EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP)

Active substance (International Nonproprietary Name (INN) or common name)	Odevixibat (INN)
Pharmaco-therapeutic group (Anatomic Therapeutic Chemical (ATC) Code):	Other drugs for bile therapy (A05AX05)
Name of Marketing Authorisation Holder (MAH) or Applicant:	Ipsen Pharma
Number of medicinal products to which this Risk Management Plan (RMP) refers:	2
Products concerned (brand names):	Bylvay and Kayfanda

Data lock point for this RMP: 15 July 2024

Version Number: 7.0

Date of final sign off: 10 April 2025

Rationale for submitting an updated RMP: Consolidation of version 6.1, 6.2 and 6.3 of the EU RMP following approval from the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC). These EU RMPs were prepared and submitted based on new safety data available from the analysis of final study reports for Category 3 Studies A4250-008 and A4250-015.

Qualified Person for Pharmacovigilance (QPPV) name:

Frederique Korn

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation QPPV or their deputy. The electronic signature is available on file.

Administrative information on the Risk Management Plan (RMP)

Table 1 Summary of Significant Changes in this RMP

Part	Module/Annex	Significant changes in this RMP
Part I Product(s) Overview		Updated to include ALGS under current indications, dosage and approved procedure.
Part II Safety Specification	**Module SI** Epidemiology of the Indication(s) and Target Population(s)	No change
	Module SII Non-clinical Part of the Safety Specification	No change
	Module SIII Clinical Trial Exposure	Updated clinical trial exposure data from Study A4250-008.
	Module SIV Populations Not Studied in Clinical Trials	Number of patients for the pooled phase III ALGS studies were updated for patients with hepatic/renal impairment.
	Module SV Post-authorisation Experience	Post-authorisation exposure was updated based on the most recent PSUR data (DLP: 15 July 2024).
	Module SVI Additional European Union (EU) Requirements for the Safety Specification	No change
	Module SVII Identified and Potential Risks	Updated new data for important identified, potential risks and missing information from Study A4250-008. Updated new data for important identified, potential risks and missing information from pooled phase III ALGS studies and Study A4250-015.
	Module SVIII Summary of the Safety Concerns	No change
Part III Pharmacovigilance Plan (including post-authorisation safety studies)		Additional pharmacovigilance activities were updated to remove Studies A4250-008 and A4250-015.
Part IV Plans for Post-authorisation Efficacy Studies		No change

Part	Module/Annex	Significant changes in this RMP
Part V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)		Routine risk minimisation activities recommending specific clinical measures to address the risk interactions with fat-soluble drugs was updated to include SmPC sections 4.4 and 4.5. Studies A4250-008 and A4250-015 were removed from additional pharmacovigilance activities.
Part VI Summary of the RMP		Updated new data for important identified, potential risks and missing information from Study A4250-008. Updated new data for important identified, potential risks and missing information from pooled phase III ALGS studies and Study A4250-015. Studies A4250-008 and A4250-015 were removed from additional pharmacovigilance activities and other studies in post-authorisation development plan.
Part VII Annexes	Annex 1 EudraVigilance Interface	Not applicable
	Annex 2 Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme	No change
	Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	Studies A4250-008 and A4250-015 were updated as completed additional pharmacovigilance activities.
	Annex 4 Specific Adverse Drug Reaction Follow-Up Forms	Not applicable
	Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV	No change
	Annex 6 Details of proposed Additional Risk Minimisation Activities (if applicable)	No change
	Annex 7 Other Supporting Data (including referenced material)	No change
	Annex 8 Summary of Changes to the RMP Over Time	Updated to reflect the above changes made based on the consolidation of versions 6.1, 6.2, and 6.3.

Abbreviations: ALGS=Alagille syndrome; DLP=data lock point; EU=European Union; PRAC=Pharmacovigilance Risk Assessment Committee; RMP=risk management plan

Other RMP versions under evaluation:

Table 2 Other RMP Version under Evaluation

RMP version number	Submitted on	Procedure Number
Not applicable		

Details of the currently approved RMP:

Table 3 Details of the currently approved RMP

Version number	7.0
Approved with procedure	Consolidated version based on RMP version 6.2 reviewed and approved during procedure EMEA/H/C/006462/II/0001/G and RMP version 6.3 reviewed and approved during procedure EMEA/H/C/004691/II/0022/G
Date of approval (opinion date)	13 March 2025

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Wording definition
ABCB	Adenosine Triphosphate Binding Cassette Subfamily B Member
ALGS	Alagille Syndrome
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
ATP8B1	Adenosine Triphosphatase Phospholipid Transporting 8B1
BMI	Body mass index
BRIC	Benign Recurrent Intrahepatic Cholestasis
BSEP	Bile Salt Export Pump
CHMP	The Committee for Medicinal Products for Human Use
CNS	Central Nervous System
CV	Cardiovascular
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLP	Data Lock Point
eDiary	Electronic diary
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FIC1	Familial Intrahepatic Cholestasis-1
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HCC	Hepatocellular Carcinoma
IBAT	Ileal Bile Acid Transporter
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
JAG1	Jagged canonical notch ligand 1
MAH	Marketing Authorisation Holder
MDR3	Multidrug Resistance 3 Protein
Myo5b	Myosin 5B gene
NOTCH	Neurogenic locus notch homolog protein
NR1H4	Nuclear Receptor Subfamily 1 Group H Member 4
PASS	Post-authorisation safety study
P-gp	P-glycoprotein
PEBD	Partial External Biliary Diversion
PFIC	Progressive Familial Intrahepatic Cholestasis
PRAC	The Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
QoL	Quality of Life
RMP	Risk Management Plan
s-BA	Serum bile acids
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TJP2	Tight Junction Protein-2
TK	Toxicokinetic
TOC	Table of Contents
UDCA	Ursodeoxycholic Acid
US	United States

PART I: PRODUCT(S) OVERVIEW

Table 4 Product(s) Overview

Active substance (International Non-proprietary Name (INN) or common name)	Odevixibat
Pharmacotherapeutic group (ATC Code)	Other drugs for bile therapy (A05AX05)
Marketing Authorisation Holder	Ipsen Pharma
Medicinal products to which this RMP refers	Two
Invented name(s) in the European Economic Area (EEA)	Bylvay and Kayfanda
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Odevixibat is a selective inhibitor of the ileal bile acid transporter (IBAT).
	Summary of mode of action: Odevixibat is a reversible, potent and selective inhibitor of the IBAT. After oral administration, it acts locally in the distal ileum to decrease the reuptake of bile acids and increase the clearance of bile acids through the colon, lowering hepatic bile acid load and serum bile acid concentrations.
	Important information about its composition: Odevixibat is a stereochemically pure enantiomer with a molecular weight of 740.9 g/mol.
Hyperlink to the Product Information	Bylvay Product Information (Module 1.3.1) Kayfanda Product Information (Module 1.3.1)
Indication(s) in the EEA	**Current:** Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. Kayfanda is indicated for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older.
	Proposed (if applicable): Not applicable
Dosage in the EEA	**Current**: PFIC: The recommended dosage of odevixibat is 40 µg/kg administered orally once daily in the morning. Odevixibat can be taken with or without food. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 µg/kg/day. Cholestatic pruritus in ALGS: The recommended dose of odevixibat for patients with ALGS is 120 µg/kg administered orally once daily in the morning. Dose reduction to 40 µg/kg/day may be considered if tolerability issues occur in the absence of other causes. Once tolerability issues stabilise, dose may be increased to 120 µg/kg/day as tolerated. Odevixibat can be taken with or without food. The maximum daily dose in both indications is 7200 µg per day or similar.
	Proposed (if applicable): Not applicable

Pharmaceutical form(s) and strengths	**Current**: Hard capsule <u>Odevixibat 200 µg hard capsules</u> Size 0 capsule (21.7 mm × 7.64 mm) with ivory opaque cap and white opaque body; imprinted "A200" with black ink. <u>Odevixibat 400 µg hard capsules</u> Size 3 capsule (15.9 mm × 5.82 mm) with orange opaque cap and white opaque body; imprinted "A400" with black ink. <u>Odevixibat 600 µg hard capsules</u> Size 0 capsule (21.7 mm × 7.64 mm) with ivory opaque cap and body; imprinted "A600" with black ink. <u>Odevixibat 1200 µg hard capsules</u> Size 3 capsule (15.9 mm × 5.82 mm) with orange opaque cap and body; imprinted "A1200" with black ink. The larger 200 µg and 600 µg capsules are intended to be opened and sprinkled on food or in a liquid but may be swallowed whole. The smaller 400 µg and 1200 µg capsules are intended to be swallowed whole but may be opened and sprinkled on food or in a liquid.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ALGS=Alagille syndrome; ATC=Anatomical Therapeutic Chemical; EEA=European Economic Area; EU=European Union; IBAT=Ileal bile acid transporter; INN=international non-proprietary name; PFIC=progressive familial intrahepatic cholestasis; RMP=risk management plan

PART II: SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the Indication(s) and Target Population(s)

<u>Indication</u>:

Odevixibat is currently indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older and for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older.

Progressive familial intrahepatic cholestasis

<u>Disease Background:</u>

PFIC is the clinical diagnosis applied to a heterogeneous group of life-threatening and debilitating rare autosomal recessive genetic diseases, all of which result in cholestasis with impaired bile acid secretion and transport [1,2].

PFIC is generally categorised into three main subtypes, PFIC1, PFIC2 and PFIC3, although at least other subtypes have been described in the literature [3,4,5,6,7]. All three types of PFIC are caused by mutations in genes encoding proteins involved in the secretion and transport of bile acids, which in turn result in accumulation of bile acids [6].

PFIC1, also referred to as familial intrahepatic cholestasis-1 (FIC1) protein deficiency, is associated with defects in the adenosine triphosphatase phospholipid transporting 8B1 (ATP8B1) gene, which encodes for FIC1 protein, a flippase located on the canalicular membrane of hepatocytes. The FIC1 protein facilitates movement of aminophospholipids from the outer to inner leaflet of the plasma membrane of the hepatocyte.

PFIC2, also referred to as bile salt export pump (BSEP) deficiency, results from mutations in the adenosine triphosphate (ATP) binding cassette subfamily B Member 11 (ABCB11) gene, which encodes for BSEP,

a transporter protein expressed at the canalicular membrane of hepatocytes and which is the main exporter of bile acids from hepatocytes to canaliculi against a concentration gradient.

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

The underlying mutations for PFIC1 and PFIC2 both, either directly or indirectly, affect BSEP expression and function in the canalicular membrane of the hepatocyte leading to impaired bile acid secretion [7]; whereas, in PFIC3 the basic defect results in reduced secretion of biliary phospholipids, resulting in injury to the biliary epithelia and canaliculi, as the concentration of free bile acids is increased in the extracellular space.

Mutations in genes tight junction protein-2 (TJP2), Nuclear Receptor Subfamily 1 Group H Member 4 (NR1H4), or Myosin 5B gene (Myo5b) have also been proposed as causes of PFIC (subtypes 4, 5 and 6, respectively) [8]. In addition, some patients with PFIC do not have a mutation in any of the ATP8B1, ABCB11, ABCB4, TJP2, NR1H4, or Myo5b genes. In these cases, the cause of the condition is unknown [9].

Within PFIC1 and PFIC2 there is a range in severity of symptoms and rate of progression of hepatic injury. Previously, the term benign recurrent intrahepatic cholestasis (BRIC) was used to identify a group of patients with episodic cholestasis including severe pruritus and jaundice. While some of these patients recover between episodes, cases have been reported in which initially episodic cholestasis has subsequently transitioned to a persistent progressive form of the disease [10]. Genetic analysis of patients with episodic cholestasis have identified mutations in the ATP8B1 and ABCB11 genes (the same mutations as PFIC1 and PFIC2). It is now generally recognised that, within each subtype, PFIC and BRIC represent two extremes of a continuous spectrum of phenotypes of the one disease [2,11,12].

Incidence and Prevalence:

Progressive familial intrahepatic cholestasis is estimated to affect between one in every 50,000 to 100,000 children [13]. There are no published reports of global studies on the epidemiology of PFIC; therefore, the true incidence and prevalence of the disease remain unknown. Based on a present analysis and findings made by Baker 2019, the actual prevalence of PFIC in Europe is estimated at 0.07/10,000. At a population of 519.2 million [14], this corresponds to a total number of approximately 3650 subjects affected by the disease in the European Economic Area (EEA). Based on an internal survey of United States (US)-based physicians, there are estimated to be approximately 3000 patients with PFIC in the US. Of those, approximately 45% have the BRIC phenotype.

Progressive familial intrahepatic cholestasis represents 10% to 15% of cases of cholestasis in children and 10% to 15% of liver transplantation indications in children. Progressive familial intrahepatic cholestasis1 and PFIC2 together represent approximately two-thirds of cases of PFIC and PFIC3, approximately one-third [13].

Demographics of the population in the authorised indication and risk factors for the disease:

Progressive familial intrahepatic cholestasis affects both males and females equally [13] and has been reported in all geographical regions [6]. Higher rates of the disease have been reported in populations that have less genetic admixture [15,16]. All types of PFIC are autosomal recessive genetic diseases and the severity of the clinical symptoms depends upon the specific mutation.

The main existing treatment options:

Odevixibat was authorised in July 2021 for the treatment of PFIC in patients 6 months or older. In March 2024, FDA approved Livmarli (maralixibat), an IBAT inhibitor, for the treatment of cholestatic pruritus in patients 12 months of age and older with PFIC. On 28 June 2024, Livmarli was approved by European Commission for treatment of PFIC in patients 3 months of age and older. Other than IBAT inhibitors, therapeutic choices are restricted to non-specific therapy for the clinical symptoms of the disease, including nutritional support, prevention of vitamin deficiencies and symptomatic treatment of extrahepatic features, including pruritus. Medical treatment options include off-label use of ursodeoxycholic acid (UDCA), rifampicin, antihistamines including hydroxyzine and naltrexone but none of these therapies have proven benefits for the long-term prognosis of patients with PFIC [7,17]. A minority of patients respond nominally and transiently to these interventions [7].

Ursodeoxycholic acid has been shown to improve symptoms and hepatic biochemical parameters in up to 50% of patients with PFIC3, yet limited effects of off-label use have been reported in patients with PFIC1 and PFIC2 [17,18]. Some patients respond to UDCA therapy with improved symptoms and liver function tests if it is administered early in the disease course before development of cirrhosis [5,6,7]. However, the criteria for identifying patients who might benefit from UDCA are unclear. The ability of UDCA to mitigate liver damage has not been evaluated in controlled trials in patients with PFIC1 or PFIC2.

Rifampicin, an antibiotic, inhibits bile acid uptake into hepatocytes. Though the mechanism of its effect on pruritus is unknown [19,20], it may include alterations of intestinal flora leading to changes in the secondary bile acid pool [21]. Rifampicin has been associated with drug-induced hepatitis [22] and severe adverse reactions that include hepatotoxicity of hepatocellular, cholestatic, and mixed pattern origins; hypersensitivity reactions; bleeding; and Stevens Johnson syndrome [23,24].

Antihistamines that block histamine-1 receptors are often considered early in the treatment of pruritus given their efficacy in Type 1 allergic disease. Raised histamine levels can be found in patients with cholestasis [25]. However, antihistamines are often ineffective in treating pruritus associated with cholestasis [26] and some are known to cause drowsiness, which may limit their use to night-time only.

As symptomatic medical treatment is rarely effective, surgical options are considered including biliary diversion (such as partial external biliary diversion (PEBD) or ileal exclusion) and liver transplant. Treatment-resistant pruritus is the leading indication for surgical biliary diversion, particularly in patients with PFIC2 where it is listed as an indication for surgery in 89% of patients [27]. Biliary diversion interrupts the enterohepatic circulation of bile acids by diverting bile from the gallbladder, thereby decreasing bile acid delivery to the gut and reuptake from the small intestine, which, in turn, lowers the bile acid pool and hepatic load. Surgical biliary diversion often results in rapid and dramatic reductions in serum bile acids and pruritus, as well as in improvements in sleep disturbance; in the long-term, it is associated with less fibrosis and a catch-up in linear growth over 1 to 2 years [28,29,30,31]. The beneficial impact of surgical biliary diversion on long-term native liver survival has recently been shown to correlate with the reduction in serum bile acids observed following the surgery [32].

For many patients, biliary diversion is not a permanent solution due to refractory pruritus or end-stage liver disease [18, 27, 33]. Continued elevated serum bile acids and pruritus are also seen in some patients after biliary diversion surgery. While biliary diversion surgery may postpone or eliminate the need for liver transplantation and improve pruritus associated with PFIC in some patients, it is an invasive procedure with unwanted cosmetic consequences. Patients may experience complications related to the external stoma requiring surgical revision and biliary diversion can lead to post-operative cholangitis [3]. High rates of clinically significant dehydration and hyponatremia have also been reported after biliary diversion surgery [5].

Liver transplantation is considered when patients have end-stage liver disease, hepatocellular carcinoma (HCC), or have failed medical treatment and/or biliary diversion surgery and refractory pruritus results in a poor quality of life (QoL). Reported rates of liver transplantation range between 40% and 100% in patients with PFIC1 and PFIC2 [18]. A recent large case series reported that 30% of a cohort of patients with PFIC2 underwent liver transplant a median of 2.4 years after surgical biliary diversion and by 18 years of age only 32% of patients with PFIC2 were alive with the native liver [27]. This underscores how common liver transplantation is in this disease. Although liver transplantation may resolve cholestasis in patients with PFIC1 and PFIC2, the overall outcome remains unsatisfactory in many patients with PFIC1; this is mainly due to extrahepatic manifestations, organ rejection and the complications and the risks associated with chronic immune-suppressant therapy [18,33]. Specific to PFIC1, an undesired effect of liver transplant is worsening of the extrahepatic manifestations, such as diarrhoea and short stature. The increase in bile acid secretion in the stool post-transplant causes high-volume osmotic diarrhoea that has a significant impact on QoL [5]. High-volume osmotic diarrhoea is often associated with severe liver steatosis and/or steatohepatitis that may lead to cirrhosis and to an indication for re-transplantation [13].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Progressive familial intrahepatic cholestasis is a life-limiting condition with a high level of associated debilitating symptoms and morbidity that has a major impact on the QoL of both the affected patients and their families [34,35]. Severe pruritus is common in patients diagnosed with PFIC and the need for some form of relief is critical. Significant pruritus can lead to severe cutaneous mutilation (often drawing blood), loss of sleep, irritability, poor attention and impaired school performance [5]. Symptoms develop early; median age at onset of symptoms is approximately 3 months; 78% of patients develop jaundice before 12 months of age [36]. Patients with PFIC often present with worsening jaundice and severe pruritis within the first few years of life [5].

Examination reveals icterus, hepatomegaly, scratch marks with excoriation and hyperpigmentation of skin and shiny nails. Liver biopsy reveals canalicular cholestasis and, later, the appearance of portal fibrosis. Liver biochemistry shows cholestasis with hyperbilirubinemia and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The concentrations of bile acids in serum are typically very high, while serum gamma-glutamyl transferase (GGT) is normal or low (except for PFIC3); and cholesterol concentrations are typically normal [7]. Portal hypertension and decompensation may be evident earlier in the first year of life in PFIC2 and in early childhood in PFIC1 [6,13]. Other features include fat malabsorption resulting in weight and height below normal centiles and fat-soluble vitamin (A, D, E and K) deficiency. Deficiencies in fat-soluble vitamin levels manifest as xeropthalmia and night blindness (vitamin A deficiency), persistent neuropathy (vitamin E deficiency), bleeding/haemorrhage (vitamin K deficiency), and rickets and osteomalacia (vitamin D deficiency) [37,38,39,40]. Patients with PFIC1 have extrahepatic manifestations, such as diarrhoea, malabsorption, pancreatitis, short height, an increased sweat electrolyte concentration and hepatic steatosis [3]. Children (male or female) with PFIC2 are at risk for hepatobiliary malignancy (15% may develop HCC or cholangiocarcinoma) [41]. The prognosis is poor; many PFIC patients progress to end-stage liver disease and require liver transplantation [5]. Survival in patients with PFIC not undergoing surgical diversion or liver transplant is 50% at 10 years of age and <10% at 20 years of age, highlighting the rapid rate of progression of this life-threatening disease [36].

Table 5 presents the main features of the PFIC Types 1, 2 and 3 [6].

Table 5 Main Features of PFIC, Types 1-3

FEATURE	PFIC1	PFIC2	PFIC3
Age at presentation	Infancy	Neonatal period-early infancy	Late Infancy (30%) to early adulthood
End-stage liver disease	First decade	Rapid, first few years	First to second decade of life
Course of disease	Moderately severe	Very severe	Insidious
Pruritus	Severe	Very severe	Moderate
Extrahepatic features	Present	Absent	Absent
Risk of development of liver tumours[a]	Not reported	High	Low
Serum ALT	Mild elevation	Moderate elevation	Mild elevation
Serum GGT	Normal	Normal	Elevated
Serum bile acids	Raised++	Raised +++	Raised +

Abbreviations: ALT=alanine aminotransferase; GGT=gamma-glutamyl transferase; PFIC=progressive familial intrahepatic cholestasis

a hepatocellular carcinoma, cholangiocarcinoma

Important co-morbidities:

Patients with PFIC have multiple co-morbidities that include, but are not limited to, diarrhoea, malabsorption, fat-soluble vitamin deficiencies, coagulopathy, hepatic impairment with deranged hepatic biochemical parameters (e.g. ALT, AST, total bilirubin, alkaline phosphatase (ALP) and for PFIC3 GGT), clinical hepatitis and exacerbation of cholestasis. Table 6 presents the known co-morbidities in patients with PFIC [18].

Table 6 Co-morbidities of Progressive Familial Intrahepatic Cholestasis

• Hepatocellular carcinoma (PFIC2)
• Significantly elevated serum bile acid levels
• Jaundice with hepatomegaly and/or splenomegaly
• Clinically significantly abnormal hepatic biochemical parameters
• Liver decompensation
• Liver cirrhosis and end-stage liver disease
• Severe pruritus: severe cutaneous mutilation (often drawing blood), loss of sleep, irritability, poor attention and impaired school performance
	• Diarrhoea
	• Poor growth and failure to thrive
	• Coagulopathy
	• Prone to infections
	• Pancreatitis
	• Fat malabsorption with fat-soluble vitamin deficiencies and poor growth
	  • Vitamin A: tiredness, weight loss, hair loss
	  • Vitamin D: rickets
	  • Vitamin E: neuropathy
	  • Vitamin K: bleeding (e.g. cerebral, gastrointestinal, severe and recurrent epistaxis)

Abbreviation: PFIC2=Progressive familial intrahepatic cholestasis2

Alagille syndrome

Disease Background:

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 (CNS), kidneys and facial features [42,43]. 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 [43,44,45]. Cholestasis is one of the most common features of ALGS, typically presenting with unremitting pruritus. The progressive liver damage due to the cholestasis can lead to cirrhosis with end-stage liver disease requiring transplantation before adulthood [46]. 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 Childhood Liver Disease Research Network and the Global Alagille Alliance Study Group [47,48].

Alagille syndrome is caused by defects in components of the neurogenic locus notch homolog protein (NOTCH) signalling pathway, one of the basic signalling pathways during foetal development, involved in both cell-type specification and organogenesis [49]. In about 90% of patients, the disease is caused by mutations in jagged canonical NOTCH ligand (JAG1), which is one of five NOTCH signalling ligands. A smaller number of patients (<5%) have mutations in the gene for the NOTCH2 receptor [43,46,50,51]. 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 [52]. Consequently, mutations in JAG1 and NOTCH2 affect multiple organs, though the clinical manifestations can vary.

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 [43,53]. With the advent 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.

Incidence and Prevalence:

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 of 790,385 children born in Victoria

during the period of 1963-1974 in which 11 children had the condition now called ALGS, giving an incidence at birth of 1/70,000 or 0.139/10,000 live births [54]. Better diagnostic tools, including the advent of molecular testing, have indicated that a more accurate incidence is closer to 1/30,000 or a prevalence of 0.33/10,000 live births [53,55].

Therefore, the prevalence of ALGS in the European Union (EU) is still assumed to be 0.33/10,000. At a population of approximately 447.7 million (EU-27), this corresponds to ca. 14,800 people affected with the disease.

Demographics of the population in the proposed indication and risk factors for the disease:

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 [47,48,56].

The main existing treatment options:

There is no approved pharmacological therapy aimed at correcting the underlying genetic defect in ALGS. In 2021, the US approved Livmarli (maralixibat), an IBAT inhibitor, for the treatment of cholestatic pruritus in patients with ALGS ≥1 year of age [57] and approved Bylvay for the same indication in June 2023. On 09 December 2022, EMA approved Livmarli (maralixibat) for the treatment of cholestatic pruritus in patients with ALGS 2 months of age and older [58]. Additionally, on 19 September 2024, the European Commission has approved Kayfanda (odevixibat) for the treatment of cholestatic pruritus in patients with ALGS aged 6 months or older. Other current treatments, target the symptoms of the disease. Symptomatic treatment of pruritus includes off-label use of UDCA, cholestyramine, rifampin, ondansetron and/or naltrexone; these agents are at best partially effective [51].

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 (GI) tract have been shown to relieve symptoms such as pruritus and xanthomas and improve QoL [31,45]. This procedure is reported in only about 5% of patients with ALGS; in these patients reduced survival with native liver was observed [48]. 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 [47,48]. 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%) [48]. Other factors reported as leading to liver transplant include bone fractures, refractory fat-soluble vitamin deficiency, liver failure and manifestation of portal hypertension [46,48]. Liver transplantation is associated with postoperative mortality and the requirement for lifelong immunosuppression. Furthermore, coexisting cardiopulmonary and vascular abnormalities, as well as post-surgical renal impairment, may render patient's ineligible for liver transplantation and if they do undergo the procedure, may impact the success of the surgery [55,59,60].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Table 7 outlines the multiple clinical manifestations that can occur in patients with ALGS, including the approximate frequency of presentation.

Table 7 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.
Ophthalmologic	78%-90%	Ocular xanthelasma, posterior embryotoxon.

Organ System	Mean Frequencies	Clinical Presentation
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.

Abbreviation: NR=not reported

Source: [43,46,47,48,61,62,63]

Alagille syndrome is a complex, multisystem developmental disorder comprising a broad range of clinical features that generally presents in early childhood. Patients with ALGS experience cholestasis with jaundice, unrelenting pruritus, disfiguring or disabling xanthomas, growth impairment, and a variety of other significant co-morbidities, including fat-soluble vitamin deficiency, vascular complications and increased risk for bone fractures [46]. Surgical options can potentially relieve pruritus and may improve the liver disease [64]. However, these surgeries are associated with other risks and not all ALGS patients may be eligible for surgery due to their underlying comorbid conditions, primarily related to cardiac and vascular abnormalities [43,64].

The rate of overall survival at 5, 10 and 18-years was 92.8%, 91.2% and 88.1%, respectively. The median age of death was 2.6 years. Liver-related complications, including liver transplant complications, were the leading cause of death (22%), followed by cardiac-related complications (18%) and multi-organ failure and non-cardiac vascular complications (15% each) [48].

Important co-morbidities:

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 [45]. 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 increased risk of bone fracture, bleeding and other sequalae. As cholestasis progresses, portal hypertension with oesophageal varices and ascites can develop with 40% of patients developing definitive portal hypertension by age 20 [47]. Thrombocytopenia is not uncommon as portal hypertension ensues leading to splenomegaly, which can result in splenic sequestration of platelets.

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 knockout mouse model with cholestasis showing elevated levels of hepatic bile acids, the serum levels of ALT and AST, ALP and bile acids were also markedly elevated [66]. 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 PFIC, it has been shown that a reduction in serum bile acid levels is associated with prolonged native liver survival [32,67,68].

Elevation of liver enzymes in serum, including ALT and AST, that is a result of damage or destruction of 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 for 95% of the time [48].

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 [46,47]. The impact of pruritus for patients with ALGS occurs early in childhood with a median age at onset of 12 months [48]. The precise mechanism of cholestatic pruritus remains unclear, but elevated serum bile acid levels are most commonly considered as direct or indirect pruritic mediators [5]. The pruritus is associated with skin lesions, difficulty with sleep and mood disturbances. Patients with ALGS and their caregivers confirm that pruritus is the most bothersome symptom.

Xanthomas have been reported in 24% of patients, first manifesting at a median age of 25 months [48]. At 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 [46].

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 indicating a significant deficit in growth [47]. The growth deficit may be related to fat malabsorption resulting in failure to thrive. Malabsorption of fat-soluble vitamins can lead to other significant co-morbidities, 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 [69,70,71].

Part II: Module SII – Non-clinical Part of the Safety Specification

The data lock point (DLP) of this Module was 04 December 2020 for the purposes of the initial RMP. As there were no new non-clinical findings as of 15 July 2024 (new or re-classified safety concerns), the marketing authorisation holder (MAH) has provided updates only for Relevance to Human Use with updated PFIC clinical data through 15 February 2024 and ALGS data through 07 February 2024.

Odevixibat has been evaluated in a comprehensive non-clinical programme to assess toxicology (including evaluation of impurities) and safety pharmacology. Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3(R2), the toxicology programme included single administration tolerability studies in mice and rats, repeat-administration range-finding and definitive toxicity and toxicokinetic (TK) studies for up to 13 weeks (mice), 26 weeks (rats), 39 weeks (dogs) and 7 days (marmoset). The programme also included in vitro non-mammalian cell system (bacterial reverse mutation), in vitro mammalian system (mouse lymphoma cell thymidine kinase locus) and in vivo mammalian system (rat micronucleus) assays (ICH S2(R1)) to access the potential for genotoxicity.

Carcinogenicity studies were completed in rats and mice (ICH S1B). For reproductive and developmental toxicity (ICH S5(R2); ICH S11), a comprehensive battery of range-finding and pivotal fertility and early embryonic development, embryo-foetal development, prenatal development, postnatal development (including maternal function) and juvenile studies, including TK, were performed in the rat. Range-finding and pivotal embryo-foetal development studies, including TK, were performed in the rabbit as the second species.

In addition, qualification (ICH Q3A) of drug substance process-related organic impurities of odevixibat was accomplished by their presence in bulk material used to conduct pivotal toxicology studies of various duration, including 26 weeks in rats, 13 and 39 weeks in dogs and a 7-week assessment in juvenile rats. There were no unexpected findings in these studies that were considered related to the impurity profile of odevixibat. Additionally, a structure-based mutagenicity assessment was performed on all the identified odevixibat drug substance impurities (ICH M7(R1)). The structures were evaluated using the in-silico tools Deductive Estimation of Risk from Existing Knowledge and Leadscope. No structural alerts were observed for any of the identified drug substance impurities. Based on this assessment and the current specifications, there are no general toxicity or genotoxicity concerns for the drug substance process-related organic odevixibat impurities.

Formal local tolerance studies with odevixibat were not conducted. Local (GI tract) tolerance of odevixibat was evaluated within the context of the exploratory and definitive rodent and non-rodent toxicology studies. In addition, a repeat-administration phototoxicity study was performed to determine the effects of oral odevixibat on the eyes and skin of pigmented rats (ICH S10).

Odevixibat was also evaluated in a standard battery of Good Laboratory Practice-compliant safety pharmacology studies (ICH 7A, ICH 7B), including an in vitro human ether a-go-go related gene hERG assay and in vivo cardiovascular (CV), renal, GI, respiratory and CNS studies. These studies, as well as several other safety studies, are summarised in Table 8.

Table 8 Key Safety findings from non-clinical studies and relevance to human usage

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
Toxicity	
Single dose toxicity studies with oral administration of odevixibat were performed in mice and rats. At the maximum dose administered (2000 mg/kg) there were no clinical signs other than loose stool and transient loss of body weight in mice, while no findings were seen in rats. The acute toxicity was low. In repeat-dose oral toxicity studies, odevixibat administered to mice was well tolerated for 14 days up to the highest dosage tested (1500 mg/kg/day) and for 13 weeks by female mice at all dose levels (10, 100, or 300 mg/kg/day) and by males given 10 or 100 mg/kg/day. Mortality and reduced food consumption and body weight gain were noted at 300 mg/kg/day in male mice; the cause of death could not be established. The no-observed-adverse-effect level (NOAEL) was defined as 100 mg/kg/day for males and 300 mg/kg/day for females. In rats, odevixibat was well tolerated when dosed orally once daily for up to 28 days at 0, 20, 200 and 2000 mg/kg/day. The low dosage of 20 mg/kg/day (27 µmol/kg/day) odevixibat was considered to be the NOAEL. Persistent soft faeces and reduced body weight gain were noted at 2000 mg/kg/day. Mild mucosal hypertrophy in the large intestine (caecum and colon) and diffuse basophilia of the parotid salivary glands at ≥200 mg/kg were reversible and of uncertain toxicological significance. In a 26-week study in rats with daily oral dosing at 0,10, 100 and 300 mg/kg/day, there were no adverse effects and no treatment-related macro- or microscopic pathology findings. The NOAEL was 300 mg/kg/day in the 26-week study. In dogs, odevixibat was orally dosed for 14 days at doses 0, 30, 300 and 1000 mg/kg/day, for 13 weeks at doses of 0, 3, 30 and 300 mg/kg/day (1000-fold over intended clinical dose) and for 39 weeks at doses up to 150 mg/kg/day. The compound was well tolerated with mainly pharmacologically related findings, such as sporadic soft loose stools and decreased cholesterol levels. The NOAEL in the 13-week study was 300 mg/kg/day and 150 mg/kg/day in the 39-week study. Odevixibat was given to marmosets at a dose of 250 mg/kg for 7 days. The only findings were fluid/soft faeces and weight reduction. Chronic effects on organ systems are detailed under Carcinogenicity.	In the clinical development programme, most common types of drug-related treatment-emergent adverse events (TEAE) were gastrointestinal (GI) disorders. The most commonly reported adverse drug reactions in patients with PFIC and ALGS were gastrointestinal disorders, primarily mild to moderate reports of diarrhoea. Diarrhoea can lead to dehydration and electrolyte imbalance. In odevixibat clinical trials, treatment interruption and dehydration were associated with adverse events of diarrhoea. Based on this and supportive evidence from non-clinical data, clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance is considered as an important identified risk.
Genetic Toxicology Studies	
A core battery of GLP studies was conducted to assess the genotoxic potential of odevixibat. Odevixibat was not mutagenic in vitro in the Ames *Salmonella typhimurium* and *Escherichia coli* reverse mutation test or in the mouse lymphoma L5178Y $tk^{\pm}$ cellular assay, including testing with and without metabolic activation. Odevixibat was also negative in an in vivo micronucleus study in the rat showing no	The data from these studies indicated no genotoxic risk for odevixibat use in humans.

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
damage to chromosomes or cell division apparatus up to the regulatory maximum oral dosage of 2000 mg/kg.	
Carcinogenicity	
In the 2-year GLP carcinogenicity studies administration of 0 (water), 0 (vehicle), or odevixibat at doses of 10, 30, or 100 mg/kg/day to mice and rats did not affect survival or increase the formation of neoplastic lesions at dosages up to 100 mg/kg/day. In the mouse, there was an increase in the incidence of non-neoplastic lesions in the gallbladder (cystic hyperplasia and basophilic amorphous contents) for both sexes at all dosage levels. In the rat, slight decrements in plasma cholesterol and lipoproteins in males (all dosages) were considered non-adverse. In rats an increased incidence of non-neoplastic lesions in the kidney (hyperplasia of the urothelium and associated mineralisation in the pelvis) and liver (biliary hyperplasia and basophilic foci of alteration) were also noted. In both species, these non-adverse changes showed no signs of advancing towards a proliferative lesion and were, therefore, not considered to represent a neoplastic risk. The NOAEL for tumour formation in both mouse and rat studies was 100 mg/kg/day, the highest dosage administered to both males and females.	The data from these studies suggest that odevixibat is unlikely to be carcinogenic in humans.
Reproductive and Developmental Studies	
For reproductive and developmental toxicity, a comprehensive battery of range-finding and pivotal fertility and early embryonic development, embryo-foetal development, prenatal and postnatal development (including maternal function), were performed in the rat. Range-finding and pivotal embryo-foetal development studies, including TK, were also performed in the rabbit as the second species. There were no effects on the male and female reproductive organs or fertility in reproductive toxicity studies. During the embryo-foetal toxicity study in rats (0, 100, 300, or 1000 mg/kg/day), there was a higher incidence of slight transient ossification delays of several bones and thick ribs in foetuses from the 1000 mg/kg/day group when compared with concurrent and historical control data. Evaluation of rat foetuses was performed on gestational day (GD) 20 rather than the more commonly used day of GD 21. Ossification of the foetal skeleton in rats shows a higher degree of variability on GD 20 versus GD 21. These findings were considered to be a transient change in normal development, not representative of a permanent structural change and are therefore considered not to be toxicologically significant. The embryo-foetal NOAEL in the rat was 1000 mg/kg/day. This represents a 133-fold (total area under the curve (AUC)) therapeutic margin of safety, relative to the maximum recommended human dosage (MRHD) of 0.12 mg/kg/day (7.2 mg/day), assuming a total maximum plasma concentration (AUC) of 5.99 ng/mL*h in humans. In pregnant New Zealand White rabbits, early delivery/abortion was observed in two rabbits receiving odevixibat during the period of foetal organogenesis at an exposure multiple of ≥1.6 of the anticipated clinical exposure (based on total plasma odevixibat AUC_{0-24}). Reductions in maternal body weight and food consumption were noted in all dose groups (transient at the exposure multiple 0.5 of the anticipated dose). Starting from the exposure multiple of 0.5 of the clinical human exposure, (based on total plasma odevixibat AUC_{0-24}), seven foetuses (1.3% of all foetuses from odevixibat exposed does) in all dose groups were found to have CV defects (i.e. ventricular diverticulum, small ventricle and dilated aortic arch). No such malformations were	In the clinical development programme, there was no exposure of odevixibat in patients with PFIC or in patients with ALGS who were pregnant or became pregnant while receiving odevixibat. Animal studies have shown reproductive toxicity, therefore odevixibat is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether odevixibat or its metabolites are excreted in human milk. A risk to breastfed newborns/infants cannot be excluded.

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
observed when odevixibat was administered to pregnant rats. Because of the findings in rabbits, an effect of odevixibat on CV development cannot be excluded. Odevixibat had no effect on the reproductive performance, fertility, embryo-foetal development, or prenatal/postnatal development studies in rats at the exposure multiple of 133 of the anticipated clinical exposure (based on total plasma odevixibat AUC_{0-24}), including juveniles (exposure multiple of ≥58-fold of the total anticipated human exposure). In a pre- and postnatal study, there were no adverse effects observed in the pregnant rat (F0 females) at doses up to 1000 mg/kg/day. Furthermore, no adverse effects were seen on subsequent postnatal development or reproductive performance of the F1 offspring. A NOAEL of 1000 mg/kg for maternal (F0) toxicity and the postnatal development and subsequent reproductive performance of the first generation (F1) offspring was also established for rats. There is insufficient information on the excretion of odevixibat in animal milk. The presence of odevixibat in breast milk was not measured in animal studies. Exposure was demonstrated in the pups of lactating dams in the pre- and post-natal developmental toxicity study with rats (3.2-52.1% of the odevixibat plasma concentration of the lactating dams). It is therefore possible that odevixibat is present in breast milk.	
Juvenile Toxicology Studies	
The potential toxicity of odevixibat in the juvenile rat was studied in an initial exploratory study. Pups were dosed by daily oral gavage with odevixibat at dosages of 0, 10, 100 and 300 mg/kg/day from postnatal day (PND) 14 to PND 29. In the subsequent pivotal study, odevixibat was administered at dosages of 0, 10, 30 and 100 mg/kg/day from PND 14 (preweaning) to PND 63 (adult), followed by a 1-month recovery period. In both studies the plasma exposure of odevixibat following a single dosage (i.e. on PND 14 before weaning) was higher than after weaning. This was attributed to the known differences in drug handling between juvenile and adult rodents and reflected the immaturity of the GI system on PND 14. Odevixibat was generally well tolerated; however, in the exploratory study in juvenile rats, administration of 300 mg/kg/day odevixibat caused dosage-limiting focal hepatic toxicity (hepatocyte necrosis/apoptosis). Since there was no recovery period in the exploratory study, it is unknown if this lesion is reversible. Assessment of clinical pathology parameters was not included in the design of the non-GLP study; however, no change in clinical pathology parameters, including hepatic indices, was noted in the GLP study. The NOAEL in both studies was 100 mg/kg/day. Following a single administration on PND 14 (preweaning) of the 100 mg/kg/day dosage in the pivotal study, the total therapeutic margin of safety (AUC) was 700- and 1000-fold relative to the human MRHD for males and female rats, respectively. On the last day of dosing (Day 63; similar to human adulthood) the (free) therapeutic margin of safety in male and female rats was 10- and 4-fold, respectively, relative to the human MRHD. Odevixibat was well tolerated by juvenile animals (≤100 mg/kg/day).	Considering the paediatric indication, the safety profile of odevixibat in juvenile animals has been assessed. The target organ of toxicity (the liver) in the juvenile animals appears similar to that of humans. In the PFIC and ALGS studies, an independent expert panel conducted an adjudication of all events meeting the criteria for suspected drug-induced liver injury (DILI). Review of the data indicated that most excursions in hepatic biochemical parameters were considered related to the patient's underlying disease. One event occurring in a patient with PFIC and one event in a patient with ALGS was assessed as related to study drug by the DSMB. A population PK model showed that age did not explain variability in PK parameters for odevixibat. Simulations for patients <1 year of age demonstrated that no dose adjustment was needed for this population.
Safety Pharmacology	
Cardiovascular (CV) effects	
The effect of odevixibat on the human ether-a-go-go-related gene (hERG) potassium channel was evaluated. Odevixibat had no effect	Patients with PFIC do not have cardiac co-morbidities as part of their

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
on the hERG potassium channel at the tested concentration (1 µmol/L (740.9 µg/L)). In a GLP CV telemetry study, odevixibat administered at single doses of 1, 10 and 100 µmol/kg (0.741, 7.41, or 74.09 mg/kg) by the oral route did not induce any significant changes in arterial blood pressure and heart rate during a 24-hour period of measurement after dosing in conscious normotensive rats. Odevixibat administered by the intravenous route at 3 increasing doses (0.001, 0.01 and 0.1 µmol/kg [0.741, 7.41, or 74.09 µg/kg]) did not cause any effect on CV function and electrocardiogram (ECG) morphology in anaesthetised dogs. No effect on ECG parameters was noted in the 13-week (0, 3, 30 and 300 mg/kg/day) and 39-week (0, 3, 30 and 150 mg/kg/day) toxicity studies in dogs following oral odevixibat administration.	underlying disease. Patients with ALGS can present with cardiac abnormalities. Odevixibat is considered to have a very low potential for affecting or prolonging cardiac repolarisation or affecting other electrocardiographic parameters, heart rate, or blood pressure.
Overt central and peripheral effects	
In GLP safety pharmacology studies performed in conscious rats, odevixibat did not affect behaviour, spontaneous locomotor activity, motor coordination, or body temperature at doses 1 to 100 µmol/kg (0.741 to 74.09 mg/kg). No CNS effects were noted in single- and repeat-administration toxicity studies for up to 13 weeks (mouse), 26 weeks (rat), 39 weeks (dog) and 7 days (marmoset).	Odevixibat had no effect on CNS function.
Respiratory effects	
In a GLP safety pharmacology study, there were no treatment-related effects in rats on respiratory parameters (respiratory rate; peak inspiratory and peak expiratory flows; inspiration and expiration times; airway resistance; tidal volume; and minute volume) following single oral doses of 1-100 µmol/kg (0.741 – 74.09 mg/kg). Respiratory effects were not noted in single- and repeat-administration toxicity studies for up to 13 weeks (mouse), 26 weeks (rat), 39 weeks (dog) and 7 days (marmoset).	Odevixibat had no effect on respiratory function.
Renal effects	
Odevixibat did not significantly modify urine output, urinary pH, electrolyte balance and glomerular filtration rate in rats with a saline overload at single doses of 1-100 µmol/kg (0.741 – 74.09 mg/kg). Following oral administration of [14C] odevixibat (4 mg/kg) to rats, excretion in urine accounted for approximately 0.07% of the administered dose. Odevixibat had no effect upon renal uptake transporters (Organic anion transporter (OAT) 1, OAT 3 and Organic cation transporter (OCT) 2), and renal multidrug and toxin extrusion (MATE)1 and MATE2 proteins at clinically efficacious concentrations. Hyperplasia of the urothelium and associated mineralisation in the renal pelvis were only seen in the rat carcinogenicity study (≥10 mg/kg/day), were of late onset, not adverse and without neoplastic risk.	Patients with PFIC do not have renal co-morbidities as part of their underlying disease. Patients with ALGS can present with clinical manifestations affecting the kidney. The impact of renal impairment is expected to be small due to low systemic exposure and the fact that odevixibat is not excreted in the urine.
Gastrointestinal effects	
Odevixibat has been shown to be a highly selective inhibitor of the human IBAT with an IC50 of 0.13 nmol/L when the transporter was recombinantly expressed in human embryonic kidney 293 cells in vitro. Odevixibat (0.625 µmol/kg [0.463 mg/kg]) had a significant inhibitory (up to 86%) effect (ED50 of 0.073 µmol/kg (0.054 mg/kg)) on intestinal bile acid absorption following a single oral administration	In phase I studies in healthy adult volunteers, diarrhoea with associated abdominal pain was the most common GI-related event reported with odevixibat treatment; reports were mild to moderate in severity and

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
in ApoE knockout mice in vivo; with a 28% inhibition of bile acid salt absorption being seen at 10 hours post-administration. Low bioavailability of odevixibat in rats, following administration of pharmacologically efficacious oral dosages, indicated odevixibat would predominantly be excreted unchanged in faeces, without being absorbed from the GI tract. In fact, following intracolonic treatment with cholestyramine suspension in dogs, oral odevixibat (30 mg/kg, Days 1 and 4) normalised faecal consistency and defecation incidence relative to placebo controls. In addition, single administration of odevixibat (≤100 µmol/kg (≤74.09 mg/kg)) had no effect on intestinal length or transit time (assessed via charcoal propulsion) in male rats. Following oral administration, the GI tract was the primary target organ of toxicity in adult animals (mouse, rat and dog). Diarrhoea/soft faeces was the primary clinical sign and typically reversed during the drug-free recovery. Reduced faecal output was noted in pregnant rabbit does across all dosing groups and was consistent with reduced food consumption. In summary, odevixibat normalised faecal consistency and defecation incidence after intracolonic cholestyramine treatment in dogs, while showing periodic diarrhoea/soft faeces across all toxicology species during the dosing period. Except for gravid rabbits, faecal changes did not correlate well with reduced food consumption.	transient (Studies A4250-001, A4250-004, A4250-007, A4250-013 and A4250-022). Diarrhoea was the most common GI TEAE among patients participating in the PFIC and ALGS clinical studies.
Other toxicity-related information or data	
Hepatic Effects:	
In the mouse Mdr2 -/- model of cholestasis, odevixibat (0.01% w/w in the feed for 4 weeks) was shown to provide beneficial reductions in liver/body weight ratios, serum markers of liver damage (ALT, AST, ALP) and cholestasis. Odevixibat metabolites seen in human hepatocytes in vitro were observed in hepatocytes from at least 1 other species. While 3 oxidative metabolites were characterised in hepatocytes during the in vitro study, only parent drug was observed in human faeces. Minimal signs of reversible, non-adverse liver toxicity were noted in rats (adult and juvenile). In the dose range-finding study in juvenile rats, administration of 300 mg/kg/day odevixibat caused minimal to slight focal hepatic toxicity (hepatocyte necrosis/apoptosis). Although no recovery period occurred in the range-finding study, these lesions were not noted in the subsequent GLP study in juvenile rats up to the highest dosage tested, 100 mg/kg/day. In the oral carcinogenicity study in rats, biliary hyperplasia/ basophilic foci of alteration were noted at 100 mg/kg/day; these lesions were of late onset, not adverse and without neoplastic risk. Although slight hepatic effects were noted following odevixibat exposure, they were considered non-adverse in the context of repeated administrations.	Odevixibat poses a low hepatotoxicity risk. During the phase III PFIC clinical development programme, improvements in liver function tests were noted in odevixibat-treated versus placebo-treated patients. Most excursions in ALT, AST and total bilirubin were considered related to the underlying disease and/or intermittent concomitant viral illnesses, which are common to paediatric patients. In the ALGS clinical studies, an early increase in mean transaminase levels was observed during treatment with odevixibat to week 4. No clinically significant increase occurred over the next 20 weeks. Mean changes in total bilirubin from baseline varied around zero through week 24 and little change in bilirubin was noted over longer term treatment. A systematic review of the data indicated that the changes were not indicative of DILI.

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
Drug interactions	
Pharmacodynamic drug interactions Non-clinical studies on pharmacodynamic drug interactions have not been conducted. **Pharmacokinetic (PK) drug interactions** Odevixibat has been studied in vitro to determine interactions with cytochrome P450 (CYP) enzymes and drug transporters. Odevixibat does not inhibit heterologously expressed human CYP1A2 or CYP2C19 in vitro up to 30 µmol/L. The IC_{50} for CYP2C9 was 1.2 µmol/L, CYP2D6 16.0 µmol/L and CYP3A4 16.2 µmol/L. A subsequent in vitro study with human liver microsomes evaluated the time- and metabolism-dependent inhibition potential of human CYP450 isoforms by odevixibat. Odevixibat was a direct inhibitor of CYP1A2, CYP2B6 and CYP3A4/5 (as measured by midazolam 1´-hydroxylation and testosterone 6β-hydroxylation) with IC_{50} values of 13 nmol/L, 5.6 nmol/L, 4.0 µM (midazolam as probe) and 14 µM (testosterone as probe), respectively. IC_{50} values for CYP2C8, CYP2C9, CYP2C19, or CYP2D6 were above 100 nmol/L, the highest concentration tested. Odevixibat was a metabolism-dependent inhibitor of both CYP3A4/5 activities examined with lower IC_{50} values after pre-incubation. The metabolism-dependent inhibition of CYP3A4/5 (as measured for midazolam 1′-hydroxylation) was irreversible and the associated K_I and k_{inact} values were determined to be 7.6 µM and 0.06 min-1, respectively. No in vivo studies have been performed. The induction potential of several important CYP450 enzymes was studied in liver samples taken from male and female rats given oral doses of odevixibat at 1000 mg/kg/day for 7 days. The enzyme levels were measured by enzyme-linked immunosorbent assay (ELISA) and the results showed that this treatment did not result in any biologically significant induction of the studied CYP isoforms: CYP1A1/2, 2B1/2, 3A2, or 4A1. In addition, the induction potential of odevixibat on CYP1A2, CYP2B6, or CYP3A4 isoforms has also been investigated in cultured, cryopreserved human hepatocytes from 3 donor livers. The cultured human hepatocytes were pre-treated with odevixibat (0.002-20 µmol/L), positive, or negative controls for 3 days. Odevixibat did not induce CYP1A2, CYP2B6, or CYP3A4 mRNA levels. The induction potential of odevixibat on CYP isoforms is low. Odevixibat was an inhibitor of OATP1B1, OATP1B3 and OAT3 with IC_{50} values of 0.308, 0.697 and 0.504 µM, respectively. Approximately 50% inhibition of OAT1 and OCT2 was observed at the highest concentration tested, indicating approximate IC_{50} values of 1 µM for these transporters. Odevixibat caused less than 50% inhibition of P-gp (as determined using Caco-2 and MDCKII-P-gp cells), breast cancer resistance protein, multidrug and toxin extrusion protein 1, or multidrug and toxin extrusion protein 2, kidney-specific under the conditions examined (up to 30 µM). Odevixibat was a substrate of P-gp but not breast cancer resistance protein.	To determine whether the in vitro drug interaction results extended to the clinical setting, a clinical trial was performed to determine the effect of odevixibat on the PK of midazolam, a sensitive CYP3A4 substrate and the effect of the P-gp inhibitor, itraconazole, on the PK of odevixibat in heathy adult subjects. In this clinical study, concomitant use of odevixibat decreased the area under the curve of oral midazolam by 30% and 1-OH-midazolam exposure by less than 20%, which is not considered clinically relevant. The study showed that inhibition of the P-gp transport system by itraconazole mildly increased systemic exposure of odevixibat. However, given the low systemic concentration and exposure of odevixibat, this interaction was not considered to be clinically significant. It was hypothesised that odevixibat could impair the absorption of lipophilic oral contraceptives by increasing bile acid excretion via the faeces. A DDI study (A4250-022) was conducted to assess the potential effect of dosing with odevixibat on the PK of the combination oral contraceptive EE (0.03 mg)/LVN (0.15 mg). Administration of odevixibat 3 mg QD for 6 days, prior to co-administration with a single dose of EE/LVN, had no clinically relevant effect on exposure of the lipophilic combination oral contraceptive.
Phototoxicity	
Odevixibat was found to absorb light within the range of natural light (290-700 nm) and had molar extinction coefficients greater than 1000 L/mol/cm within this range. In a repeat-administration phototoxicity study performed to determine the effects of oral odevixibat on the eyes and skin of pigmented rats, there was no	Phototoxicity is not expected with odevixibat.

Key Safety Findings (from Non-clinical studies)	Relevance to Human Usage
evidence of ocular (confirmed by histopathology) or cutaneous phototoxicity after repeat oral administration of odevixibat at dosages up to 1000 mg/kg/day that were followed approximately 4 hours later by a single exposure to ultraviolet radiation /Sham ultraviolet radiation.	
Oral Absorption Characteristics	
Oral odevixibat showed relatively rapid but low absorption across all species, with little evidence of accumulation over time in both adult and juvenile animals. Following oral administration, odevixibat was rapidly absorbed with a T_{max} of generally 1 to 4 hours in the non-clinical species evaluated (mouse, rat, rabbit, dog and marmoset). In toxicology studies with mouse, rat and dog, exposures (both area under the curve and C_{max}) generally increased in an approximately dose-proportional or less than dose-proportional manner. Exposures remained consistent with repeated dosing (≤3-fold accumulation), thereby demonstrating little evidence for a change in clearance with time. The single dose PK properties of odevixibat in the marmoset showed a moderate clearance value of 12% of liver blood flow [72]. In general, gravid rats and rabbits displayed similar TK as did their non-gravid counterparts. Likewise, odevixibat exposure in juvenile animals generally paralleled exposure trends seen in adults. Presumably, due to the known differences in drug handling between juvenile and adult rodents and to the relative immaturity of GI system function on postnatal day (PND) 4 (neonate) and PND 20 (approximate start of weaning), systemic exposures were appreciably higher compared to PND 63 (approximates human adulthood). Therefore, with the exception of potentially higher drug levels in neonate and pre-weanling animals, odevixibat exposure trends behaved similarly in adult and juvenile animals.	A population PK model showed that age did not explain variability in PK parameters for odevixibat. Simulations for patients <1 year of age demonstrated that no dose adjustment was needed for this population.

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the curve; C_{max}=maximum plasma concentration; CNS=central nervous system; CV=cardiovascular; CYP=cytochrome P450; DDI=drug-drug interaction; ECG=electrocardiogram; EE=ethinyl estradiol; GD=gestational day; GI=Gastrointestinal; GLP=Good Laboratory Practice; IC_{50}=half maximal inhibitory concentration; hERG=human ether-a-go-go-related gene; LVN=levonorgestrel; MRHD=maximum recommended human dosage; NOAEL=no-observed-adverse-effect level; OAT=organic anion transporter; OCT=organic cation transporter 2; PFIC=progressive familial intrahepatic cholestasis; P-gp=P-glycoprotein; PK=pharmacokinetic; PND=postnatal day; QD=once daily; SOC=system organ class; TK=toxicokinetic

The safety concerns for odevixibat from the non-clinical development programme include:

- Important identified risks:
  - Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance.
- Important potential risks:
  - Hepatotoxicity
  - Embryo-foetal toxicity

Part II: Module SIII – Clinical Trial Exposure

As of 15 July 2024, a clinical development programme with odevixibat has been conducted in 185 healthy subjects and approximately 441 patients, including 125 patients with PFIC, 58 patients with ALGS and 258 patients with other cholestatic liver diseases. In addition, nine subjects were enrolled in an investigator-initiated trial (IIT; 4250PBCpruritus) for the indication of primary biliary cirrhosis. Of the 635 subjects participating in clinical studies, approximately 507 subjects have received odevixibat.

An inventory of ongoing and completed clinical trials as of 15 July 2024 is presented in Table 9 below:

Table 9 Inventory of Ongoing and Completed Odevixibat Clinical Trials as of 15 July 2024

Study	Study Phase and High-Level Objective	Study Status
A4250-001	Phase I single and multiple ascending-dose administration in healthy subjects.	Completed
A4250-007	Phase I absorption, distribution, metabolism and excretion (ADME) in healthy subjects.	Completed
A4250-003	Phase II efficacy and safety in paediatric patients with cholestatic liver disease.	Completed
A4250PBCpruritus	Investigator Initiated Trial for the treatment of cholestatic pruritus in primary biliary cholangitis.	Completed
A4250-004	Phase I food interaction in healthy subjects.	Completed
A4250-013	Phase I drug-drug interaction in healthy subjects.	Completed
A4250-022	Phase I open-label study, interaction of multiple dose odevixibat on pharmacokinetics of single dose combined oral contraceptive steroids in healthy females.	Completed
A4250-005	Phase III efficacy and safety in patients with PFIC 1 and PFIC 2.	Completed
A4250-008	Phase III open-label extension, long- term efficacy and safety in patients with PFIC.	Completed [a]
A4250-011	Phase III efficacy and safety in patients with biliary atresia.	Ongoing
A4250-012	Phase III study efficacy and safety in patients with ALGS.	Completed
A4250-015	Phase III open-label extension, long-term efficacy and safety in patients with ALGS.	Completed [a]
A4250-016	Phase III open-label extension, long-term efficacy and safety in patients with biliary atresia.	Ongoing
A4250-022	Phase I drug-drug interaction in healthy subjects.	Completed
A4250-J001	Phase I multiple dose administration in healthy Japanese subjects.	Completed
A4250-J005	Phase III open-label study to evaluate efficacy and safety of odevixibat (A4250) in Japanese patients with PFIC.	Ongoing
A4250-J012	Phase III open-label study to evaluate efficacy and safety of odevixibat (A4250) in Japanese patients with ALGS.	Ongoing

a An optional/voluntary extension period to the 72-week study is ongoing.

Abbreviations: ADME=absorption, distribution, metabolism and excretion; ALGS=Alagille syndrome; PBC=primary biliary cholangitis; PFIC=progressive familial intrahepatic cholestasis

The primary data in patients with PFIC was derived from the phase III, randomised, double-blind, placebo-controlled 24-week study, A4250-005, conducted in 62 paediatric patients with a genetically confirmed diagnosis of PFIC1 or PFIC2 and from pooled data as of 15 February 2024 from 121 patients who received odevixibat across two phase III studies, A4250-005 and A4250-008. Study A4250-008 is a long-term extension study which allows continued treatment with odevixibat 120 µg/kg/day for patients from Study A4250-005 and for the treatment of an additional cohort of patients who were not eligible for or were enrolled after closure of Study A4250-005. Additional long-term safety data are available through the data cutoff of 15 February 2024 for 116 patients who were enrolled in Study A4250-008.

The primary data in patients with ALGS are derived from the phase III, multicenter, multinational, randomised, double-blind, placebo-controlled Study A4250-012, conducted in 52 patients with a genetically confirmed diagnosis of ALGS. The study evaluated the administration of 120 µg/kg/day or placebo (randomisation 2:1) for 24 weeks. Following this study, patients were invited to participate in a 72-week open-label extension study (A4250-015) in which all patients received odevixibat 120 µg/kg/day. Data from studies A4250-012 and A4250-015 with a data cutoff of 07 February 2024 were pooled to provide an overall evaluation of the safety profile of longer-term treatment with odevixibat.

In total, 183 patients have received at least one dose of odevixibat in phase II (A4250-003) and phase III studies (A4250-005, A4250-008, A4250-012, and A4250-015) in patients with PFIC and ALGS as of the PSUR DLP 15 July 2024. Study A4250-003 included patients with biliary atresia (3) and other cholestatic diseases (2). Cumulative exposure for all clinical trials is presented in Table 10. For patients with PFIC, exposure by age group, gender and race is presented in Table 11. For patients with ALGS, exposure by age group, gender and race is presented in Table 12.

Table 10 Cumulative Subject Exposure from all Clinical Trials

Treatment	Number of Subjects [a]
Drug	507 [b]
Placebo	128
Total	635

a Data as of data lock point, 15 July 2024.

b Estimated cumulative exposure calculated using randomisation ratio for subjects currently enrolled in a blinded Study A4250-011.

Table 11 Cumulative Subject Exposure to Investigational Drug by Age, Sex and Race for Indication (PFIC)

	Number of Subjects		
Age group	Male	Female	Total
PFIC[a]			
<2 years	28	16	44
2 to < 6 years	20	18	38
6 to < 12 years	8	12	20
12 to < 18 years	9	7	16
18 to < 65 years	4	3	7
≥65 years	0	0	0
Race [a]	**Number of Subjects**		
White	101		
Black or African American	4		
Asian	3		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Other	10		
Unknown*	7		
Not reported	0		

	Number of Subjects		
Age group	Male	Female	Total
Total	**125**		

a Pooled PFIC patients from two phase III studies (A4250-005/A4250-008) with 10 PFIC patient from phase II Study A4250-003.

Three subjects from Study A4250-003 are subsequently enrolled in Study A4250-005 (then rolled over to Study A4250-008) are counted once, and the age is carried from Study A4250-003. Fifty-six subjects enrolled in Study A4250-005 and rolled over in Study A4250-008 are counted once, and the age is carried from Study A4250-005. Three subjects enrolled in Study A4250-005 and re-enrolled in Study A4250-008 as a new subject are counted once, and the age is carried from Study A4250-005. One subject rolled over to Study A4250-008 and re-enrolled in Study A4250-008 as a new subject is counted once, and the age is carried from Study A4250-005.

*Race information was not collected in Study A4250-003. The race information of three subjects from Study A4250-003 that subsequently enrolled in Study A4250-005 (then rolled over to Study A4250-008) is carried from Study A4250-008.

Table 12 Cumulative Subject Exposure to Investigational Drug by Age, Sex and Race for Indication (ALGS)

	Number of Subjects		
Age group	Male	Female	Total
ALGS[a]			
<2 years	5	5	10
2 to < 6 years	9	9	18
6 to < 12 years	14	9	23
12 to < 18 years	4	3	7
18 to < 65 years	0	0	0
≥65 years	0	0	0
Race [a]	**Number of Subjects**		
White	43		
Black or African American	4		
Asian	3		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Other	2		
Unknown*	6		
Not reported	0		
Total	58		

a Pooling studies A4250-012 and A4250-015 and six Alagille syndrome patients from Study A4250-003.

Age is calculated based on date of birth and date of informed consent in Study A4250-012. Fifty subjects enrolled in Study A4250-012 and rolled over in Study A4250-015 are counted once.

*Race information was not collected in Study A4250-003.

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

The main exclusion criteria for the pivotal clinical studies (A4250-005 and A4250-012) are detailed below. Exclusion criteria applied to ensure standardisation of the study population (rather than safety-related exclusion criteria) are not presented.

The exclusion criteria applicable to both the PFIC and ALGS clinical studies are presented together in Table 13. Exclusion criteria applicable to only the PFIC or ALGS clinical studies are presented separately in Table 14 and Table 15, respectively.

Table 13 Important Exclusion Criteria applicable to both PFIC and ALGS clinical studies

Exclusion Criteria	Reason for exclusion	Missing Information (Yes/No)	Rationale
Patients with a past medical history or ongoing presence of any	These patients were excluded to ensure that	No	The mechanism of action of odevixibat requires that the

Exclusion Criteria	Reason for exclusion	Missing Information (Yes/No)	Rationale
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; administration of bile acid or lipid binding resins and medications that slow GI motility.	the safety and efficacy data was not confounded by a condition which would affect the efficacy of odevixibat, which acts locally in the GI tract.		enterohepatic circulation of bile acids and bile salt transport into biliary canaliculi is preserved. Conditions, medications or surgical procedures that impair either gastrointestinal motility, or enterohepatic circulation of bile acids, including bile salt transport to biliary canaliculi have the potential to reduce the efficacy of odevixibat.
Patients with past medical history or ongoing chronic (i.e. >3 months) diarrhoea requiring intravenous fluid or nutritional intervention for treatment of the diarrhoea and/or its sequelae.	Patients with chronic diarrhoea were excluded to ensure that safety data was not confounded by a pre-existing condition.	No	Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance is considered an important identified risk for patients treated with odevixibat.
Patients with a confirmed past diagnosis of infection with human immunodeficiency virus or other present and active, clinically significant, acute, or chronic infection, or past medical history of any major episode of infection requiring hospitalisation or treatment with parenteral anti-infective treatment within 4 weeks of treatment start (Study Day 1) or completion of oral anti-infective treatment within 2 weeks prior to start of Screening Period. Per protocols, erythromycin was the only oral anti-infective excluded during the studies due to its known prokinetic effect or known effect of increasing gastrointestinal motility.	These patients were excluded to ensure that the safety and efficacy data was not confounded by a pre-existing condition. The anti-infective erythromycin is an excluded concomitant medicine in Phase III odevixibat study protocols for PFIC and ALGS because of its known prokinetic effect or impact on gut motility.	No	There is no reason to anticipate drug-drug interactions with oral or parenteral anti-infective treatments and odevixibat. Erythromycin was the only oral anti-infective excluded during the study due to its known prokinetic effect or known effect of increasing gastrointestinal motility.
Patients with suspected or confirmed cancers except for basal cell carcinoma and non-liver cancers treated at least 5 years prior to screening with no evidence of recurrence.	These patients were excluded to ensure that the safety and efficacy data was not confounded by a pre-existing condition, i.e. AEs related to either cancer or chemotherapy.	No	There is no reason to expect any issues with target population attributable to odevixibat use.
Patients with a past medical history of chronic kidney disease with an impaired renal function and a glomerular filtration rate <70 mL/min/1.73 m^2.	These patients were excluded to ensure that the safety and efficacy data was not	No	Patients with PFIC do not have renal co-morbidities as part of their underlying disease. Patients with ALGS can present with clinical

Exclusion Criteria	Reason for exclusion	Missing Information (Yes/No)	Rationale
	confounded by a pre-existing condition.		manifestations affecting the kidney. The impact of renal impairment is expected to be small due to low systemic exposure and the fact that odevixibat is not excreted in the urine.
Patients with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of screening period.	Patients with such surgical history were excluded to ensure that the efficacy data was not confounded.	No	There is no reason to expect any issues with target population attributable to odevixibat use.
Patients who have had a liver transplant or a liver transplant is planned within 6 months of randomisation.	Patients with a liver transplant or planned liver transplant were excluded to ensure that the efficacy data was not confounded.	No	There is no reason to expect any issues with target population attributable to odevixibat use.
Patients who have decompensated liver disease, coagulopathy, history or presence of clinically significant ascites, variceal haemorrhage and/or encephalopathy.	These patients were excluded to ensure that the safety and efficacy data was not confounded.	No	There is no reason to expect any issues with target population attributable to odevixibat use.
International normalized ratio >1.4. Patients treated with intravenous Vitamin K and with INR is ≤1.4 following treatment were eligible for study enrolment.	Patients with elevated INR were excluded to ensure safety and efficacy data was not confounded. INR was measured routinely during the study and change from baseline INR was an exploratory efficacy endpoint.	No	There is no reason to expect any issues with patients with an INR >1.4.
Patients with serum ALT >10 × upper limit of normal (ULN) at Screening; Serum ALT >15 × ULN at any time point during the last 6 months unless an alternate aetiology was confirmed for the elevation.	These patients were excluded to ensure that the safety and efficacy data was not confounded.	No	There is no reason to expect any issues with patients with elevated ALT and AST.
Patients with uncontrolled, recalcitrant pruritic condition other than PFIC or ALGS.	These patients were excluded to ensure that efficacy data was not confounded by a pre-existing condition.	No	There is no reason to expect any issues with this population attributable to odevixibat use.
Patients who are pregnant or lactating or who are planning to become pregnant within 24 weeks of randomisation.	Excluded for ethical reasons, as safety has not been established in pregnant or	Yes	Not applicable.

Exclusion Criteria	Reason for exclusion	Missing Information (Yes/No)	Rationale
	breastfeeding women. One non-clinical reproductive and developmental study (out of two) conducted with odevixibat identified possible teratogenic potential on cardiac development.		
Sexually active males and females who are not using a reliable contraceptive method with <1% failure rate.	Excluded for ethical reasons, as safety has not been established in pregnant or breastfeeding women. It is not known if odevixibat is present in semen. One non-clinical reproductive and developmental study (out of two) conducted with odevixibat identified possible teratogenic potential on cardiac development.	Yes	Not applicable.
Patients with a past medical history of alcohol or substance abuse.	These patients were excluded to ensure that the safety and efficacy data was not confounded.	No	There is no reason to expect any issues with this population attributable to odevixibat use.
Patients who have had exposure to an investigational drug, biologic agent or medical device within 30 days or five half-lives of the study agent prior to screening (whichever is longer).	These patients were excluded to ensure that efficacy data was not confounded.	No	There is no reason to expect any issues with this population attributable to odevixibat use.

Abbreviations: AE=adverse event; ALGS=Alagille syndrome; ALT=alanine aminotransferase; PFIC=progressive familial intrahepatic cholestasis; GI=gastrointestinal; INR=international normalized ratio; ULN=upper limit of normal

Table 14 Important Exclusion Criteria specific to the PFIC clinical studies

Exclusion Criteria	Reason for exclusion	Missing Information (Yes/No)	Rationale
Patients with PFIC who have known pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein.	Patients with PFIC with complete absence of the BSEP protein (BSEP3 genotype) were excluded as these patients do not transport bile acids from the hepatocytes into the intestine. In the absence of bile acids in the terminal ileum, blockade of IBAT would have no effect on the enterohepatic circulation and, as such, these patients are not expected to benefit from odevixibat therapy.	No	Patients with PFIC who have complete absence of functioning BSEP protein are not included in the target population to be treated with odevixibat.
Patients with past medical history or ongoing presence of other types of liver disease including but not limited to the following: Patients with biliary atresia of any kind, benign recurrent intrahepatic cholestasis, suspected or proven liver cancer or metastasis to the liver and non-PFIC related aetiology of cholestasis.	These patients were excluded to ensure that the safety and efficacy data was not confounded by a pre-existing condition unrelated to the indication.	No	There is no reason to expect any issues with target population to be treated with odevixibat.
Patients with a total bilirubin >10 × ULN at screening.	These patients were excluded to ensure that the safety and efficacy data was not confounded.	No	There is no reason to expect any issues with this population attributable to odevixibat use.
Patients who have been previously treated with an IBAT inhibitor whose pruritus has not responded to treatment.	These patients were excluded to ensure that efficacy data was not confounded.	No	There is no reason to expect any issues with this population attributable to odevixibat use.

Abbreviations: BSEP=bile salt export pump; IBAT=ileal bile acid transporter; PFIC=progressive familial intrahepatic cholestasis; ULN=upper limit of normal

Table 15 Important Exclusion Criteria specific to the ALGS clinical studies

Exclusion Criteria	Reason for exclusion	Missing Information (Yes/No)	Rationale
Patients with past medical history or ongoing presence of other types of liver disease Patients with past medical history or ongoing presence of other types of liver disease, including, but not limited to PFIC, biliary atresia, benign recurrent intrahepatic cholestasis and suspected or proved liver cancer or metastasis to the liver.	These patients were excluded to ensure that the safety and efficacy data was not confounded by a pre-existing condition unrelated to the indication.	No	There is no reason to expect any issues with target population to be treated with odevixibat.
Patients with a total bilirubin >15 × ULN at screening.	These patients were excluded to ensure that the safety and efficacy data was not confounded.	No	There is no reason to expect any issues with this population attributable to odevixibat use.

Abbreviation: PFIC=progressive familial intrahepatic cholestasis; ULN=upper limit of normal

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare (frequency ≥1/10,000 to <1/1000) or very rare (frequency <1/10,000) adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 16 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme.
Elderly patients	There are no data on use of odevixibat in the elderly population as exposure is not anticipated in this patient population due to the nature of the disease.
Patients with relevant co-morbidities: Patients with hepatic impairment	PFIC: In the studies A4250-005 and A4250-008 pooled data from 121 patients in phase III studies, based on Child-Pugh classification, 77 patients (64.0%) had mild hepatic impairment and 44 (36.0%) had moderate hepatic impairment; no patients had severe impairment. In Study A4250-003, of the 10 patients with PFIC, nine (90%) had mild hepatic impairment and one (10%) had moderate hepatic impairment. By National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, most patients had mild hepatic dysfunction (34 patients, 40.5%), followed by moderate (23

Type of special population	Exposure
	patients, 27.4%) and severe hepatic dysfunction (20 patients, 23.8%) while seven had normal hepatic function. In Study A4250-003, of the 10 patients with PFIC, five (50%) had mild hepatic impairment, three (30%) had moderate hepatic impairment and two (20%) had severe hepatic impairment. ALGS: All patients in the studies A4250-012 and A4250-015 studies had some degree of hepatic impairment. In the pooled data from 52 patients in the ALGS phase III studies, based on Child-Pugh classification, 51 (98.1%) patients had moderate hepatic impairment and one (1.9%) patient had severe impairment; no patients had mild impairment. By National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, most patients had severe hepatic impairment (23 patients, 44%); followed by moderate (15 patients, 29%) and mild (14 patients, 27%).
Patients with renal impairment	PFIC: The majority of patients in the phase III studies had normal renal function. The mean (SD) estimated glomerular filtration rate (eGFR) of patients in the studies A4250-005 and A4250-008 pooled phase III group was 163.5 (±34.20) mL/min/1.73 m^2 (minimum eGFR 78.4 mL/min/1.73 m^2 and maximum 268.7 mL/min/1.73 m^2) calculated by modified Schwartz equation for patients <18 years old and based on the Modification of Diet in Renal Disease (MDRD) Study equation for patients ≥18 years old. The mean eGFR of patients with PFIC in Study A4250-003 was 144.50 (±30.91) mL/min/1.73 m^2 (minimum eGFR 98.7 mL/min/1.73 m^2 and maximum 187.8 mL/min/1.73 m^2). No data are available for patients with moderate to severe renal impairment or end-stage renal disease requiring haemodialysis. ALGS: Children with ALGS can present with renal defects at birth. The majority of patients in the ALGS phase III studies had normal renal function. The mean (SD) estimated glomerular filtration rate (eGFR) of patients in the studies A4250-012 and A4250-015 odevixibat pooled phase III group was 163.80 (±52.590) mL/min/1.7m^2. (minimum eGRF 80.5 mL/min/1.73 m^2 and maximum 316.4 mL/min/1.73 m^2) calculated by modified Schwartz equation for patients <18 years old.
Patients with cardiovascular impairment	Baseline cardiac function was normal in patients participating in the PFIC phase III studies. Children with ALGS can present with cardiac defects at birth. In the ALGS phase III study, cardiac abnormalities presenting in ≥5% of patients overall included pulmonary artery stenosis in 21 patients (40.4%), cardiac murmur in seven patients (14.0%), atrial septal defect in six patients (12.0%), ventricular septal defect in five patients (9.6%) and aortic stenosis in four patients (7.7%).
Immunocompromised patients	The following patients were not included in the development programme: Confirmed past diagnosis of infection with human immunodeficiency virus Other present and active, clinically significant, acute, or chronic infections

Type of special population	Exposure
	Past medical history of any major episode of infection within 4 weeks of Study Day 1.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with end-stage liver disease were excluded by the criterion that excluded patients with ALT>10 × ULN, INR >1.4 and total bilirubin >10 × ULN (PFIC) or >15 × ULN (ALGS).
Population with relevant different ethnic origin	The ethnicity of subjects exposed to odevixibat in the phase II and phase III clinical studies is presented in Table 11 and Table 12.
Subpopulations carrying relevant genetic polymorphisms	Not applicable to the odevixibat clinical development programme.

Abbreviations: ALGS=Alagille syndrome; ALT=alanine aminotransferase; eGFR=estimated glomerular filtration rate; INR=international normalized ratio; MDRD=modification of diet in renal disease; NCI-ODWG=National Cancer Institute Organ Dysfunction Working Group; PFIC=progressive familial intrahepatic cholestasis; ULN=upper limit of normal

Part II: Module SV – Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1. Method used to calculate exposure

Estimation of exposure was based on drug unit volume supplied.

SV.1.2. Exposure

Cumulatively, since the first launch of odevixibat up to 15 July 2024, a total of 737 patients were exposed (363 in the European Economic Area [EEA] and 374 in non-EEA countries); see Table 17. The estimated numbers include patients who transitioned from Study A4250-008 study, managed access programmes and expanded access programmes (EAPs), named patient programme onto commercial drug, as well as patients in countries with marketing authorisation approval where drug was not commercially launched, but supplied on a foreign pack exemption.

Table 17: Estimated Cumulative Exposure to Odevixibat from Post-authorisation Experience

Country	Cumulative Patients Exposed to Odevixibat[a]
EEA	
EEA Total	**363**
Non-EEA	
Non-EEA Total	**374**

Abbreviations: ALGS=Alagille syndrome; EEA=European Economic Area; PFIC=Progressive familial intrahepatic cholestasis

a Includes total number of unique patients.

Part II: Module SVI – Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Radiolabelled odevixibat biodistribution studies in animals concluded that odevixibat does not significantly penetrate the brain. Furthermore, non-clinical studies with odevixibat demonstrated that there were no observed behavioural changes suggestive of abuse potential. Based on the mechanistic, biodistribution, non-clinical and clinical data, the applicant believes that odevixibat does not have CNS activity that is either associated with abuse potential or which could be used in the facilitation of assault.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The primary evaluation of the safety and tolerability profile of odevixibat is based on integration and presentation of data from the two phase III studies A4250-005 and A4250-008 conducted in paediatric patients with PFIC and the phase II Study A4250-003 conducted in paediatric patients with cholestatic liver disease, including PFIC. Pooled phase III Group refers to pooling of studies A4250-005 and A4250-008 data in this document.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

The following are not classified as important risks based on the nature of the adverse reactions observed in PFIC and ALGS clinical trials and are expected to be easily managed during the use of odevixibat:

Abdominal pain

Hepatomegaly

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Hypersensitivity reactions

  Anaphylactic reactions have not been observed in the clinical development programme, but it is recognised that life-threatening anaphylactic reactions may occur with some medications. Within the Summary of Product Characteristics (SmPC), the administration of odevixibat is contraindicated in individuals with a known hypersensitivity to the active substance(s) or any of the excipients.

Known risks that do not impact the risk-benefit profile:

Drug interactions

Odevixibat has been studied in vitro to determine interactions with Cytochrome P (CYP) enzymes and drug transporters. Based on kinetic parameters, odevixibat is a weak, time-dependent inhibitor of CYP3A4/5 in vitro. An oral dosage of odevixibat may increase exposure to co-administered CYP3A substrates by transient inhibition of intestinal CYP3A. A clinical drug-drug interaction (DDI) Study A4250-013 with oral midazolam, a sensitive CYP3A4/5 substrate, was conducted to evaluate the potential impact of odevixibat as a perpetrator of CYP3A4/5 mediated drug interactions in the intestine. However, no clinically relevant drug-drug interactions with odevixibat and midazolam were identified. The Study A4250-013 evaluated the potential impact of a strong P-glycoprotein (P-gp) inhibitor, itraconazole, on the PK of odevixibat (a substrate for P-gp). While inhibition of the P-gp transport system by itraconazole increased systemic exposure of odevixibat, given the low systemic concentration and exposure of odevixibat, this interaction was not clinically relevant. Given the lack of interactions with drug metabolising enzymes in vitro, the impact of inhibition or induction of metabolising enzymes in vivo is anticipated to be low.

There is currently insufficient evidence to justify the inclusion of drug interactions as an important risk of odevixibat.

New or worsening fat-soluble vitamin deficiency refractory to treatment

Patients with cholestatic liver disease, including patients with PFIC and patients with ALGS, are at risk for fat malabsorption resulting in weight and height below normal centiles and fat-soluble vitamin (A, D, E and K) deficiency. Deficiencies of fat-soluble vitamins can manifest clinically as night blindness (vitamin A), osteomalacia (vitamin D), increased oxidative cell stress (vitamin E) and haemorrhage (vitamin K) [38].

PFIC Clinical Trials: In the Study A4250-005, one patient treated with odevixibat 40 µg/kg/day experienced decreased levels of vitamin D; in the Study A4250-008, two patients treated with odevixibat 120 µg/kg/day had decreased vitamin D levels reported as adverse reactions. Adverse events of new or worsening fat-soluble vitamin deficiencies were selected as AEs of interest; however, no new events or events of worsening of fat-soluble vitamin deficiency refractory to vitamin supplementation occurred in patients treated with odevixibat.

ALGS Clinical Trials:

Review of changes from baseline in vitamins A, D and E and INR levels over time indicated small mean changes to the last assessment on study in both the pooled phase III group with generally similar results observed in the odevixibat and placebo groups in Study A4250-012. Review of changes from baseline in levels of vitamins A, D, E and INR over time indicated small mean changes to the last assessment on study in both the pooled phase III group and in the odevixibat and placebo groups in Study A4250-012. These mean changes over time were not considered clinically meaningful. Some patients experienced treatment-emergent shifts to low in vitamins D and E and some had clinical meaningful shifts in INR to >1.2. A clear association with odevixibat treatment was not established, as other factors, including potential laboratory/sample processing errors, low baseline levels and lack of adequate vitamin supplementation may have contributed to these shifts.

There is currently insufficient evidence to justify the inclusion of new or worsening fat-soluble vitamin deficiency refractory to treatment as an important risk of odevixibat.

<u>Other reasons for considering the risks not important:</u>

Off-label use

Odevixibat is intended for the treatment of PFIC and other cholestatic diseases such as ALGS and biliary atresia (BA). It is possible that odevixibat could be used off-label to treat same cholestatic liver diseases. However, the safety profile of the product is not anticipated to be different in these patient populations. Therefore, there is currently insufficient evidence to justify the inclusion of off-label use as an important risk for odevixibat.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The risks included in the safety concerns as important identified risks, important potential risks or missing information are discussed in this section.

Important Identified Risks:

The identified risks considered important for inclusion as a safety concern in the RMP are presented in Table 18.

Table 18 Important Identified Risks

Important identified risk	Risk-benefit impact
Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	Drug-related diarrhoea was observed in non-clinical studies with mice, rats and dogs. Diarrhoea is the most likely dose-limiting effects of odevixibat as indicated by preliminary toxicity studies. Diarrhoea is considered to be anticipated due to the pharmacological action of odevixibat (i.e. IBAT inhibition), with a resultant increased bile acid load to the colon and subsequent increases in faecal water

Important identified risk	Risk-benefit impact
	content and colonic motility, which may explain the observed non-clinical findings and the observed gastrointestinal tolerability in humans. In patients with cholestatic liver diseases, (PFIC ALGS), malabsorption and diarrhoea are known co-morbidities. Patients with PFIC1 are known to have presence of extrahepatic manifestations in the form of persistent diarrhoea. In the PFIC phase III Study A4250-005, the most commonly reported drug-related TEAE was diarrhoea associated with odevixibat use. Adverse events of diarrhoea assessed as related to odevixibat were mild to moderate in severity; most were of short duration and did not require treatment intervention. One patient randomised to 120 µg/kg/day withdrew from the study as a result of diarrhoea. Clinically significant or severe diarrhoea, defined as any of the following, diarrhoea that persists for 21 or more days without any other aetiology based on medical review of other concurrent AEs for possible other causes of the diarrhoea or diagnostic testing (e.g. viral infections); reported by the investigator as severe in intensity or reported as an SAE due to the requirement for hospitalisation or as an important medical event; or diarrhoea with concurrent dehydration requiring treatment with oral or intravenous rehydration and/or other treatment intervention, was observed in nine (7%) patients in the pooled PFIC phase III group, including two during Study A4250-005 (one patient each in the 40 and 120 µg/kg/day groups). The incidence of diarrhoea in the odevixibat-treated population in Study A4250-005 compared to the placebo-treated population was 31% versus 5%. In the long-term extension study A4250-008, as of the 15 February 2024 data cutoff, diarrhoea has been reported in 24% of the patients; seven patients were reported meeting the definition of clinically significant diarrhoea have been received. Of seven patients with clinically significant diarrhoea, two patients were reported to have serious diarrhoea events during treatment. Similarly, in the ALGS phase III Study A4250-012, diarrhoea was the most commonly reported drug-related TEAE associated with odevixibat use. Drug-related diarrhoea was reported in nine (17.0%) patients. Adverse events of diarrhoea assessed as related to odevixibat were mostly Grade 1 or 2 in intensity; most were of short duration and did not require treatment intervention. Clinically significant diarrhoea, defined as diarrhoea that persisted for 3 or more days without any other aetiology, severe in intensity or reported as an SAE, or diarrhoea with concurrent dehydration requiring treatment with oral or intravenous rehydration or other treatment intervention, was observed in 31.0% of patients in the pooled ALGS phase III group, primarily due to a duration of ≥3 days. The incidence of diarrhoea in the

Important identified risk	Risk-benefit impact
	odevixibat-treated population in the pivotal ALGS phase III Study A4250-012 compared to the placebo-treated population was 28.6% versus 5.9%. No patients experienced the serious adverse event of diarrhoea. In the long-term extension Study A4250-015, as of the 07 February 2024 data cutoff, diarrhoea has been reported in 26.0% of the patients; 12 (24.0%) of 50 patients were reported meeting the criteria for clinically significant diarrhoea (six patients each in study and placebo group). Most cases met the criteria for clinical significance based on duration ≥3 days; median duration in the study was 4.5 days. All events of diarrhoea were Grade 1 or 2 in intensity and, in general, were not dose limiting and did not require treatment. One patient had diarrhoea with concurrent dehydration requiring treatment with oral or intravenous rehydration and/or other treatment intervention. Two patients had clinically significant diarrhoea that led to treatment interruption. None of the clinically significant diarrhoea events led to treatment discontinuation. No patients experienced the serious adverse event of diarrhoea. Given the potential consequences of diarrhoea, patients may require immediate medical intervention. Clinically significant or severe diarrhoea will be monitored as an important identified risk for odevixibat.

Abbreviations: AE=adverse event; ALGS=Alagille syndrome; IBAT=ileal bile acid transporter; PFIC=progressive familial intrahepatic cholestasis; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Important Potential Risks:

The potential risks considered important for inclusion as a safety concern in the RMP are presented in Table 19.

Table 19 Important Potential Risks

Important potential risk	Risk-benefit impact
Hepatotoxicity	In patients with pre-existing liver dysfunction due to underlying disease participating in the PFIC phase III trials, odevixibat did not lead to a worsening of liver dysfunction in odevixibat-treated patients compared to placebo-treated patients. Overall, 63 (52%) of the 121 patients in the pooled phase III group had TEAEs in the SMQ of Drug-related Hepatic Disorders. The most common TEAEs reported in the SMQ were blood bilirubin increased (30 patients, 25%), INR increased (19 patients, 16%), ALT increased (17 patients, 14%), AST increased (11 patients, 9%), and hepatomegaly and jaundice (seven patients each, 6%). Most of these events were mild to moderate in intensity. Data for 69 (57%) of 121 patients in the pooled phase III group underwent review and adjudication by the DSMB and the majority of patients underwent adjudication for laboratory data that met the criteria for suspected DILI (60 of 121 patients, 50%). Cases were most commonly brought to the DSMB for elevations in total bilirubin

Important potential risk	Risk-benefit impact
	levels. There were no reported cases of liver decompensation events and out of 69, only one event from Study A4250-008 was adjudicated as related to odevixibat. In the ALGS phase III studies, A4250-012 and A4250-015, no liver decompensation events were reported, nor were there any reports of new or worsening portal hypertension, hepatic cirrhosis, ascites, hepatic encephalopathy or variceal haemorrhage. In the pivotal study A4250-012, the overall incidence of liver-related events in the SMQs of *Drug-related hepatic disorders – comprehensive search (narrow and broad), Biliary tract disorders, Gallbladder-related disorders and Gallstone-related disorders,* was similar in the odevixibat and placebo groups (11.0% and 12.0% respectively). A detailed review of changes from baseline to Week 24 for transaminase levels of the pooled data from studies A4250-012 and A4250-015, showed larger mean increases for ALT and AST for patients who received odevixibat compared with patients who received placebo; for total bilirubin, the changes from baseline were similar in the odevixibat and placebo groups. The increases in ALT and AST were observed by Week 4 and then plateaued through Week 24. Further review of the data based on modified evaluation of drug-induced serious hepatotoxicity (eDISH) plots indicated that none of the patients in either treatment group had ALT elevations >3 × baseline concurrent with total bilirubin >2 × baseline. Three patients, including two in the odevixibat group and one in the placebo group had ALT and AST elevations >3 × baseline without concurrent elevations in total bilirubin >2 × baseline. Review of the pertinent clinical and diagnostic information for the two patients treated with odevixibat suggests that the occurrence of DILI was unlikely. In toxicology studies in juvenile rats, dose-limiting focal hepatic toxicities (hepatocyte necrosis/apoptosis) were observed. Mottled/discoloured livers were noted in gravid rabbits that had been administered odevixibat. The cause for increased hepatic toxicity in juvenile and gravid rats following odevixibat administration is not known. Based on the clinical significance of hepatotoxicity and the potential for development of serious/life-threatening events, hepatotoxicity, including cases of suspected cases of DILI, liver decompensation and hepatotoxicity is considered as an important potential risk for odevixibat.
Embryo-foetal toxicity	An uncertain relationship of exposure to odevixibat and foetal cardiovascular events in the rabbit embryo-foetal development study was found. Starting from the exposure multiple of 1.1 of the clinical human exposure (based on total plasma odevixibat $AUC_{0\text{-}24}$), seven foetuses (1.3% of all foetuses from odevixibat exposed does) in all dose groups were found to have

Important potential risk	Risk-benefit impact
	cardiovascular defects (i.e. ventricular diverticulum, small ventricle and dilated aortic arch). No such malformations were observed when odevixibat was administered to pregnant rats. Because of the findings in rabbits, an effect of odevixibat on cardiovascular development cannot be excluded, hence, embryo-foetal toxicity is considered an important potential risk for odevixibat.
Interactions with fat-soluble drugs	Patients with PFIC and patients with ALGS have fat malabsorption and fat-soluble vitamin deficiencies (vitamins A, D, E and K) caused by their underlying disease. Odevixibat acts locally in the gut and has the potential to interact with fat-soluble drugs. Given this hypothesis, a DDI Study A4250-022 was conducted to assess the potential effect of dosing with odevixibat on the PK of the combination oral contraceptive, which found no clinically relevant effect on exposure of the lipophilic combination oral contraceptive. From the fat-soluble vitamin level perspective, 30% of 121 patients in the pooled phase III group had TEAEs of fat-soluble vitamin deficiency. The most commonly reported events were related to INR increased/vitamin K deficiency and vitamin D deficiency. All TEAEs of fat-soluble vitamin deficiency were mild to moderate in intensity and none of the TEAEs were serious or led to study drug discontinuation. Given that treatment with odevixibat results in decreased recirculation of bile acids, the absorption of fat-soluble vitamins and lipophilic drugs may be affected; therefore, interactions with fat-soluble drugs is considered an important potential risk. In the pooled ALGS group, from the fat-soluble vitamin level perspective, 17 (33%) of the 52 patients in the pooled phase III group had TEAEs of fat-soluble vitamin deficiency including vitamin D deficiency and blood 25-hydroxycholecalciferol decreased (eight patients; 15%), INR increased and vitamin K deficiency (seven patients; 14%), vitamin E deficiency/decreased (six patients; 12%), vitamin A decreased one patient; 2%) and hypovitaminosis (one patient; 2%). For one patient, the TEAE of INR increased was Grade 3 in severity and reported as an SAE (Study A4250-012), this event was considered by the Investigator to be drug-related. All other TEAEs related to fat-soluble vitamin deficiency were Grade 1 or 2 in severity and non-serious. No dose modifications or discontinuations of treatment were reported for vitamin deficiency TEAEs. In Study A4250-012, the incidence of TEAEs related to levels of fat-soluble vitamins was 9% and 18% in the odevixibat and placebo groups, respectively A review of fat-soluble vitamin deficiency levels over time showed small mean changes in fat-soluble vitamin levels and INR with some variability in the data over time during treatment with odevixibat. At baseline, most of the 52 patients in the pooled phase III group had vitamin A and E levels above the normal range. For

Important potential risk	Risk-benefit impact
	vitamin D and INR, most patients had baseline levels within normal range. Mean changes from baseline to Week 72 for the pooled phase III group were -0.368 (0.5859) µmol/L (-0.105 [0.1679] mg/L) for vitamin A, 4.9 (27.01) nmol/L (1.9 [10.77] ng/mL) for vitamin D, -4.45 (11.902) µmol/L (-1.92 [5.126] mg/L) for vitamin E, and 0.04 (0.171) for INR.

Abbreviations: ALGS=Alagille syndrome; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the curve; DDI=drug-drug interaction; DILI=drug-induced liver inquiry; DSMB=Data and Safety Monitoring Board; GGT=gamma-glutamyl transferase; INR=International normalized ratio; PFIC=progressive familial intrahepatic cholestasis; PK=pharmacokinetics; TEAE=treatment emergent adverse event

Missing information:

The missing information considered important for inclusion as a safety concern in the RMP are presented in Table 20.

Table 20 Missing Information

Missing information	Risk-benefit impact
Long-term use	There are limited long-term data in the odevixibat clinical studies. In Study A4250-008, a 72-week open-label extension study that is ongoing with allowance for an optional extended treatment period, median duration of exposure to odevixibat was 98.9 weeks and ranged from 4.3 to 248.7 weeks (4.8 years). Eighty-five (73.0%) patients had received ≥72 weeks of treatment and 61 patients (53.0%) had received ≥96 weeks of treatment as of 15 February 2024. There least 20 patients in study A4250-008 who have been exposed to odevixibat for 4 years. In the pooled ALGS phase III group, as of the data cutoff 07 February 2024, overall, 48 (87.0%) of 52 patients had received treatment with odevixibat for >72 weeks and 32 (62%) patients received odevixibat for >96 weeks. Total patient-years of exposure to odevixibat as of the data cutoff date was 92.3 years in the pooled phase III group. Odevixibat was overall well tolerated in patients with PFIC treated for at least 72 weeks and in patients with ALGS treated for 72 weeks or longer. Further evaluation is required to determine whether there are any risks associated with cumulative or long-term exposure.
Use during pregnancy and use in breastfeeding women	There are no clinical data on the use of odevixibat in pregnant or breastfeeding women. In pregnant New Zealand White rabbits, early delivery/abortion was observed in two rabbits receiving odevixibat during the period of foetal organogenesis at an exposure multiple of ≥1.6% of the anticipated clinical exposure (based on total plasma odevixibat AUC_{0-24}). Reductions in maternal body weight and food consumption were noted in all dose groups (transient at the exposure multiple 0.5 of the anticipated dose). Starting from the exposure multiple of 0.5 of the clinical human exposure, (based on total plasma odevixibat

Missing information	Risk-benefit impact
	AUC_{0-24}), seven foetuses (1.3% of all foetuses from odevixibat exposed does) in all dose groups were found to have cardiovascular defects (i.e. ventricular diverticulum, small ventricle and dilated aortic arch). These findings were not found in the pregnant rats. Additionally, it is unknown whether odevixibat or its metabolites are excreted in human milk. There is insufficient information on the excretion of odevixibat in animal milk. The presence of odevixibat in breast milk was not measured in animal studies. Exposure was demonstrated in the pups of lactating dams in the pre- and post-natal developmental toxicity study with rats. It is therefore possible that odevixibat is present in breast milk. A risk to the newborns/infants cannot be excluded. The SmPC notes that a decision should be made whether to discontinue breastfeeding or to discontinue/abstain from odevixibat therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother. As this patient population has not been studied, the safety of odevixibat is unknown; therefore, use in pregnant/breastfeeding women is considered missing information.

Abbreviation: ALGS=Alagille syndromes; AUC=Area under the curve; PFIC=progressive familial intrahepatic cholestasis

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Table 21 Important Identified Risks: Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance

Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	
Potential mechanisms:	IBAT inhibition results in increased bile acid load to the colon with consequential increase in faecal water content and increased colonic motility.
Evidence source(s) and strength of evidence:	Diarrhoea related to odevixibat treatment was observed in patients with PFIC and patients with ALGS in the clinical studies. Adverse events of diarrhoea assessed as related to odevixibat were mostly mild to moderate in severity, self-limiting and manageable by dose modifications. Diarrhoea is the most commonly reported adverse reaction for investigational drugs of the same class, e.g. volixibat, maralixibat and elobixibat. Study discontinuations in studies of the same drug class were reported due to TEAEs of diarrhoea. In the PFIC pivotal study A4250-005, one patient in the 120 µg/kg/day group discontinued treatment due to an event of clinically significant diarrhoea and experienced an SAE of acute dehydration (severe) requiring hospitalisation. In the long-term extension study A4250-008, as of the 15 February 2024 data cutoff, two patients had discontinued treatment due to diarrhoea. No patients in the ALGS phase III studies A4250-012 and A4250-015 discontinued treatment due to diarrhoea. Drug-related diarrhoea was observed in non-clinical studies with mice, rats and dogs. Diarrhoea is the most likely dose-limiting effects of odevixibat as indicated by preliminary toxicity studies.
Characterisation of the risk:	Diarrhoea (limited to the MedDRA Preferred Term of diarrhoea) was one of the most common TEAEs in patients treated with odevixibat, occurring in 36

Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	
	(29.8%) of 121 patients in the pooled PFIC phase III group as of the 15 February 2024 data cutoff and in 15 (28.8%) of the 52 patients in the pooled ALGS phase III group. No TEAE of diarrhoea occurred in patients with PFIC in Study A4250-003; one TEAE of diarrhoea occurred in a patient with ALGS in Study A4250-003. One TEAE of diarrhoea, concurrent with rotavirus infection, occurring in a patient with ALGS in Study A4250-015, met seriousness criteria. In Study A4250-005, events of diarrhoea occurred in 39% and 21% of patients in the 40 and 120 µg/kg/day groups, respectively and in 10% of patients in the placebo group. The exposure-adjusted incidence rate (EAIR) for the preferred term of diarrhoea did not indicate an increase in incidence with longer term exposure to odevixibat with an incidence per patient year (PPY) of 0.2 in the pooled phase III group and 1.2 and 0.6 events PPY for the 40 and 120 µg/kg/day groups, respectively, during treatment in Study A4250-005. The 95% confidence interval (CI) on the difference in the EAIR with placebo for diarrhoea included 0 for the comparison of the pooled phase III group and the 120 µg/kg/day group but was above 0 for the 40 µg/kg/day group for the rate reported in Study A4250-005. In Study A4250-012, events of diarrhoea occurred in 28.6% of patients receiving odevixibat and 5.9% of patients receiving placebo. Similar to patients in the PFIC pivotal trial, EAIR for the preferred term of diarrhoea did not indicate an increase in incidence with longer term exposure to odevixibat with 0.31 events PPY in the pooled phase III group and 0.76 PPY during odevixibat treatment in Study A4250-012. In the pooled ALGS phase III group, events of diarrhoea and faeces soft occurred in 19 (37%) patients. Adverse events of diarrhoea assessed as related to odevixibat in the PFIC and ALGS clinical studies were mostly mild to moderate in severity, of short duration and did not require treatment intervention. Very few patients required interruption of odevixibat due to diarrhoea and most of those patients were eligible for reintroduction of odevixibat after a drug holiday and remained on odevixibat. As noted above, one patient in the PFIC pivotal Study A4250-005 randomised to 120 µg/kg/day and two patients in the long-term extension study A4250-008 withdrew from the study as a result of diarrhoea. In the PFIC pooled phase III group, nine patients met the criteria for clinically significant diarrhoea, including two patients during the Study A4250-005 (one patient each in the 40 µg/kg/day and 120 µg/kg/day groups) and seven patients during Study A4250-008. Following the 15 February 2024 data cutoff, two patient in Study A4250-008 experienced SAEs of diarrhoea that were assessed as treatment related and medically important event. No treatment was administered for the events of diarrhoea. For one patient, the diarrhoea slowly decreased after stopping the study drug and eventually resolved five months after discontinuation of study drug. The patient withdrew from study due to the SAE of diarrhoea. For other event the study drug was interrupted due to the event. After the diarrhoea resolved, the study drug was restarted without further reports of diarrhoea. In the ALGS pooled phase III group, 16 (31.0%) patients experienced clinically significant diarrhoea, i.e. diarrhoea lasting >3 days or concurrent with dehydration. Two patients had clinically significant diarrhoea that led to treatment interruption. None of the clinically significant diarrhoea events led to treatment discontinuation. No patients experienced the serious adverse event of diarrhoea.
<u>Risk factors and risk groups:</u>	Malabsorption and diarrhoea are known co-morbidities in patients with PFIC and patients with ALGS. Moreover, patients with PFIC1 are known to show extrahepatic manifestations in the form of persistent diarrhoea. In general, other risk factors for diarrhoea include the following: • Malabsorption • Biliary diversion surgery (partial external or internal)

Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	
	• Paediatric population, more susceptible to viral infections and infections • Side effects following liver transplantation • Diet and food sensitivities • Other medications known to cause diarrhoea
Preventability:	Monitoring patients for signs and symptoms of diarrhoea during treatment will enable detection at an early stage. The risk to patients can be minimised by increasing healthcare professionals and patient/caregivers awareness of the risk of diarrhoea. Dose reduction or discontinuation of treatment in patients will also minimise this risk. Dose reduction or discontinuation of treatment in patients and ensuring adequate hydration (e.g. electrolyte solution) at early signs of diarrhoea will also minimise the risk.
Impact on the risk-benefit balance of the product	Clinically significant or severe events of diarrhoea may cause serious complications. In the pivotal clinical trial A4250-005, three events of clinically significant diarrhoea were reported and of these, one event led to acute dehydration requiring hospitalisation. In the long-term extension Study A4250-008, as of the 15 February 2024 data cutoff, seven events of clinically significant diarrhoea were reported. Of the seven events with clinically significant diarrhoea, two were reported as serious during treatment. In the ALGS Study A4250-012, clinically significant diarrhoea was reported in 6 (17.1%) patients who received odevixibat and one (5.9%) patient who received placebo; two patients in the odevixibat group also had clinically significant diarrhoea during treatment in Study A4250-015. In the ALGS pooled phase III group, 16 (31.0%) patients experienced clinically significant diarrhoea. Most cases met the criteria for clinically significant diarrhoea based on duration of ≥3 days. Informing patients, caregivers and healthcare professionals of this risk should increase their awareness and encourage patients/caregivers to notify their healthcare professional so that they can obtain appropriate treatment. Considering the significant co-morbidities associated with PFIC and ALGS, the benefits of treatment outweigh the risk of the potential impact of clinically significant or severe events of diarrhoea.
Public health impact:	Not yet established.

Abbreviations: AE=adverse event; ALGS=Alagille syndrome; CI=confidence interval; EAIR=exposure-adjusted incidence rate; IBAT=ileal bile acid transporter; MAH=marketing authorisation holder; MedDRA=Medical Dictionary for Regulatory Activities; PFIC=progressive familial intrahepatic cholestasis; PPY=per patient year; PT=preferred term; RMP=risk management plan; SAE=serious adverse event; SMQ=standardised MedDRA query; TEAE=treatment-emergent adverse event

Table 22 Important Potential Risks: Hepatotoxicity

Hepatotoxicity	
Potential mechanisms:	Unknown
Evidence source(s) and strength of evidence:	Minimal signs of reversible, non-adverse liver toxicity were noted in rats (adult and juvenile). The safety margin based on the NOAEL in the juvenile toxicity study is high (based on adult human PK data), about 300-fold, related to both dose and exposure. In the oral carcinogenicity study in mice and rats, gallbladder and biliary hyperplasia/ basophilic foci of alteration were of late onset, not adverse and without neoplastic risk. Although slight hepatic effects were noted following odevixibat exposure, they were considered non-adverse in the context of repeated administrations. In the PFIC clinical studies, improvements in liver function tests were noted in odevixibat-treated versus placebo-treated patients. In these clinical studies, most excursions in ALT, AST and total bilirubin were considered related to the underlying disease and/or intermittent concomitant viral illnesses which are common to paediatric patients. Overall, 52% of patients in the Pooled Phase 3

Hepatotoxicity	
	group had TEAEs in the SMQ of Drug-related Hepatic Disorders – comprehensive search (narrow and broad). The most common TEAEs reported in this SMQ were blood bilirubin increased, INR increased, ALT increased, AST increased, hepatomegaly and jaundice. The majority of TEAEs were mild to moderate in intensity. Eight patients (0.66%) reported severe events from this SMQ, three of which serious and considered by the investigator to be unrelated to study drug. In PFIC clinical trials, Drug Safety Monitoring Board (DSMB) was conducting an independent, adjudication of hepatic events. Overall, 69 (57%) of the 121 patients in the Pooled Phase 3 groups had an event that underwent adjudication by the DSMB. Based on review of 69 cases by the DSMB, all but one case (increased ALT and total bilirubin) were adjudicated as unrelated to study treatment. In the ALGS phase III studies, A4250-012 and A4250-015, no liver decompensation events were reported, nor were there any reports of new or worsening portal hypertension, hepatic cirrhosis, ascites, hepatic encephalopathy or variceal haemorrhage. In the pivotal study A4250-012, the overall incidence of liver-related events in the SMQs of *Drug-related hepatic disorders – comprehensive search (narrow and broad), Biliary tract disorders, Gallbladder-related disorders and Gallstone-related disorders*, was similar in the odevixibat and placebo groups (11% and 11%, respectively). A detailed review of changes from baseline to Week 24 for transaminase levels of the pooled data from studies A4250-012 and A4250-015, showed larger mean increases for ALT and AST for patients who received odevixibat compared with patients who received placebo; for total bilirubin, the changes from baseline were similar in the odevixibat and placebo groups. The increases in ALT and AST were observed by Week 4 and then plateaued through Week 24. Further review of the data based on modified evaluation of drug-induced serious hepatotoxicity (eDISH) plots indicated that none of the patients in either treatment group had ALT elevations > 3 × baseline concurrent with total bilirubin >2 × baseline. Three patients, including two in the odevixibat group and one in the placebo group had ALT and AST elevations >3 × baseline without concurrent elevations in total bilirubin >2 × baseline. Review of the pertinent clinical and diagnostic information for the two patients treated with odevixibat suggests that the occurrence of DILI was unlikely. No patient in either the PFIC or ALGS clinical trials experienced an event of liver decompensation, defined as: • INR elevation > 1.5 that is refractory to vitamin K administration • In a patient who developed portal hypertension and cirrhosis post-baseline, transition to decompensated cirrhosis evidenced by any of the following: • Presence of ascites • Hepatorenal syndrome • Portopulmonary hypertension • Hepatopulmonary syndrome • Variceal haemorrhage • Hepatic encephalopathy Generally, odevixibat poses a low hepatotoxicity risk. This important potential risk is based on the odevixibat clinical and non-clinical studies.
<u>Characterisation of the risk:</u>	Overall, data for 69 (57.0%) of 121 patients in the PFIC pooled phase III group underwent adjudication by the DSMB; the reason for adjudication was predominantly based on clinical safety laboratory parameters that met the criteria for suspected DILI as outlined in Section 10.2 of the protocol of Study A4250-005 and Study A4250-008, respectively, including increases in ALT and/or AST, increases in total bilirubin and/or increases in INR. There were no reported cases of liver decompensation events. Based on review by the DSMB, all but one case was adjudicated as due to the patient's underlying disease or other cause (acute gastroenteritis).

Hepatotoxicity	
	Overall, 63 (52%) of the 121 patients in the pooled phase III group had TEAEs in the SMQ of Drug-related Hepatic Disorders – Comprehensive Search. The incidence of these TEAEs during Study A4250-005 was 26% and 42%, respectively, in patients who received odevixibat 40 µg/kg/day and 120 µg/kg/day, respectively, and 15% in patients who received placebo. The most common TEAEs reported in the SMQ in the pooled phase III group were blood bilirubin increased (30 patients, 25%), INR increased (19 patients, 16%), ALT increased (17 patients, 14%), AST increased (11 patients, 9%), and hepatomegaly and jaundice (seven patients each, 6%). The majority of TEAEs in the Drug-related Hepatic Disorders SMQ in the pooled phase III group were mild to moderate in intensity. Eight (7%) of the 121 patients reported severe events, which included blood bilirubin increased and cholestasis in two patients each and one patient each with LFT increased, chronic hepatic failure, bile acids increased, ALT increased; and ALT, AST, and GGT increased. In the ALGS pooled phase III group, five patients had undergone review and adjudication by the Hepatic Safety Adjudication Committee (HSAC) for suspected DILI as of the data cutoff of 07 February 2024. One event of elevated INR was considered by the HSAC to be likely related to study medication, although the natural history of the disease with severe cholestasis could not be ruled out; the three remaining cases were considered related to the patients' underlying disease and unrelated to odevixibat. In general, the patients were asymptomatic and clinically stable at the time they met the criteria for liver monitoring. Except as noted above, all other cases in the PFIC and ALGS studies adjudicated by the expert committees were assessed as unrelated to treatment with the study drug.
Risk factors and risk groups:	Patients with cholestatic liver diseases suffer from the excess of bile acids in the liver, which are thought to play a contributory role in hepatic oxidative stress, inflammation resulting in tissue damage, fibrosis, cirrhosis and eventually end-stage liver disease. Other risk factors for hepatotoxicity include the following: • Malnourishment • Use of hepatotoxic drugs • Other underlying co-morbidities (e.g. viral infections or pre-existing liver disease)
Preventability:	Routine care for patients with PFIC and patients with ALGS include monitoring for worsening hepatic function, including evaluation of hepatic biochemical parameters, jaundice, portal hypertension, or liver decompensation; thus, it is expected that any significant worsening of liver function would be detected early on and allow for prompt treatment [17]. Hepatotoxicity can also be mitigated by avoidance of inappropriate use of hepatotoxic medications and use with caution in patients with other risk factors or co-morbidities.
Impact on the risk-benefit balance of the product	In the PFIC clinical studies A4250-005 and A4250-008 and in the ALGS clinical studies A4250-012 and A4250-015, no patient developed liver decompensation and the majority of the hepatic events were independently adjudicated as unrelated to the study drug. The benefit of odevixibat as an effective treatment of PFIC and cholestatic pruritus in ALGS is expected to outweigh any potential risk of hepatotoxicity.
Public health impact:	Not yet established.

Abbreviations: AE=adverse event; ALGS=Alagille syndrome; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DILI=drug-induced liver injury; DSMB=Data Safety Monitoring Board; GGT=gamma-glutamyl transferase; HSAC=hepatic safety adjudication committee; INR=international normalized ratio; MAH=marketing authorisation holder; MedDRA=Medical Dictionary for Regulatory Activities; NOAEL=no-observed-adverse-effect level; PFIC=progressive familial intrahepatic cholestasis; PK=pharmacokinetics; PT=preferred term; RMP=risk management plan; SMQ=standardised MedDRA query; SOP=standard operating procedure

Table 23 Important Potential Risks: Embryo-foetal toxicity

Embryo-foetal toxicity	
Potential mechanisms:	Unknown
Evidence source(s) and strength of evidence:	In an embryo-foetal development study in the rabbits, cardiovascular malformations in foetal rabbits were observed at low frequency (1.3%) at all dosages (10, 30, or 100 mg/kg/day) tested. No findings were observed in the corresponding rat study. Because of the findings in rabbits, an effect of odevixibat on cardiovascular development cannot be excluded.
Characterisation of the risk:	Pregnant women and women of childbearing potential not on adequate contraception were excluded from the clinical development programme. There was no exposure during pregnancy of either a female subject or the partner of a male subject during the clinical development programme. The risk of embryo-foetal toxicity is based solely on pre-clinical data.
Risk factors and risk groups:	Women of childbearing potential who take odevixibat.
Preventability:	The risk can be minimised through avoiding odevixibat exposure during pregnancy.
Impact on the risk-benefit balance of the product	The extent of exposure during pregnancy is likely to be minimal considering the patient population. However, in the event of exposure during pregnancy the impact on the foetus can be substantial as malformations may occur. Further characterisation of the risk in humans will be limited due to the anticipated limited exposure during pregnancy.
Public health impact:	Not yet established.

Abbreviations: AE=Adverse Event; MAH=marketing authorisation holder; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; RMP=risk management plan; SMQ=Standardised MedDRA Query

Table 24 Important Potential Risks: Interactions with fat-soluble drugs

Interactions with fat-soluble drugs	
Potential mechanisms:	Bile acids are essential to the absorption of fat-soluble vitamins and other lipophilic drugs. Patients with PFIC and patients with ALGS have low bile acid levels in the bile/duodenum. Odevixibat is expected to increase bile acid levels in the distal ileum and colon and as a result lowers bile acid levels in serum/plasma and in the liver. It is unknown how odevixibat will affect bile acid levels in bile and duodenum where vitamin absorption occurs. Patients with PFIC and patients with ALGS have difficulties in excreting bile acids from the liver and whether lowering hepatic bile acid levels will lead to further reductions in biliary/duodenal bile acid levels is unknown.
Evidence source(s) and strength of evidence:	This risk is related to the background disease pathology and not to odevixibat per se. Fat-soluble vitamin malabsorption has been reported in both the PFIC and ALGS patient population [3]. Clinical data to date in patients with PFIC treated with odevixibat for 72 weeks or longer and in patients with ALGS treated for 48 weeks or longer has not demonstrated any unwarranted effect on fat-soluble vitamin levels (Vitamin A, D, E) and INR.
Characterisation of the risk:	Due to decreased release of bile acids into the intestine and malabsorption, paediatric patients with PFIC and with ALGS with chronic cholestasis are at risk for fat-soluble vitamin deficiency that can occur despite supplementation. In pooled PFIC phase III data, 36 (30.0%) of 121 patients had treatment-emergent adverse events of fat-soluble vitamin deficiency with an overall incidence of 17%. The TEAEs of fat-soluble vitamin deficiency were mild to moderate in intensity and most events were assessed as unrelated to study drug. None of the TEAEs of fat-soluble vitamin deficiency were serious or led to study drug discontinuation. Six patients had TEAEs of vitamin D decreased or INR increased that were assessed as related to study drug, including three patients with vitamin D deficiency/decreased, two patients with INR increased, and one patient with both vitamin D and E deficiency. Three of the six patients received odevixibat 120 µg/kg/day during the Study A4250-005. All the events resolved and no patients required additional treatment. Review of the

Interactions with fat-soluble drugs	
	fat-soluble vitamin levels over time for these patients indicated that the levels overall remained stable or improved. As of 15 February 2024, data cutoff, four (3.0%) patients in the pooled phase III group met the criteria for fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation. Among the four patients, whom all received odevixibat 120 µg/kg/day after enrolling in Cohort 2 of Study A4250-008, two had refractory vitamin D deficiency with one of these patients also having refractory vitamin E deficiency, one had refractory vitamin E deficiency, and one patient had refractory vitamin K deficiency (elevation in INR). All events were nonserious and mild in intensity, and none led to discontinuation from treatment. In PFIC clinical studies over long-term treatment with odevixibat, mean (SD) changes from baseline in vitamin levels to Week 70 and to the last assessment on treatment showed small improvements for Vitamins D, A and E. For INR, small mean (SD) increases from baseline were noted to Week 70 and to the last assessment on treatment. For the INR based on shift analysis to high it was noted that 66 (73%) of 90 patients in the pooled phase III group with data available had a shift in INR to a level above the ULN. INR data for these patients were reviewed to evaluate clinically relevant increases from baseline specifically, an increase to an INR level >1.5 if baseline INR was in the normal range. Among the 66 patients with shifts from normal or low levels at baseline to high postbaseline INR levels, 14 patients had on-treatment INR levels >1.5. In 11 of the 14 patients, the INR levels improved during continued treatment with odevixibat and for three patients the shift was report at the last assessment at the time of the data cutoff; two of these patients remain on treatment as of the data cutoff and one had transitioned to commercial product. In the ALGS clinical studies, a review of changes from baseline in vitamins A, D and E and INR levels over time indicated small mean changes to the last assessment on study in both the pooled phase III group and in the odevixibat and placebo groups in Study A4250-012. These mean changes over time were not considered clinically meaningful. Some patients experienced treatment-emergent shifts to low in vitamins D and E and some had clinically meaningful shifts in INR to >1.2. A clear association with odevixibat treatment was not established, as other factors, including low baseline levels and lack of adequate vitamin supplementation may have contributed to these shifts. In order to further characterise the profile of odevixibat when used with fat-soluble drugs such as oral hormonal contraception, the MAH conducted an interaction study with odevixibat and an oral hormonal contraceptive as a post-authorisation commitment. As it was hypothesised that odevixibat could impair the absorption of lipophilic oral contraceptives by increasing bile acid excretion via the faeces, a DDI study (Study A4250-022) aimed to assess the potential effect of dosing with odevixibat on the PK of the combination oral contraceptive EE (0.03 mg)/LVN (0.15 mg) was conducted. Administration of odevixibat 3 mg QD for 6 days, prior to co-administration with a single dose of EE/LVN, had no clinically relevant effect on exposure of the lipophilic combination oral contraceptive.
<u>Risk factors and risk groups:</u>	Fat malabsorption and fat-soluble vitamin deficiencies are known co-morbidities in patients with PFIC and in patients with ALGS. No clinical DDI studies have been conducted with other lipophilic drugs. It cannot be excluded that the absorption of lipophilic drugs other than oral contraceptives is affected by odevixibat.
<u>Preventability:</u>	Routine monitoring of fat-soluble vitamins will enable detection and risk mitigation. The risk to patients can be minimised by increasing healthcare professionals and patients/caregivers' awareness of the potential risk of interactions with lipophilic drugs. Monitoring patients for adverse events related to fat-soluble vitamin deficiency, e.g. night blindness and rickets, can enable detection.

Interactions with fat-soluble drugs	
Impact on the risk-benefit balance of the product:	Impaired fat-soluble vitamin absorption can lead to impaired growth, vision, bone development, neurological problems and impaired blood clotting. Per standard clinical practice, monitoring of fat-soluble vitamin levels and monitoring for adverse events associated with vitamin deficiencies should enable patients to obtain appropriate treatment when necessary. Some of the more widely prescribed lipophilic drugs such as HMG-CoA reductase inhibitors (statins) and some beta blockers are not commonly prescribed in patients with PFIC as this patient population does not have cardiovascular co-morbidities as a result of their underlying disease. Considering the significant co-morbidities of PFIC and of ALGS, the benefits of treatment outweigh the risk of the potential impact of interactions with lipophilic drugs.
Public health impact:	Not yet established.

Abbreviations: AE=adverse event; ALGS=Alagille syndrome; DDI=drug-drug interaction; EE=ethinyl estradiol; HMG-CoA=3-hydroxy-3-methylglutaryl-coenzyme A; INR=international normalized ratio; LVN=levonorgestrel; MAH=marketing authorization holder; PFIC=progressive familial intrahepatic cholestasis; PK=pharmacokinetics; QD=once daily; RMP=risk management plan; TEAE=treatment-emergent adverse event

SVII.3.2. Presentation of the Missing Information

Table 25 Missing Information 1: Long-term use

Long term use	
Evidence source:	There are limited long-term data in the odevixibat clinical studies. In Study A4250-008, a 72-week open-label extension study in patients with PFIC, that is ongoing with an allowance for optional extended treatment, median duration of exposure to odevixibat was 98.9 weeks and ranged from 4.3 to 248.7 weeks (4.8 years). Eighty-five (73.0%) patients had received ≥72 weeks of treatment and 61 patients (53.0%) had received ≥ 96 weeks of treatment as of 15 February 2024. In the ALGS pooled phase III group, 48 (87.0%) patients had received treatment with odevixibat for >72 weeks and 32 (62%) patients had received odevixibat for >96 weeks of treatment as of 07 February 2024. Odevixibat was overall well tolerated in patients with PFIC treated for at least 72 weeks and in patients with ALGS treated for at least 48 weeks. At this time, it is unknown whether prolonged exposure to odevixibat will alter the risk-benefit profile of the drug. Population in need of further characterisation: Long-term safety in patients will continue to be evaluated in optional extension period of A4250-008/A4250-015 studies. Additionally, long-term safety will be further evaluated in post-marketing, non-interventional long-term registry-based studies for PFIC (A4250-019, ongoing) and ALGS (planned).

Abbreviations: ALGS=Alagille syndrome; PFIC=progressive familial intrahepatic cholestasis

Table 26 Missing Information 2: Use during pregnancy and use in breastfeeding women

Use during pregnancy and use in breastfeeding women	
Evidence source:	There are no available data regarding odevixibat use in pregnant or breastfeeding women. One non-clinical reproductive and developmental study (out of two) conducted with odevixibat identified a possible teratogenic potential on cardiac development. It is unknown whether odevixibat or its metabolites are excreted in human milk. There is insufficient information on the excretion of odevixibat in animal milk. The presence of odevixibat in breast milk was not measured in animal studies. Exposure was demonstrated in the pups of lactating dams in the pre- and post-natal developmental toxicity study with rats. It is therefore possible that odevixibat is present in breast milk.

Use during pregnancy and use in breastfeeding women	
	Population in need of further characterisation: Women who were pregnant or breastfeeding or women of childbearing potential not on adequate contraception were excluded from clinical trials with odevixibat. As this patient population has not been studied, the safety of odevixibat is unknown; therefore, use in women who are pregnant or breastfeeding is considered as missing information.

Part II: Module SVIII – Summary of the Safety Concerns

Table 27 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance
Important potential risks	• Hepatotoxicity • Embryo-foetal toxicity • Interactions with fat-soluble drugs
Missing information	• Long-term use • Use during pregnancy and use in breastfeeding women

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are presented below.

Specific adverse reaction follow-up questionnaires:

Ipsen does not propose to utilise event-specific follow-up questionnaires.

Other forms of routine pharmacovigilance activities:

Ipsen does not propose to utilise any other forms of routine pharmacovigilance activities.

III.2 Additional Pharmacovigilance Activities

The planned and ongoing additional pharmacovigilance activities are presented below:

The MAH is conducting a registry-based post-authorisation safety study (PASS), Study A4250-019, to collect safety information in patients with PFIC.

Additionally, the MAH has proposed a prospective registry-based post-authorisation safety study (PASS), to collect and assess long-term safety information on hepatotoxicity in patients with ALGS.

Registry-based safety study (A4250-019):

Study short name and title:

Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC

Rationale and study objectives:

Rationale

Additional safety data will provide conclusions on the long-term safety of odevixibat use in patients with ALGS. The objective of this registry-based study is to assess the long-term, real-world safety profile of odevixibat treatment in patients with PFIC compared to patients not receiving odevixibat (untreated control cohort).

Study objectives

- The overall objectives of this registry-based study are:

- To evaluate the impact of odevixibat treatment on the occurrence of severe diarrhoea
- To evaluate the impact of odevixibat treatment on clinical manifestations of fat-soluble vitamin deficiency
- To evaluate the impact of odevixibat treatment on the effectiveness of fat-soluble drugs
- To evaluate the impact of odevixibat treatment on nutritional status
- To evaluate the impact of odevixibat treatment on hepatic function and signs of hepatotoxicity

Study design:

This PASS represents a registry-based study analysing secondary data. This registry-based safety study will examine the real-world usage of odevixibat for the treatment of PFIC using data prospectively collected in the TreatFIC registry.

The study will continue until a minimum of 50 patient with PFIC treated with odevixibat have been followed for a minimum of 3 years.

The TreatFIC registry captures individual patient data including:

- Demographics: date of birth, gender, diagnosis, age at diagnosis, specific mutation, extra hepatic manifestations, other diagnoses, genetic analysis not (yet) performed and growth parameters
- Odevixibat treatment: start date, dosage, treatment end date and reasons for dose modification/treatment discontinuation
- Other treatments: vitamin supplementation (type, dosage, response to supplementation and route of administration), UDCA, rifampicin, cholestyramine, surgical interruption of the enterohepatic circulation (PEBD and other variants), medical interruption of the enterohepatic circulation (IBAT-I, odevixibat maralixibat)
- Monitoring: longitudinal serum biochemical parameters, including pre-and post-odevixibat treatment changes as far as available: ALP, total bilirubin, albumin, GGT, AST, ALT, bile acids, thrombocytes, vitamins A, D and E, triglycerides, cholesterol and INR
- Clinical symptoms: pruritus and sleep disturbance, if (semi-)objective scoring data are available
- Clinical outcomes: alive with native liver, with or without biliary diversion (internal or external) and with or without IBAT-I therapy, imaging indications of liver cirrhosis and portal hypertension, liver transplantation, indication for transplantation (pruritus, end-stage liver disease, HCC, other), death, cause of death, variceal haemorrhage, diagnosis of HCC
- Growth: height, weight and body mass index (BMI) over time. Nutritional interventions (e.g. special diets, nasogastric feeding, gastrostomy, parenteral nutrition
- Safety: diarrhoea (>3 days), bloody diarrhoea, dehydration, hepatotoxicity, fat-soluble vitamin levels, clinical manifestations of fat-soluble vitamin deficiency (e.g. fractures, bleeding, rickets), fat-soluble vitamin deficiency refractory to dose increase

Study population:

A minimum of 50 patients with PFIC treated with odevixibat for a minimum of 3 years.

Milestones:

MILESTONE	PLANNED DATE
Start of data collection	26 June 2023
First interim study report	30 September 2024
Second interim study report	30 September 2025
Third interim study report	30 September 2026
Fourth interim study report	30 September 2027

MILESTONE	PLANNED DATE
End of data collection	30 Jun 2028
Final report of study results	31 December 2028

Prospective registry-based post-authorisation safety study (PASS) in patients with ALGS

Study short name and title:

Prospective Registry-based Study evaluating the Long-term Safety of Odevixibat in Patients with Alagille syndrome (ALGS).

Rationale and study objectives:

Rationale

This will be a long-term, observational and voluntary participation registry-based safety study designed to examine the real-world usage and long-term safety of odevixibat in patients with ALGS using prospectively collected data.

Study objectives

The aim of this study is to assess the long-term, real-world safety profile of odevixibat treatment in patients with ALGS. The overall objective of this registry-based study is to evaluate the long-term safety of odevixibat.

Study design:

This will be a long-term, observational and voluntary participation registry-based safety study designed to examine the real-world usage and long-term safety of odevixibat in patients with ALGS using data collected prospectively.

The minimum number of patients will be determined following feasibility assessment conducted as part of registry-based safety study protocol preparation. The interim results will be provided annually as part of the annual reassessment. The length of time for duration of follow-up will be adjusted as needed to ensure the study provides meaningful results.

Milestones:

STUDY MILESTONE	PLANNED DATE
Submission of feasibility assessment	Within 3 months of EC decision
Protocol submission	Within 6 months of EC decision
Interim report	Within 5 years from study start
Interim results	Yearly reporting with annual reassessment

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 28 Summary of Ongoing and Planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities, which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in	The aim of this study is to assess the long-term, real-world safety profile of odevixibat treatment in patients with ALGS	Hepatotoxicity Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	(1) Feasibility assessment (2) Protocol submission	(1) Within 3 months of EC decision

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Patients with ALGS Planned	using the data collected prospectively.	Long-term use Interactions with fat-soluble drugs. Embryofetal toxicity Use during pregnancy and breastfeeding women.	(3) Interim results (4) Interim report	(2) Within 6 months of EC decision (3) Yearly reporting with annual reassessment (4) Within 5 years from study start
Category 3 - Required additional pharmacovigilance activities				
A4250-019 Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC Ongoing	Collect safety data on adverse events including, but not limited to: Episodes of diarrhoea lasting more than 3 days, bloody diarrhoea or diarrhoea leading to dehydration or electrolyte imbalance and any treatment Episodes of fat-soluble vitamin deficiencies, including symptoms and treatment Hospitalisations including diagnoses and treatments - Collect available specified laboratory data ALT, AST, bilirubin, INR and fat-soluble vitamin levels • Collect data on growth (height and weight z-scores)	Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance Hepatotoxicity Long-term use Interactions with fat-soluble drugs	Final study report	31 December 2028

Abbreviations: ALGS=Alagille syndrome; ALT=alanine aminotransferase; AST=aspartate aminotransferase; EC=European Commission; INR=international normalized ratio; PASS=post-authorization safety study; PFIC=progressive familial intrahepatic cholestasis; QoL=quality of life; QTc=corrected qt interval; s-Bas=serum bile acids; SmPC=Summary of Product Characteristics

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 29 Planned and Ongoing Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A4250-018 Prospective Registry-based Study of the Long-term Efficacy of Odevixibat in Patients with PFIC Ongoing	To assess the time to biliary diversion surgery, liver transplantation and death for the overall population of patients with PFIC as well as the populations of patients with different PFIC subtypes	Long-term efficacy	Interim results	Annual re-assessment

Abbreviation: PFIC=Progressive Familial Intrahepatic Cholestasis

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table 30 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	Routine risk communication: SmPC section 4.4 and 4.8 Package leaflet (PL) section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation regarding monitoring for events of diarrhoea and regular monitoring to ensure adequate hydration during episodes of diarrhoea in SmPC section 4.4. Instruction for patients to notify their doctor if they develop diarrhoea while taking odevixibat and recommendation for drinking sufficient liquid in patients with diarrhoea in PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Hepatotoxicity	Routine risk communication: SmPC section 4.4 and 4.8 PL section 2 and 4

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4 of the SmPC that patients with severe hepatic impairment (Child-Pugh C) have not been studied. Periodic liver function tests should be considered for patients with severe hepatic impairment. Guidance on assessment of liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and total bilirubin) for all patients prior to initiating odevixibat, with monitoring per standard clinical practice in SmPC sections 4.4 and PL section 2. Recommendations for more frequent monitoring for patients with liver function test elevations in SmPC section 4.4 and PL section 2. Instruction for patients with PFIC to notify their doctor or pharmacist before taking Bylvay if they have been diagnosed with a complete absence or lack of function of bile salt export pump protein and if they have severely reduced liver function in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Embryo-foetal toxicity	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.6 and PL section 2 notes that odevixibat is not recommended for use during pregnancy and in women of childbearing potential not using contraception. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Interactions with fat-soluble drugs	Routine risk communication: SmPC section 4.4, 4.5 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.5 notes that based on the completed interaction study with a lipophilic combination oral contraceptive containing ethinyl estradiol (EE) (0.03 mg) and levonorgestrel (LVN) (0.15 mg) conducted in adult healthy females, concomitant use of odevixibat had no impact on the area under the curve (AUC) of LVN and decreased the AUC of EE by 17%, which is not considered clinically relevant. Interaction studies with other lipophilic medicinal products have not been performed, therefore, effect on the absorption of other fat-soluble medicinal products cannot be excluded. Recommendation for monitoring of levels of fat-soluble vitamins in SmPC sections 4.4 and 4.5. Guidance on assessment of fat-soluble vitamin levels (Vitamins A, D. E) and INR for all patients prior to initiating odevixibat, with monitoring per standard clinical practice in SmPC section 4.4. Warning in sections 4.4 and 4.5 of the SmPC that treatment with odevixibat may impact the absorption of fat-soluble medicinal products.

Safety concern	Routine risk minimisation activities
	Instruction for patients in PL section 2 to notify their doctor or pharmacist if they are using, have recently used or might use any other medicines. Treatment with odevixibat may impact the absorption of fat-soluble vitamins such as Vitamin A, D, E and K. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Long-term use	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Use during pregnancy and use in breastfeeding women	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.6 and PL section 2 notes that odevixibat is not recommended for use during pregnancy and in women of childbearing potential not using contraception. SmPC section 4.6 mentions that patients are advised that the doctor will help to decide whether to discontinue breastfeeding or to discontinue/abstain from odevixibat therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother. Guidance in section 2 of the PL advising the patient that the doctor will help the patient to decide whether to stop breastfeeding or to avoid odevixibat treatment considering the benefit of breastfeeding to the baby and odevixibat to the mother. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Abbreviations: AUC=area under the curve; EE=ethinyl estradiol; INR=international normalized ratio; LVN=levonorgestrel; PFIC=progressive familial intrahepatic cholestasis; PIL=Patient Information Leaflet; PL=Package Leaflet; SmPC=Summary of Product Characteristics

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 31 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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 A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with ALGS
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 A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with ALGS
Embryo-foetal 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: Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with ALGS
Interactions with fat-soluble drugs	Routine risk minimisation measures: SmPC section 4.4, 4.5 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 A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with ALGS

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term use	Routine risk minimisation measures: None 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 A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with ALGS
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: Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with ALGS

Abbreviations: ALGS=Alagille syndrome; PIL=Patient Information Leaflet; PL=Package Leaflet; SmPC=Summary of Product Characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for odevixibat

This is a summary of the risk management plan (RMP) for odevixibat. The RMP details important risks of odevixibat, how these risks can be minimised and how more information will be obtained about odevixibat's risks and uncertainties (missing information).

Odevixibat's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how odevixibat should be used.

This summary of the RMP for odevixibat should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of odevixibat's RMP.

I. The Medicine and What is it Used for

Odevixibat is authorised for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older and cholestatic pruritus in Alagille syndrome (ALGS) in patients aged six months or older (see SmPC for the full indication). Odevixibat is the active substance and it is given orally.

Further information about the evaluation of odevixibat's benefits can be found in odevixibat's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <*https://www.ema.europa.eu/en/medicines/human/EPAR/bylvay*> and <*https://www.ema.europa.eu/en/medicines/human/EPAR/kayfanda*>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of odevixibat, together with measures to minimise such risks and the proposed studies for learning more about odevixibat's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of odevixibat is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of odevixibat are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of odevixibat. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information

Important identified risks	• Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance
Important potential risks	• Hepatotoxicity • Embryo-foetal toxicity • Interactions with fat-soluble drugs
Missing information	• Long-term use • Use during pregnancy and use in breastfeeding women

II.B Summary of Important Risks

Important identified risk, Important potential risk and Missing information

Important identified risk: Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	
Evidence for linking the risk to the medicine	Diarrhoea related to odevixibat treatment was observed in patients with PFIC and in patients with ALGS in the clinical studies. Adverse events of diarrhoea assessed as related to odevixibat were mild to moderate in severity and self-limiting. Diarrhoea is the most commonly reported adverse reaction for investigational drugs of the same class, e.g. volixibat, maralixibat and elobixibat. Study discontinuations in studies of the same drug class were reported due to TEAEs of diarrhoea. In the PFIC pivotal study A4250-005, one patient in the 120 µg/kg/day group in Study A4250-005 discontinued treatment due to an event of clinically significant diarrhoea and experienced an SAE of acute dehydration (severe) requiring hospitalisation. In the long-term extension study A4250-008, as

	of the 15 February 2024 data cutoff, two patients had discontinued treatment due to diarrhoea. No patient in the ALGS phase III studies discontinued treatment due to diarrhoea. Drug-related diarrhoea was observed in non-clinical studies with mice, rats and dogs. Diarrhoea is the most likely dose-limiting effects of odevixibat as indicated by preliminary toxicity studies.
Risk factors and risk groups	Malabsorption and diarrhoea are known co-morbidities in patients with PFIC and patients with ALGS. Patients with PFIC1 are known to show extrahepatic manifestations in the form of persistent diarrhoea. In general, other risk factors for diarrhoea include the following: Malabsorption Biliary diversion surgery (partial external or internal) Paediatric population, more susceptible to viral infections and infections Side effects following liver transplantation Diet and food sensitivities Other medications known to cause diarrhoea
Risk minimisation measures	<u>Routine risk minimisation measures</u>: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine. <u>Additional risk minimisation measures</u>: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Minimal signs of reversible, non-adverse liver toxicity were noted in rats (adult and juvenile). The safety margin based on the NOAEL in the juvenile toxicity study is high (based on adult human PK data), about 300-fold, related to both dose and exposure. In the oral carcinogenicity study in mice and rats, gallbladder and biliary hyperplasia / basophilic foci of alteration were of late onset, not adverse and without neoplastic risk. Although slight hepatic effects were noted following odevixibat exposure, they were considered non-adverse in the context of repeated administrations. In the PFIC clinical studies, improvements in liver function tests were noted in odevixibat-treated versus placebo-treated patients. In these clinical studies, most excursions in ALT, AST and total bilirubin were considered related to the underlying disease and/or intermittent concomitant viral illnesses, which are common to paediatric patients. Overall, 52% of patients in the Pooled Phase 3 group had TEAEs in the SMQ of Drug-related Hepatic Disorders – comprehensive search (narrow and broad). The most common TEAEs reported in this

	SMQ were blood bilirubin increased, INR increased, ALT increased, AST increased, hepatomegaly and jaundice. The majority of TEAEs were mild to moderate in intensity. Eight patients (0.66%) reported severe events from this SMQ, three of which serious and considered by the investigator to be unrelated to study drug. In PFIC clinical trials, Drug Safety Monitoring Board (DSMB) was conducting an independent, adjudication of hepatic events. Overall, 69 (57%) of the 121 patients in the Pooled Phase 3 groups had an event that underwent adjudication by the DSMB. Based on review of 69 cases by the DSMB, all but one case (increased ALT and total bilirubin) were adjudicated as unrelated to study treatment.
	
	In the ALGS phase III clinical trials, no liver decompensation events were reported, nor were there any reports of new or worsening portal hypertension, hepatic cirrhosis, ascites, hepatic encephalopathy or variceal haemorrhage. In Study A4250-012, the overall incidence of liver-related events in the SMQs of *Drug-related hepatic disorders – comprehensive search (narrow and broad), Biliary tract disorders, Gallbladder-related disorders and Gallstone-related disorders*, was similar in the odevixibat and placebo groups (11.0% and 12.0%, respectively). A detailed review of changes from baseline to Week 24 for transaminase levels of the pooled data from studies A4250-012 and A4250-015, showed larger mean increases for ALT and AST for patients who received odevixibat compared with patients who received placebo; for total bilirubin, the changes from baseline were similar in the odevixibat and placebo groups. The increases in ALT and AST were observed by Week 4 and then plateaued through Week 24. Further review of the data based on modified evaluation of drug-induced serious hepatotoxicity (eDISH) plots indicated that none of the patients in either treatment group had ALT elevations >3 × baseline concurrent with total bilirubin >2 × baseline. Three patients, including two in the odevixibat group and one in the placebo group had ALT and AST elevations >3 × baseline without concurrent elevations in total bilirubin >2 × baseline. Review of the pertinent clinical and diagnostic information for the two patients treated with odevixibat suggests that the occurrence of DILI was unlikely.
	
	No patients in either the PFIC or ALGS clinical trials experienced an event of liver decompensation defined as:
	• INR elevation >1.5 that is refractory to vitamin K administration
	• In a patient who developed portal hypertension and cirrhosis post-baseline, transition to decompensated cirrhosis evidenced by any of the following:
	  • Presence of ascites
	  • Hepatorenal syndrome
	  • Portopulmonary hypertension
	  • Hepatopulmonary syndrome
	  • Variceal haemorrhage
	  • Hepatic encephalopathy
	
	Generally, odevixibat poses a low hepatotoxicity risk. This important potential risk is based on the odevixibat clinical and non-clinical studies.

Risk factors and risk groups	Patients with cholestatic liver diseases suffer from excess bile acids in the liver, which are thought to play a contributory role in hepatic oxidative stress, inflammation resulting in tissue damage, fibrosis, cirrhosis and eventually end-stage liver disease. Other risk factors for hepatotoxicity include the following: Malnourishment Use of potentially hepatotoxic drugs Other underlying co-morbidities (e.g. viral infections or pre-existing liver disease)
Risk minimisation measures	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
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	In an embryo-foetal development study in the rabbit, cardiovascular malformations in foetal rabbits were observed at low frequency (1.3%) at all dosages (10, 30, or 100 mg/kg/day) tested. No findings were observed in the corresponding rat study. Because of the findings in rabbits, an effect of odevixibat on cardiovascular development cannot be excluded.
Risk factors and risk groups	Women of childbearing potential who take odevixibat.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Interaction with fat-soluble drugs	
Evidence for linking the risk to the medicine	This risk is related to the background disease pathology and not to odevixibat per se. Fat-soluble vitamin malabsorption has been reported in the patient population [3]. Clinical data to date in patients with PFIC treated with odevixibat for 72 weeks or longer and in patients with ALGS treated for 72 weeks or longer

	has not demonstrated any unwarranted effect on fat-soluble vitamin levels (Vitamin A, D, E) and INR.
Risk factors and risk groups	Fat malabsorption and fat-soluble vitamin deficiencies are known co-morbidities in patients with PFIC and in patients with ALGS. No clinical drug-drug interactions studies have been conducted with other lipophilic drugs. It cannot be excluded that the absorption of lipophilic drugs other than oral contraceptives is affected by odevixibat.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.5 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Long-term use	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use during pregnancy and use in breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ALGS=Alagille syndrome; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CD=controlled document; CSR=clinical study report; EMA=European Medicines Agency; GGT=gamma-glutamyl transferase; INR=international normalized ratio; NOAEL=no observed adverse effect level; PFIC=progressive familial intrahepatic cholestasis; PK=pharmacokinetics; PL=package leaflet; RMP=risk management plan; SAE=serious adverse event; SmPC=Summary of Product Characteristics; SMQ=Standardised MedDRA Query; SOP=standard operating procedure; TEAE=Treatment-Emergent Adverse Event

II.C Post-authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

PFIC

A4250-018 Registry-based Efficacy Study:

Study short name and title:

Prospective Registry-based Study of the Long-term Efficacy of Odevixibat in Patients with PFIC

Purpose of the Study:

To assess the time to biliary diversion surgery, liver transplantation and death for the overall population of patients with PFIC as well as the populations of patients with different PFIC subtypes and to compare the outcomes in odevixibat-treated and untreated patients.

ALGS

Registry-based Safety Study:

Study short name and title:

Prospective Registry-based Study evaluating the Long-term Safety of Odevixibat in Patients with Alagille syndrome (ALGS)

Purpose of the study:

The aim of this study is to assess the long-term, real-world safety profile of odevixibat treatment in patients with ALGS using prospectively collected data.

II.C.2 Other studies in post-authorisation development plan

A4250-019 Registry-based Safety study

Study short name and title:

Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC

Purpose of the Study:

- Assess the long-term, real-world safety profile of odevixibat treatment in patients with PFIC compared to patients not receiving odevixibat (untreated control cohort).

PART VII: ANNEXES

Table of contents

Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

None.

Annex 7 - Other Supporting Data (including referenced material)

REFERENCE

1. Alissa FT, Jaffe R, Shneider BL. Update on progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr. 2008;46(3):241-252.
2. Bull LN, Thompson RJ. Progressive Familial Intrahepatic Cholestasis. Clin Liver Dis. 2018b;22(4):657-669.
3. Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. Hepat Med. 2018;10:95-104.
4. Jacquemin E. Progressive familial intrahepatic cholestasis. Genetic basis and treatment. Clin Liver Dis. 2000;4(4):753-763.
5. Mehl A, Bohorquez H, Serrano MS, Galliano G, Reichman TW. Liver transplantation and the management of progressive familial intrahepatic cholestasis in children. World J Transplant. 2016;6(2):278-290.
6. Srivastava A. Progressive Familial Intrahepatic Cholestasis. J Clin Exp Hepatol. 2014;4:25-36.
7. Hori T, Nguyen JH, Uemoto S. Progressive familial intrahepatic cholestasis. Hepatobiliary Pancreat Dis Int. 2010;9(6):570-578.
8. Henkel SA, Squires JH, Ayers M, Ganoza A, McKiernan P, Squires JE. Expanding etiology of progressive familial intrahepatic cholestasis. World journal of hepatology. 2019;11(5):450-463.
9. Goldberg A, Mack CL. Inherited Cholestatic Diseases in the Era of Personalized Medicine. Clinical liver disease. 2020;15(3):105-109.
10. Van Ooteghem NA, Klomp LW, van Berge-Henegouwen GP, Houwen RH. Benign recurrent intrahepatic cholestasis progressing to progressive familial intrahepatic cholestasis: low GGT cholestasis is a clinical continuum. J Hepatol. 2002;36(3):439-443.
11. Stapelbroek JM, van Erpecum KJ, Klomp LW, Houwen RH. Liver disease associated with canalicular transport defects: current and future therapies. J Hepatol. 2010;52(2):258-271.
12. Sticova E, Jirsa M, Pawłowska J. New Insights in Genetic Cholestasis: From Molecular Mechanisms to Clinical Implications. Canadian journal of gastroenterology & hepatology. 2018;2018:2313675.
13. Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis. 2009,4(1).
14. Eurostat. Population on 1 January. DEMO_GIND 2020; https://ec.europa.eu/eurostat/databrowser/view/tps00001/default/table?lang=en. Accessed 01 Sep 2020.
15. Nielsen IM, Eiberg H. Cholestasis Familiaris Groenlandica: an epidemiological, clinical and genetic study. Int J Circumpolar Health 2004;63(Suppl. 2):192-194.
16. Shagrani M, Burkholder J, Broering D, Abouelhoda M, Faquih T, El-Kalioby M et al. Genetic profiling of children with advanced cholestatic liver disease. Clin Genet 2017;92:52-61.
17. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51(2):237-267.
18. Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RHJ. Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2019;43(1):20-36.
19. Galeazzi R, Lorenzini I, Orlandi F. Rifampicin-induced elevation of serum bile acids in man. Digestive diseases and sciences. 1980;25(2):108-112.
20. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterology. 1988;94(2):488-493.
21. Kriegermeier A, Green R. Pediatric Cholestatic Liver Disease: Review of Bile Acid Metabolism and Discussion of Current and Emerging Therapies. Frontiers in medicine. 2020;7:149.
22. Prince MI, Burt AD, Jones DE. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut. 2002;50(3):436-439.
23. Rifadin™ Prescribing Information. Bridgewater, NJ: Sanofi-Aventis U.S. LLC. 2020.

24. Rifampicin Summary of Product Characteristics. Mumbai, India: Macleods Pharmaceuticals Ltd. 2017.
25. Gittlen SD, Schulman ES, Maddrey WC. Raised histamine concentrations in chronic cholestatic liver disease. Gut. 1990;31(1):96-99.
26. Hägermark O. Peripheral and central mediators of itch. Skin pharmacology: the official journal of the Skin Pharmacology Society. 1992;5(1):1-8.
27. van Wessel D, Thompson R, Grammatikopoulos T, et al. Predicting long-term outcome after surgical biliary diversion in Bsep-deficiency patients: Results from the NAPPED consortium [Abstract # PS-195]. Journal of Hepatology. 2019;70:e121.
28. Arnell H, Papadogiannakis N, Zemack H, Knisely AS, Németh A, Fischler B. Follow-up in children with progressive familial intrahepatic cholestasis after partial external biliary diversion. J Pediatr Gastroenterol Nutr. 2010;51(4):494-499.
29. Melter M, Rodeck B, Kardorff R, et al. Progressive familial intrahepatic cholestasis: partial biliary diversion normalizes serum lipids and improves growth in noncirrhotic patients. Am J Gastroenterol. 2000;95(12):3522-3528.
30. Schukfeh N, Metzelder ML, Petersen C, et al. Normalization of serum bile acids after partial external biliary diversion indicates an excellent long-term outcome in children with progressive familial intrahepatic cholestasis. J Pediatr Surg. 2012;47(3):501-505.
31. Yang H, Porte RJ, Verkade HJ, De Langen ZJ, Hulscher JB. Partial external biliary diversion in children with progressive familial intrahepatic cholestasis and Alagille disease. J Pediatr Gastroenterol Nutr. 2009;49(2):216-221.
32. van Wessel DBE, Thompson RJ, Gonzales E, et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. J Hepatol. 2020;73(1):84-93.
33. Bull LN, Pawlikowska L, Strautnieks S, et al. Outcomes of surgical management of familial intrahepatic cholestasis 1 and bile salt export protein deficiencies. Hepatol Commun. 2018a;2(5):515-528.
34. Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cirrhosis. Baillieres Best Pract Res Clin Gastroenterol. 2000;14(4):643-655.
35. Cies JJ, Giamalis JN. Treatment of cholestatic pruritus in children. Am J Health Syst Pharm. 2007;64(11):1157-1162.
36. Pawlikowska L, Strautnieks S, Jankowska I, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. J Hepatol. 2010;53(1):170-178.
37. Agarwal S, Lal BB, Rawat D, Rastogi A, Bharathy KG, Alam S. Progressive Familial Intrahepatic Cholestasis (PFIC) in Indian Children: Clinical Spectrum and Outcome. J Clin Exp Hepatol. 2016;6(3):203-208.
38. Albahrani A, Greaves R. Fat-Soluble Vitamins: Clinical Indications and Current Challenges for Chromatographic Measurement. Clin Biochem Rev. 2016;37(1):27–47.
39. Davit-Spraul A, Fabre M, Branchereau S, et al. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. Hepatology. 2010;51(5):1645-1655.
40. Whitington PF, Freese DK, Alonso EM, Schwarzenberg SJ, Sharp HL. Clinical and biochemical findings in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr. 1994;18(2):134-141.
41. Alsalloom A. Hepatocellular Carcinoma in a Boy with Progressive familial Intrahepatic Cholestasis Type II: Challenging Identification: Case report. Int J Health Sci (Qassim). 2013;7(2):252-255.
42. Krantz ID, Piccoli DA, Spinner NB, Alagille syndrome. J Med Genet. 1997;34:153-157.

43. Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. European Journal of Human Genetics. 2012; (20); 251-257.
44. Diaz-Frias J, Kondamudi NP. Alagille Syndrome. [Updated 2022 Jun 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2022.
45. Emerick KM, Whitington PF, Partial external biliary diversion for intractable pruritus and Xanthomas in Alagille Syndrome. Hepatology. 2002; 35:1501-1506.
46. Kamath BM, Baker A, Houwen R et al. Systematic review: the epidemiology, natural history and burden of Alagille syndrome. J Pediatr Gastroenterol Nutr. 2018; Aug;67(2):148-156.
47. Kamath BM, Ye W, Goodrich NP, et al. Outcomes of childhood cholestasis in Alagille Syndrome: Results of a multicenter observational study. Hepatol. Commun. 2020;4:387-398.
48. Vandriel SM, Li LT, She H, et al. Natural History of Liver Disease in a Large International Cohort of Children with Alagille syndrome: Results from The GALA Study. Hepatology. 2022.
49. Penton A, Leonard L, Spinner N. Notch signaling in human development and disease. Semin Cell Dev Biol. 2012: 23(4): 450-457.
50. Oda T, Elkahloun AG, Pike BL, et al. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. Nat Genet. 1997;16:235-243.
51. Singh SP, Pati GK. Alagille syndrome and the liver: current insights. Euroasian J Hepato-Gastroenterol. 2018:8:140-147.
52. Ayoub MD, Kamath BM. Alagille Syndrome: Current Understanding of Pathogenesis, and Challenges in Diagnosis and Management. Clinics in liver disease. 2022;26(3):355-370.
53. Kamath BM, Bason L, Piccoli DA, Krantz ID, Spinner NB. Consequences of JAG1 mutations. J Med Genet. 2003;40:891–895.
54. Danks DM, Campbell PE, Jack I, Rogers J, Smith AL. Studies of the aetiology of neonatal hepatitis and biliary atresia. Arch Dis Child. 1977; 52:360-367.
55. Kamath BM, Schwarz KB, Hadzic Nedim. Alagille Syndrome and Liver Transplantation. JPGN. 2010;50: 11-15.
56. Vandriel S, Li L, She H, et al. Clinical Features and Natural History of 1154 Alagille Syndrome Patients: Results from the International Multicenter GALA Study Group. Journal of Hepatology. 2020;73:S554-S555.
57. LIVMARLI US Prescribing Information, https://livmarli.com/, accessed on 07-Sep-2022.
58. LIVMARLI EU Product Information, https://www.ema.europa.eu/en/documents/product-information/livmarli-epar-product-information_en.pdf, accessed on 06-Apr-2023.
59. Kamath BM, Yin W, Miller H, et al. Outcomes of liver transplantation for patients with Alagille syndrome: the studies of pediatric liver transplantation experience. Liver Transpl. 2012;18(8):940-948.
60. Tzakis AG, Reyes J, Tepetes K, Tzoracoleftherakis V, Todo S, Starzl TE. Liver transplantation for Alagille's syndrome. Arch Surg. 1993;128(3):337-339.
61. Junge N, Dingemann J, Petersen C, et al. [Biliary atresia and congenital cholestatic syndromes: Characteristics before, after and during transition]. Internist (Berl). 2018;59(11):1146-1156.
62. Kamath B, Mack C. From Hepatocyte to Cholangiocyte: The Remarkable Potential of Transdifferentiation to Treat Cholestatic Diseases. Hepatology. 2019;69(4):1828-1830.
63. Tam PKH, Yiu RS, Lendahl U, Andersson ER. Cholangiopathies - Towards a molecular understanding. EBioMedicine. 2018;35:381-393.
64. Pawlowska J, Socha P, Jankowska I. Factors affecting catch-up growth after liver transplantation in children with cholestatic liver diseases. Ann Transplant. 2010:15 (1);72-6.
65. Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. Hepatology. 1999;29:822-829.

66. Truong JK, Bennett AL, Klindt C, et al. Ileal bile acid transporter inhibition in Cyp2c70 KO mice ameliorates cholestatic liver injury. J Lipid Res. 2022;63(9):100261.
67. Harpavat S, Hawthorne K, Setchell KDR, et al. Serum bile acids as a prognostic biomarker in biliary atresia following Kasai portoenterostomy. Hepatology. 2022.
68. Van Wessel et al. Factors associated with the natural course of disease in patients with FC1-deficiency: the NAPPED-consortium. ABSTRACT. 2019
69. Bales CB, Kamath BM, Munoz PS, et al. Pathologic lower extremity fractures in children with Alagille syndrome. Journal of pediatric gastroenterology and nutrition. 2010;51(1):66-70.
70. Engin F, Yao Z, Yang T, et al. Dimorphic effects of Notch signaling in bone homeostasis. Nat Med. 2008;14(3):299-305.
71. Hilton MJ, Tu X, Wu X, et al. Notch signaling maintains bone marrow mesenchymal progenitors by suppressing osteoblast differentiation. Nat Med. 2008;14(3):306-314.
72. Gabrielsson J, Hjorth S. (Eds.) (2012) Quantitative Pharmacology: An Introduction to Integrative Pharmacokinetic-Pharmacodynamic Analysis. 1st Edition. Swedish Pharmaceutical Press, Stockholm.