeks after the start of odevixibat treatment, while bilirubin levels were constant. Hepatic enzyme increases are labelled in 4.8 of the SmPC.

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. As only 10 patients were exposed for >48 weeks, 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 of Bylvay. 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.

3.6. Effects Table

Table 2. Effects Table for Odevixibat (data cut-off: 09SEP2022**)**

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	Study A4250-012

Effect	Short description	Unit	Treatment	Placebo	Uncertainties / Strength of evidence	References
					18% of the placebo patients	
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

Abbreviations: sBA, serum bile acids. ALT, alanine transaminase. AST, aspartate transaminase. ObsRO, observer reported outcome.

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. This endpoint was measured as a continuous outcome with the change from baseline to 24 weeks reported on a group level. The results were corroborated by a responder analysis conducted as a secondary outcome in support of 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 in scientific advice procedures. From the validation report, 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. The observed effects were 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.

Also the associated improvements in sleep and caregiver impression of change are acknowledged. 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. Even though it is not known what levels of sBA should be aimed for as a treatment target serum bile acid levels are a logical efficacy (and pharmacodynamic) outcome.

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.

For an adequate substantiation of the treatment of cholestasis in ALGS, consistent improvements would need to be shown in sBA, pruritus, dyslipidaemia, and liver function parameters. No positive effects of treatment were observed for either 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. Due to the absence of improvements in liver function parameters the applicant agreed to amend the indication to "treatment of cholestatic pruritus".

In addition, no patients were included in the studies below 6 months of age even though they were not excluded from the study population. This is of importance as potential differences in bioavailability exist due to maturation of intestinal permeability. Furthermore Odevixibat is designed for minimal systemic exposure and the MAH assumes that the bioavailability will be very low, also in the youngest children (≤6 months). However, with a very low bioavailability, also small deviations from the assumed values would have a big impact on the simulated exposures. It was, therefore, not considered acceptable to fully extrapolate safety and efficacy data to children below the age of 6 months. After request of the CHMP to further substantiate the extrapolation the company decided to amend the indication to patients of 6 month of age and older.

In the studies no adult patients were included in the studies. However, it is not unlikely that odevixibat will be used in adults. As there is no reason to assume a different safety and efficacy in adult patients, this is not of major concern. Nevertheless, some patients are expected to turn 18 in the long-term extension study. The Applicant will be expected to provide safety and efficacy data of those patients in the annual reassessments and with the final report of study A4250-015 that is a category 3 study in the RMP.

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 a category III study in the RMP.

Dose finding has been limited, as only the 120 ug/kg/day dose has been studied in the ALGS population. Nevertheless, the efficacy and safety of the 120 ug/kg/day have been sufficiently established for a marketing authorisation under exceptional circumstances. Dose modification to a reduced dose level of 40 µg/kg/day, which is the approved dose for the PFIC indication, is included in the SmPC in order to manage any potential AEs. Dose reductions were permitted in the study protocol of the pivotal trial. Whilst 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.

However, due to the number of studied patients in this marketing authorisation under exceptional circumstances it remains uncertain whether a lower dose might prevent the observed increases in ALT/AST with comparable efficacy. Whilst it cannot reasonably be expected from the applicant to generate fully comprehensive further data, the PFIC studies showed that for the majority of patients,

40 ug/kg/day was sufficient for a response, while in the 120 ug/kg/day slightly more severe and serious TEAE's were observed. The planned registry to monitor hepatotoxicity and the time to liver transplantation in odevixibat-treated and untreated patients will therefore provide further data and is a specific obligation to this MA under exceptional circumstances.

3.7.2. Balance of benefits and risks

Odevixibat treatment led to positive 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. No beneficial effects were observed on liver function parameters. On the contrary, increases in ALT and AST were observed and they are considered balanced with precautionary statements as included in 4.4 of the SmPC. The safety database in ALGS patients is relatively limited and as only 10 patients were exposed for >48 weeks, long-term safety data is lacking. Whilst the rarity of the disease is acknowledged further information on long term use on safety and effectiveness will be generated by means of a prospective registry which is a specific obligation to this marketing authorisation under exceptional circumstances.

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.

In the course of the assessment of the marketing authorisation application for odevixibat, a third-party intervention was submitted to EMA, claiming that odevixibat and maralixibat are similar from the standpoint of principal molecular structure features. In view of the observations set out in the similarity assessment report, the foregoing claim in the third-party intervention was not considered well-founded. Please refer to the similarity assessment conclusions. Additional considerations on the benefit-risk balance

The MAH has requested a marketing authorisation under exceptional circumstances. A justification has been submitted, detailing the arguments of the MAH as to why it is not possible to provide comprehensive evidence. In the justification, the Applicant argues that the condition ALGS is so rare, that it cannot be reasonably expected that comprehensive evidence can be generated. It is agreed that ALGS is a rare disease. Nevertheless, the MAH 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. As is also pointed out by the Applicant, effects on liver transplantation and death are difficult to show as the time to event is long (The estimated liver transplant-free survival rate at the age of approximately 18 years for patients with ALGS ranges from 24% to 40%). It is, therefore, agreed with the Applicant that it is not likely that comprehensive evidence to support long-term efficacy (e.g. an effect on SNL (survival with native liver)) could be obtained. As pointed out by the MAH, there is no conclusive evidence (both from the clinical studies and from the literature), that either pruritus or serum bile acids can be used as a surrogate for Survival with native liver (SNL). However, as the indication was amended to the treatment of cholestatic pruritus this is not any more considered an open issue.

However, considering the limitations with regards to safety exposure and long term safety the data of odevixibat in the treatment of cholestatic pruritus is considered not fully comprehensive and the CHMP considers that further data on hepatotoxicity and the time to liver transplantation in odevixibat-treated and untreated patients needs to be provided by means of a registry based study that is specific obligation to this marketing authorisation under exceptional circumstances.

3.8. Conclusions

The overall B/R of Bylvay in the for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older is positive.

The following measures are considered necessary to address issues related to safety and efficacy within this marketing authorisation under exceptional circumstances:

Description	**Due date**
In order to investigate whether odevixibat treatment delays surgical biliary diversion (SBD) and/or liver transplantation (OLT), with matched comparison against untreated PFIC patients, the MAH should conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) according to an agreed protocol.	Annual interim reports are to be submitted along with the annual reassessments.
To monitor hepatotoxicity and the time to liver transplantation in odevixibat-treated and untreated patients the MAH should conduct and submit the results of a study based on data from a disease registry of patients with Alagille syndrome (ALGS) according to an agreed protocol.	Annual interim reports are to be submitted along with the annual reassessments.
In order to ensure adequate monitoring of safety and efficacy of Bylvay in the treatment of patients with progressive familial intrahepatic cholestasis and patients with cholestatic pruritus in Alagille syndrome, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Bylvay.	Annual (within annual reassessment)

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older for BYLVAY, based on 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 with a genetically confirmed diagnosis of ALGS and presence of pruritus and high serum bile acid levels at baseline. Study A4250-015 is an ongoing 72-week open-label extension trial for patients who completed Study A4250-012 and evaluates the long-

term safety and efficacy of Bylvay in patients with ALGS. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC and Annex II of the Marketing Authorisation are updated. The Package Leaflet is updated in accordance. Version 2.4 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet, Annex II and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

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.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Bylvay is not similar to Livmarli within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and does not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.