EU Risk Management Plan for LIVMARLI® (Maralixibat Chloride)

RMP version to be assessed as part of this application:

RMP version number:	4.1
Data lock point for this RMP:	25 April 2024
Date of final sign off:	29 May 2024

Rationale for submitting an updated RMP:

The RMP update is submitted in support of the proposed indication for the use of LIVMARLI in patients with progressive familial intrahepatic cholestasis (PFIC).

Summary of significant changes in this RMP:

Part I: Product(s) Overview

The information pertinent to the proposed indication was included in the product overview.

Part II: Safety Specification

Module SI was revised to include the epidemiology of the proposed indication.

Module SII was updated with findings of the category 3 post-authorisation safety study (PASS) MRXNC-006.

Module SIII was amended to include the clinical trial exposure in PFIC population.

Module SIV was updated with important exclusion criteria from the pivotal study within the PFIC clinical development programme.

Module SVII and SVIII were updated with the data collected in the PFIC clinical studies and in line with the outcomes of the Periodic Safety Update Report Single Assessment (PSUSA) procedure no. EMEA/H/C/PSUSA/00011032/202309, issued on 25 April 2024.

The important potential risk of medication error resulting from erroneous dosing (PFIC patients) and the missing information of long-term safety of chronic exposure to propylene glycol in PFIC patients and the long-term safety were added to the list of safety concerns for LIVMARLI. Additionally, the missing information of carcinogenic potential was removed from the list of safety concerns, based on the results of completed PASS MRXNC-006 (procedure EMEA/H/C/005857/II/0009). These changes were reflected throughout the document, as applicable.

Part III: Pharmacovigilance Plan

Category 2 PASS MRX-311 was amended to include also the PFIC population and accordingly, changes were implemented in the study code to MRX-803, study objectives, milestones, and milestones' due dates throughout the document. This study was further amended to address also the important potential risk of medication error resulting from erroneous dosing (PFIC patients), the missing information of long-term safety, and the missing information of long-term safety of chronic exposure to propylene glycol in the PFIC patients per updated Module SVIII.

Category 3 study MRXNC-006 was removed from the pharmacovigilance plan since this study was completed (procedure EMEA/H/C/005857/II/0009).

Category 3 studies MRX-800, MRX-801, and MRX-503 will further address the safety concern of the long-term safety in both ALGS and PFIC patient populations, as applicable by the target population of each study. Milestone due dates were updated for all three studies.

Additional retrospective analysis of study findings in studies MRX-502, MRX-503, MRX-800, and MRX-801 was added as category 3 PASS in the pharmacovigilance plan.

All these changes in the pharmacovigilance plan were reflected in Parts III.2, III.3, V.3, and VI, Annex 2, and Annex 3 of the RMP, as applicable.

Part V: Risk Minimisation Measures

The routine risk minimisation measures for the important potential risk of hepatotoxicity were updated in line with the outcomes of the PSUSA procedure no. EMEA/H/C/PSUSA/00011032/202309, issued on 25 April 2024.

The additional risk minimisation measures were implemented to address the important potential risk of medication errors resulting from erroneous dosing (PFIC patients).

These changes were reflected in Parts V.1, V.3, VI, in Annex 2, and Annex 6 of the RMP, as applicable.

Changes introduced to the body of document were reflected in Part VI of the RMP, as applicable.

Other RMP versions under evaluation:

Version number:	Not applicable.
Submitted on:	Not applicable.
Procedure number:	Not applicable.

Details of currently approved RMP:

Version number:	3.1
Approved within procedure:	EMEA/H/C/005857/IB/0007
Date of approval (opinion date):	08 November 2023

QPPV name: Zuzana Chomátová

The content of this RMP has been reviewed and approved by the marketing authorisation holder’s QPPV. The electronic signature is available on file.

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ABCB4	ATP binding cassette subfamily B member 4 gene
ABCB11	ATP binding cassette subfamily B member 11 gene
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASBT	apical sodium-dependent bile acid transporter
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATP	adenosine triphosphate
ATP8B1	ATPase phospholipid transporting 8B1 gene
BSEP	bile salt export pump
CSR	clinical study report
EC	European Commission
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EPAR	European Public Assessment Report
FXR	farnesoid X receptor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HIV	human immunodeficiency virus
IBAT	ileal bile acid transporter
INN	international nonproprietary name
INR	international normalised ratio
LPO	last patient out
max	maximum
MDR3	multidrug-resistance protein 3
min	minimum
MYO5B	myosin-5b
NOAEL	no-observed-adverse-effect level
nt-PFIC2	nontruncating progressive familial intrahepatic cholestasis 2

Abbreviation	Definition
PFIC	progressive familial intrahepatic cholestasis
PL	Package Leaflet
PND	postnatal day
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Report Single Assessment
PT	prothrombin time
Q	quarter
Q1	25th percentile
Q3	75th percentile
QPPV	qualified person for pharmacovigilance
RMP	Risk Management Plan
SAP	statistical analysis plan
sBA	serum bile acid
SD	standard deviation
SE	standard error of the mean
SLC10A2	solute carrier family 10 member 2
SmPC	Summary of Product Characteristics
t-PFIC2	truncating progressive familial intrahepatic cholestasis 2
TJP2	tight junction protein 2
TSB	total serum bilirubin
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

Part I Product(s) Overview

Active substance(s) (INN or common name)	Maralixibat chloride
Pharmacotherapeutic group(s) (ATC Code)	Bile and liver therapy, other drugs for bile therapy (A05AX04)
Marketing Authorisation Holder	Mirum Pharmaceuticals International B.V.
Medicinal product to which this RMP refers	1
Invented name in the EEA	LIVMARLI®
Marketing authorisation procedure	Centralised procedure
Brief description of the product	**Chemical class:** Maralixibat is an inhibitor of the apical sodium-dependent bile acid transporter/ileal bile acid transporter/solute carrier family 10 (sodium/bile acid cotransporter family) member 2 (ASBT/IBAT/SLC10A2)
	Summary of mode of action: Maralixibat is an inhibitor of the ASBT/IBAT/SLC10A2, a transmembrane protein localised on the luminal surface of ileal enterocytes. By virtue of its ability to inhibit bile acid absorption, it thereby increases faecal bile acid excretion and lowers serum bile acid.
	Important information about its composition: Each mL of LIVMARLI solution contains 364.5 mg propylene glycol.
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	**Current:** Treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older.
	Proposed: LIVMARLI is indicated for the treatment of: • Cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older • Progressive familial intrahepatic cholestasis (PFIC) patients 3 months of age and older.
Dosage in the EEA	**Current:** The recommended target dose is 380 µg/kg maralixibat once daily. The starting dose is 190 µg/kg maralixibat once daily and should be increased to 380 µg/kg maralixibat once daily after one week.

	Proposed: In Alagille syndrome (ALGS): The recommended target dose is 380 µg/kg maralixibat once daily. The starting dose is 190 µg/kg maralixibat once daily and should be increased to 380 µg/kg maralixibat once daily after one week. In progressive familial intrahepatic cholestasis (PFIC): The starting dose is 285 µg/kg maralixibat once daily and may be increased after 1-2 weeks to 285 µg/kg maralixibat twice daily (morning and evening). After 1-2 weeks, the dose can be increased to 570 µg/kg maralixibat twice daily, as tolerated.
Pharmaceutical form(s) and strengths	**Current:** Oral solution Each mL of solution contains maralixibat chloride equivalent to 9.5 mg maralixibat.
	Proposed: Same as current.
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC=anatomical therapeutic chemical; EEA=European Economic Area; EU=European Union; INN=international nonproprietary name; RMP =risk management plan.

Part II Safety Specification

Part II: Module SI Epidemiology of the Indication and Target Population

SI.1 Alagille Syndrome

Alagille syndrome (ALGS) is an autosomal dominant disease with variable penetration multisystem disorder. The estimated prevalence of patients with ALGS with liver disease is 1 in 30,000 to 50,000 live births worldwide (Kamath et al. 2018b). The diagnosis is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least 3 of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities, vascular abnormalities, and characteristic facial features. Blood levels of markers of bile duct obstruction, including gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP), usually are significantly elevated. Elevations of serum bilirubin up to 30 times normal and serum bile salts up to 100 times normal are not uncommon. Cholesterol levels may exceed 1000–2000 mg/dL. Multiple xanthomas are common sequelae of the disease (Coates et al. 1986). The symptoms of ALGS usually present in the first 3 months of life (Kamath et al. 2018b). The 20-year predicted life expectancy is 75% for all patients, 80% for those not requiring liver transplantation, and 60% for those who required liver transplantation (Emerick et al. 1999).

Cholestasis often leads to hepatocellular injury and progressive liver disease that ultimately requires liver transplantation. It has been reported that only 24% to 41% of patients with ALGS survive with their native liver into adulthood (Kamath et al. 2020; Vandriel et al. 2020). Pruritus represents a significant unaddressed clinical burden in ALGS, affecting 59% to 88% of patients with ALGS, of whom up to 45% experience severe pruritus (Kamath et al. 2018b). Liver transplant is a main indication for intractable pruritus even in the absence of liver failure (Mattei et al. 2006).

Pruritus in ALGS is associated with a significant burden on the quality of life. In a recently published study of pruritus in 32 patients with ALGS, the majority of patients and caregivers reported difficulty staying and falling asleep despite the use of anti-pruritic medication in over 70% of patients. In addition, over one-third of patients reported skin lesions due to scratching (Kamath et al. 2018a). Xanthomas can also be burdensome and cause cosmetic or even functional problems. Both pruritus and xanthomas may warrant biliary diversion or liver transplant in their own right, but both interventions have significant costs and a lifelong burden for the patients and families (Kamath et al. 2018a).

The management of cholestasis in patients with ALGS remains largely supportive. Surgical interruption of the enterohepatic circulation by ileal bypass (ileal exclusion) or partial external biliary diversion has been successfully used to treat cholestasis, hypercholesterolaemia, and pruritus (Emerick and Whitington 2002; Modi et al. 2007). However, both carry procedural risks (e.g., bleeding, infections, and surgical complications). External diversion also presents the long-term burden of caring for patients with a stoma and often an impact on the patient's psychosocial development, especially during adolescence (Emerick et al. 1999; Kamath et al. 2018b).

Significantly fluctuating and elevated transaminase levels are a hallmark of ALGS, and elevations approaching 300 U/L have been reported (Liu et al. 2018). Tremendous intrapatient alanine aminotransferase (ALT) variability has been identified in patients with ALGS-related cholestasis. In an analysis of 293 children with ALGS from a multicentre observational study (Kamath et al. 2020), the standard deviation of the variation of the log10

base-transformed ALT was approximately 0.18, which means that ALT can vary from 56% lower to 129% higher for 95% of the time in a given individual. Changes in median ALT and aspartate aminotransferase (AST) with age reached statistical significance in this analysis.

SI.2 Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare autosomal recessive liver disorders of childhood, characterised by intrahepatic cholestasis due to canalicular bile transport defects. PFIC represents 10% to 15% of causes of cholestasis in children (Davit-Spraul et al. 2009).

Several subtypes of PFIC were identified. PFIC1 (also known as Byler's disease) is caused by mutations in the ATPase phospholipid transporting 8B1 gene (*ATP8B1*), which encodes a phospholipid transporting transmembrane P-type ATP. PFIC2 is caused by mutations in the ATP binding cassette subfamily B member 11 gene (*ABCB11*), which encodes the bile salt export pump (BSEP). PFIC3 is caused by mutations in the ATP binding cassette subfamily B member 4 gene (*ABCB4*), which encodes multidrug-resistance protein 3 (MDR3) (Baker et al. 2019).

Other, newer types of inherited cholestatic liver diseases include PFIC4 (caused by a loss of function in tight junction protein 2 [TJP2]), PFIC5 (caused by loss of function in farnesoid X receptor [FXR]), and PFIC6 (caused by myosin-5b [MYO5B] defects) (Baker et al. 2019; Vinayagamoorthy et al. 2021).

Incidence and Prevalence:

PFIC is traditionally estimated to affect between 1 in 50,000 to 100,000 children born worldwide (Davit-Spraul et al. 2009), while the prevalence remains largely unknown (Baker et al. 2019).

PFIC1 is reported in approximately 10.4% to 37.5% of patients with PFIC. PFIC2 is the most common PFIC type, diagnosed in approximately 37.5% to 90.9% of patients with PFIC (Baker et al. 2019). Approximately 30% of PFIC cases represent PFIC3 (Baussan et al. 2004).

Demographics of the Population in Proposed Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease:

PFIC typically manifests in infancy and early childhood, however, the age of presentation varies by PFIC subtype (Pawlikowska et al. 2010; Srivastava 2014). PFIC3 may manifest from the late infancy to early adulthood (Srivastava 2014).

PFIC affects both genders equally and have been reported from all geographical areas (Srivastava 2014).

- **Risk Factors**

  PFIC is an autosomal recessive liver disorder and as such, the classic concept of disease risk factors does not apply.

Main Treatment Options:

Odevixibat, a small-molecule selective inhibitor of the ileal bile acid transporter, is the only approved treatment option in the EU for patients with PFIC aged 6 months or older (Thompson et al. 2022). There are limited or no clinical data with odevixibat in PFIC subtypes other than PFIC1 and PFIC2 (European Medicines Agency 2021).

There is currently no pharmaceutical treatment other than odevixibat approved in the EU in patients with PFIC1 and PFIC2. Ursodeoxycholic acid (UDCA) is approved in France for the treatment of PFIC3, since improvement of biochemical tests in almost 50% of patients with PFIC3 has been reported (EASL 2009).

Other therapeutic options available for the management of PFIC include supportive care, such as nutritional support, prevention of vitamin deficiencies, and symptomatic treatment of extrahepatic features, including pruritus. None of these interventions have a beneficial effect on the pruritus or underlying cholestasis.

Supplementation with medium chain triglycerides and fat-soluble vitamins is generally recommended in children with PFIC (EASL 2009).

Rifampicin may alleviate pruritus (EASL 2009). Further options to relieve pruritus include UDCA, cholestyramine, antihistamines, steroids, and naltrexone (Gunaydin and Bozkurter Cil 2018; Düll and Kremer 2019; Düll and Kremer 2020).

Surgical options include partially biliary diversion and ileal exclusion have been reported in case series to improve signs and symptoms of PFIC1 but also PFIC2 (EASL 2009). Treatment-resistant pruritus is the leading indication for surgical biliary diversion, particularly in patients with PFIC2.

Liver transplantation is the recommended treatment of end-stage liver disease in patients with PFIC (EASL 2009).

Given the burden of cholestatic disease in patients with PFIC, the inherent short- and long-term morbidity and mortality of surgical treatment options, and that there is currently only one approved pharmacological treatment for PFIC with evidence of partial efficacy only in patients with PFIC1 and PFIC2, a high unmet medical need remains for therapies for the broader PFIC population and for paediatric patients below 6 months of age.

Natural History of the Indicated Condition in the (Untreated) Population, Including Mortality and Morbidity:

PFIC is associated with early mortality, morbidity, and devastating consequences on patients' quality of life. The spectrum of clinical manifestations in PFIC varies from mild to severe leading to end-stage liver disease necessitating liver transplant (Mehl et al. 2016).

All PFIC types share manifestations of cholestasis, including elevated serum bile acid, pruritus, in severe cases with devastating consequences on patients' quality of life, growth failure from nutritional deficiencies, and progressive liver disease (Davit-Spraul et al. 2009; Srivastava 2014; Mehl et al. 2016; Baker et al. 2019; Hassan and Hertel 2022). Abnormal liver enzymes vary by PFIC type and approximately 70% of patients with PFIC1 and 95% of patience with PFIC2 have abnormal ALT levels at baseline (Sakita et al. 2018).

Children with PFIC often present with jaundice and debilitating pruritus within the first 3 months of life (Wanty et al. 2004; Englert et al. 2007; Davit-Spraul et al. 2010). Pruritus is reported to occur from 11% to 100% of patients at presentation and by 76% to 100% of patients at follow-up (Baker et al. 2019) and is reported to be severe in 76% to 80% of patients (Whitington et al. 1994; Lee et al. 2009). Pruritus is reported as the most bothersome symptom associated with PFIC and can be severely debilitating (Baker et al. 2019).

Impaired bile flow is evidenced by serum bile acid levels that are markedly and persistently elevated (Morris et al. 2015). Impaired bile flow is also responsible for growth retardation, fat malabsorption, and clinical consequences associated with deficiencies in fat-soluble vitamins, such as rickets and bleeding (Baker et al. 2019).

The intrahepatic accumulation of bile acids results in progressive liver damage and, if left untreated, leads to complications including portal hypertension, liver failure, cirrhosis, and ultimately end-stage liver disease and death (Mehl et al. 2016; Bull and Thompson 2018). As a result of these manifestations, PFIC is associated with substantial morbidity, with the mortality rate for untreated PFIC estimated as 87% (Baker et al. 2019; Alam and Lal 2022).

Due to a lack of treatment options, 70% to 80% of patients ultimately require liver transplantation (Mehl et al. 2016).

Important Co-Morbidities:

There are no known co-morbidities of PFIC.

Part II: Module SII Nonclinical Part of the Safety Specification

The nonclinical development of maralixibat for the treatment of cholestatic liver disease is supported by a series of toxicology studies in mice, rats, dogs, rabbits, and monkeys, including single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, reproductive toxicity studies, carcinogenicity studies, and juvenile toxicity studies. To support the chronic dosing of maralixibat in the proposed clinical indication, chronic toxicity testing was completed in two animal species, up to 6 months in rats and up to 1 year in dogs. The oral route of administration was selected for the definitive in vivo toxicity studies since it is the intended clinical route of administration.

eCTD Module 2.4 discusses the in vitro, in vivo, safety pharmacology, absorption, distribution, metabolism, and excretion (ADME), pharmacokinetic, toxicity, genotoxicity, carcinogenicity, and development and reproductive toxicity nonclinical studies conducted.

Nonclinical pharmacology studies indicate that maralixibat inhibits bile acid reabsorption and lowers serum total cholesterol. In vivo, maralixibat increases total bile acid excretion in rats, dogs, and monkeys in a dose-dependent manner. Maralixibat increases the activities of hepatic cholesterol 7α-hydroxylase and 3-hydroxy-3-methylglutaryl-coenzyme A reductase in dogs, consistent with inhibition of bile acid reabsorption.

No significant changes were observed in rat neurobehavioral, dog cardiovascular, or guinea pig pulmonary function safety pharmacology studies following single oral or intravenous administration of maralixibat.

Maralixibat was determined to have a very low bioavailability (≤0.5%) in the mouse, rat, rabbit, and dog. Exposures (maximum observed concentration occurring at the time sampled during a dosing interval and area under the curve) to maralixibat free form, although low after oral administration, increased after repeat-dose administration at the highest doses tested (500 mg/kg/day in the rat and 600 mg/kg/day in the dog).

There was no evidence of pronounced sex-related differences in plasma concentrations of maralixibat free form. The bioavailability of maralixibat free form did not markedly differ in fed and fasted animals, and the exposure of dogs to maralixibat free form was similar after administration of maralixibat as either a solution or as neat chemical in a capsule. The low bioavailability results from low or negligible absorption and not from a hepatic first-pass effect.

The available data support the description of maralixibat as being minimally absorbed into the systemic circulation after oral administration.

The most significant effect observed in rodents administered oral maralixibat was a prolongation of coagulation times. Prolongation of coagulation times was observed primarily in male rats and was reversible, and available data suggest it is a rodent-specific effect.

Oral gavage administration of maralixibat to rats at doses up to 150 mg/kg/day (males) and 500 mg/kg/day (females) for 13 weeks resulted in mild elevations of prothrombin time (PT) and activated partial thromboplastin time with no associated haemorrhage (no observed-adverse-effect level [NOAEL] 150 mg/kg/day). Minimal prolongation of PT was observed in dogs in the 100-mg/kg/day group after 12 months of dosing.

Several reversible changes were observed in rats and were considered to be related to the pharmacologic activity of maralixibat. These included minimal increases in serum levels of hepatic transaminases (AST, ALT) and mild to moderate decreases in absolute and relative liver weights. An increased frequency of emesis was observed in dogs administered 100 mg/kg/day of maralixibat (NOAEL 20 mg/kg/day).

Emesis was the primary toxicity observed in the dog and usually was dose-limiting. Acute oral doses up to 200 mg/kg maralixibat were well tolerated in dogs. Acute intravenous administration of maralixibat in dogs and rats caused tremors, reduced activity, and transient ataxia. Oral administration of maralixibat for up to 26 weeks in rats (at doses up to 500 mg/kg/day) and 2 weeks in monkeys (at doses up to 50 mg/kg/day) was clinically well tolerated without signs of emesis, diarrhoea, or weight loss.

Two juvenile rat toxicokinetic studies were conducted with oral gavage administration of maralixibat in single and consecutive doses. In the first study, maralixibat was well tolerated in weanling rats even at high dose levels. Juvenile rats were administered maralixibat at doses of up to 200 mg/kg/day in the males and up to 1,000 mg/kg/day in the females; no maralixibat-related effects on clinical observations, body weights, food consumption, behaviour, ophthalmology parameters, or sexual maturation were observed. There were no test-article–related effects on any parameter examined except for minor decrease in adrenal gland weights in males and increased liver weights in females.

In the second study, juvenile rats were administered maralixibat for 15 days (postnatal day (PND)7 through PND21) at doses up to 200 mg/kg/day in males and up to 1,000 mg/kg/day in females. Four deaths (1 female at 500 mg/kg/day and 3 females at 1,000 mg/kg/day) were attributed to the test article. Clinical observations and decreased body weight and body weight gain were noted in females at ≥500 mg/kg/day. Increased mean ALP and triglyceride values were observed in the 1,000-mg/kg/day females and decreased mean globulin with increased albumin to globulin ratios was observed in all female groups.

A full development and reproductive toxicity package is complete for maralixibat. In the female portion of the rat fertility study, there was a slight reduction in the mean numbers of corpora lutea, implantation sites, and viable foetuses per dam in the 500- and 2,000-mg/kg/day groups. No treatment-related effects were seen at any dose level on male fertility, and no effects on mating were noted in either sex. Results from rat and rabbit embryo/foetal development studies with doses up to 1,000 and 250 mg/kg/day, respectively, demonstrated no observed adverse effects on foetal growth or development. In the pre- and postnatal development study at doses up to 750 mg/kg/day, there was no reported maternal toxicity (F0), F1 developmental/neonatal toxicity, F1 parental systemic toxicity, F1 reproductive toxicity, or F2 neonatal toxicity when maralixibat was administered continuously in the diet to F0 female rats during gestation and lactation.

Maralixibat demonstrated no evidence of mutagenic activity in vitro and no clastogenic activity in vitro or in vivo. However, 3 impurities tested positive (mutagenic) in the bacterial reverse mutation assay and are being tested and controlled through specifications in the drug substance.

In conclusion, repeat oral dosing of maralixibat for up to 26 weeks in rats and 12 months in dogs revealed no direct adverse effects on clinical pathology parameters, ophthalmology, electrocardiography (dogs) or macroscopic and histopathology parameters. Additionally, maralixibat did not demonstrate genotoxic potential. In the juvenile rat, maralixibat was well tolerated when administered during neonatal development.

Findings from the initial nonclinical studies showed higher incidence of bronchiolo-alveolar adenoma and carcinoma in male RasTG mice administered 25 mg/kg/day maralixibat was observed compared with concurrent study vehicle controls. However, a 104-week oral gavage carcinogenicity study MRXNC-006 in Sprague Dawley rats showed no increase in the incidence of tumours.

Oral gavage administration of 10, 30, or 100 mg/kg/day maralixibat to male and female rats for up to 688 days was tolerated and had no effect on survival. Increased alveolar macrophages were noted in the lung of males administered 100 mg/kg/day and females administered ≥30 mg/kg/day and had macroscopic correlates (discoloured lung, females), but had no impact on survival or oncogenicity. Non-neoplastic, proliferative finding of basophilic foci of cellular alteration in liver was noted for animals administered ≥10 mg/kg/day but had no impact on the survival or oncogenicity. Based on these results, the dose level of 100 mg/kg/day was considered the dose level that had no impact on survival or oncogenicity.

Part II: Module SIII Clinical Trial Exposure

The overall clinical development programme for maralixibat includes data from more than 1,700 participants. Of these, 280 paediatric and adult participants had cholestatic liver disease (of whom more than 200 participants were children and infants), with data collected in 14 clinical studies (Phase 1 study SHP625-101; Phase 2 studies LUM001-301, -302, -303, -304, -305, -501, -201, and LUM001-401; Phase 3 MRX-502 and MRX-503; and studies MRX-701, MRX-800, and MRX-801).

Considering the different data cutoff dates of clinical studies in patients with ALGS and PFIC, the exposure data are not pooled across the entire development programme and instead are presented separately for each indication.

The cumulative exposure to maralixibat by indication within the respective safety populations is provided in Table SIII.1.

Full details on the clinical development programmes in ALGS and PFIC patients are provided in the respective eCTD Modules 2.7.4 Summary of Clinical Safety.

Table SIII.1: Cumulative Exposure to Maralixibat by Indication within the Respective Safety Populations

Indication Population	Participants (N)
ALGS	**86**
Paediatric participants	86
PFIC	**47**
Paediatric participants	47

ALGS=Alagille syndrome; N=total number of participants; PFIC=progressive familial intrahepatic cholestasis.

SIII.1 Alagille Syndrome Programme

The clinical programme in paediatric patients with ALGS included 5 completed Phase 2 studies in paediatric participants with ALGS (LUM001-301, -302, -303, -304, and -305), 1 ongoing Phase 2 study in paediatric participants with ALGS or PFIC (MRX-800), and 1 ongoing Phase 2 study in infants with ALGS or PFIC (MRX-801).

Given that the safety profile of maralixibat in ALGS was based upon an analysis conducted on the 5 completed Phase 2 studies in ALGS, all presented cumulative exposure data are based upon this pooled population for the ALGS indication.

Cumulative exposure for the ALGS indication is presented in Table SIII.2. Exposure data in years and months for the ALGS indication are presented in Table SIII.3 and Table SIII.4, respectively.

Cumulative exposure by age, sex, and racial group is presented in Table SIII.5 and Table SIII.6 for the ALGS indication.

Table SIII.2: Estimates of Cumulative Exposure in Participants with Alagille Syndrome – Safety Population

Study	No. of Participants			
	LUM001-301/ LUM001-305[a]	LUM001-302/ LUM001-303[b]	LUM001-304[c]	Overall
Maralixibat	36	19	31	86
Placebo	12	6	16	34

Note: Based upon actual exposure data from completed clinical trials and the enrolment/randomisation schemes. Studies LUM001-301 and LUM001-302 were 13-week, placebo-controlled studies; Study LUM001-304 had a 4-week (Weeks 18–22) randomised, placebo-controlled withdrawal period.

[a] Twelve participants were exposed to placebo in LUM001-301. Eleven of 12 participants enrolled in the extension study LUM001-305 and were exposed to maralixibat. These participants are counted for both maralixibat and placebo.

[b] Six participants were exposed to placebo in LUM001-302. Five of 6 participants enrolled in the extension study LUM001-303 and were exposed to maralixibat. These participants are counted for both maralixibat and placebo.

[c] Sixteen participants are exposed to both maralixibat and placebo in LUM001-304, and they are counted for both maralixibat and placebo.

Among the 5 completed Phase 2 studies in paediatric participants with ALGS, the duration of treatment exposure is presented in years in Table SIII.3 and in months in Table SIII.4.

Table SIII.3: Integrated Maralixibat Exposure Data in Participants with Alagille Syndrome – Safety Population

Years of Exposure	Up to 1 year	1-2 years	2-3 years	3-4 years	4-5 years	5-6 years
No. of participants	86	67	47	41	34	4

Notes: Data are for completed Phase 2 Studies LUM001-301, LUM001-302, LUM001-303, LUM001-304, and LUM001-305.
For participants with a dose interruption of >60 days (consecutive), the duration of the dose interruption is subtracted from the estimate of total treatment duration.

Table SIII.4: Exposure to Maralixibat in Participants with Alagille Syndrome – Safety Population

Statistics	No. of Months of Maralixibat Exposure by Dose			
	<400 µg/kg/day (N=86)	400 µg/kg/day (N=31)	>400 µg/kg/day (N=20)	Overall (N=86)
Mean	21.09	17.74	27.13	33.45
SD	19.541	8.825	8.113	20.661
Median	14.23	19.44	28.97	32.33
Min, max	<0.1, 59.4	<0.1, 38.5	0.9, 34.1	<0.1, 69.7

max=maximum; min=minimum; SD=standard deviation.
Notes: Data are for Phase 2 Studies LUM001-301, LUM001-302, LUM001-303, LUM001-304, and LUM001--305.
For participants with a dose interruption of >60 days (consecutive), the duration of the dose interruption is subtracted from the estimate of total treatment duration.

Table SIII.5: Cumulative Exposure to Maralixibat in Participants with Alagille Syndrome by Age and Sex – Safety Population (Received Maralixibat)

Age group [a]	No. of Participants		
	Male	**Female**	**Total**
<2 years	6	5	11
2 to 4 years	14	13	27
5 to 8 years	16	9	25
9 to 12 years	7	6	13
13 to 18 years	6	4	10
Total	**49**	**37**	**86**

Note: Data are for completed Phase 2 Studies LUM001-301, LUM001-302, LUM001-303, LUM001-304, and LUM001-305.

[a] Age group is based on age at Screening.

Table SIII.6: Cumulative Exposure to Maralixibat in Participants with Alagille Syndrome by Racial Group – Safety Population (Received Maralixibat)

Racial group	No. of Participants			
	LUM001-301/ LUM001-305	**LUM001-302/ LUM001-303**	**LUM001-304[a]**	**Overall**
White	28	16	—	44
Black or African American	5	1	—	6
Asian	1	1	—	2
Multiple	1	1	—	2
Unknown	1	0	31	32
Total	**36**	**19**	**31**	**86**

Note: Data are for completed Phase 2 Studies LUM001-301, LUM001-302, LUM001-303, LUM001-304, and LUM001-305.

[a] The study sponsor at the time decided to refrain from collection of race information in Study LUM001-304 due to data restrictions in the countries where participants were enrolled per regulation (France) or per Ethics Committee request (Canada).

SIII.2 Progressive Familial Intrahepatic Cholestasis Programme

The clinical programme in paediatric patients with PFIC includes 1 completed Phase 2 study LUM001-501, the completed pivotal Phase 3 study MRX-502, the ongoing extension (to the pivotal study) MRX-503, and 2 ongoing Phase 2 studies MRX-800 and MRX-801 in participants with ALGS or PFIC (refer also to Part III.2).

The safety profile of maralixibat in PFIC patients is based upon the analysis of data from the pivotal study MRX-502.

The cumulative exposure by investigational medicinal product and MRX-502 study cohort is provided in Table SIII.7. The mean treatment duration and exposure by dose are provided in Table SIII.8 and Table SIII.9, respectively. The demographic characteristics of study participants, including their PFIC type, are shown in Table SIII.10.

Table SIII.7: Cumulative Exposure in Pivotal Study MRX-502 by Investigational Medicinal Product and Study Cohort (Safety Population)

Study Cohort	Participants (N)		
	Maralixibat	Placebo	Total
Study MRX-502			
Primary cohort	14	17	31
PFIC cohort	33	31	64
Full cohort [a]	47	46	93

N=total number of participants; PFIC=progressive familial intrahepatic cholestasis.
[a] Full cohort is not a simple sum of primary cohort and PFIC cohort participants.
Source: Table 14.1.1.1

Table SIII.8: Cumulative Exposure to Maralixibat in Pivotal Study MRX-502 by Mean Treatment Duration and Mean Treatment Exposure (Safety Population)

Variable Statistics	Primary Cohort (N=14)	PFIC Cohort (N=33)	Full Cohort (N=47)
Treatment duration (days)			
Mean	178.9	184.4	177.1
SD (SE)	20.69 (5.53)	18.77 (3.27)	36.57 (5.33)
Median	183.0	183.0	183.0
Q1, Q3	182.0, 185.0	183.0, 186.0	182.0, 187.0
Min, max	108, 193	108, 256	12, 256
Treatment exposure (days)			
Mean	177.1	180.8	174.1
SD (SE)	20.71 (5.53)	14.25 (2.48)	35.01 (5.11)
Median	182.5	183.0	183.0
Q1, Q3	181.0, 185.0	182.0, 186.0	181.0, 186.0
Min, max	108, 192	108, 192	10, 203

max=maximum; min=minimum; N=total number of participants; PFIC=progressive familial intrahepatic

cholestasis; SD=standard deviation; SE=standard error of the mean; Q1=25th percentile; Q3=75th percentile
Treatment duration (days)=Date of last dose of study drug - Date of first dose of study drug + 1 day.
For participants who were missing the date of the last dose of study drug, the last known contact date was used to calculate treatment duration.
Treatment exposure (days)=Treatment duration in days - Number of days both morning and evening doses were missed.
Source: Table 14.3.1

Table SIII.9: Cumulative Exposure to Maralixibat in Pivotal Study MRX-502 by Dose (Safety Population)

Variable Statistic	Primary Cohort (N=14)	PFIC Cohort (N=33)	Full Cohort (N=47)
Average daily dose (µg/kg/day)			
Mean	1049.22	1005.77	962.35
SD (SE)	67.496 (18.039)	146.494 (25.501)	210.054 (30.639)
Median	1071.80	1041.80	1029.51
Q1, Q3	1023.61, 1095.33	979.56, 1091.80	934.20, 1091.80
Min, max	920.3, 1122.2	431.3, 1126.6	212.5, 1126.6
Total dose (µg/kg)			
Mean	187800.0	184081.8	172662.8
SD (SE)	25113.31 (6711.82)	26754.74 (4657.40)	46999.64 (6855.60)
Median	194550.0	190200.0	188850.0
Q1, Q3	180300.0, 204000.0	177300.0, 203700.0	170250.0, 203700.0
Min, max	110550, 207600	110400, 211800	2550, 213150

max=maximum; min=minimum; N=total number of participants; PFIC=progressive familial intrahepatic cholestasis; SD=standard deviation; SE=standard error of the mean; Q1=25th percentile; Q3=75th percentile
Note: Treatment duration (days) =Date of last dose of study drug - Date of first dose of study drug + 1 day.
Treatment exposure (days) = Treatment duration in days - Number of days both morning and evening doses were missed.
Source: Table 14.3.1

Table SIII.10: Cumulative Exposure to Maralixibat and Placebo in Pivotal Study MRX-502 by Demographic Characteristics and PFIC Type (Safety Population)

Variable Statistics or Category	Primary Cohort			PFIC Cohort			Full Cohort		
	Maralixibat (N=14)	Placebo (N=17)	Overall (N=31)	Maralixibat (N=33)	Placebo (N=31)	Overall (N=64)	Maralixibat (N=47)	Placebo (N=46)	Overall (N=93)
Age (years) [a]									
Mean	6.3	4.2	5.1	4.9	4.4	4.6	4.8	4.7	4.7
SD (SE)	5.24 (1.40)	3.56 (0.86)	4.45 (0.80)	4.10 (0.71)	3.61 (0.65)	3.85 (0.48)	4.15 (0.61)	3.57 (0.53)	3.85 (0.40)
Median	4.0	3.0	3.0	3.0	3.0	3.0	3.0	3.5	3.0
Q1, Q3	3.0, 11.0	1.0, 7.0	1.0, 8.0	2.0, 7.0	1.0, 7.0	1.0, 7.0	2.0, 7.0	1.0, 7.0	2.0, 7.0
Min, max	1, 15	1, 13	1, 15	1, 15	1, 13	1, 15	1, 17	1, 14	1, 17
Age category [a], n (%)									
1 to <6 years	9 (64.3)	11 (64.7)	20 (64.5)	22 (66.7)	19 (61.3)	41 (64.1)	32 (68.1)	29 (63.0)	61 (65.6)
6 to <13 years	2 (14.3)	5 (29.4)	7 (22.6)	8 (24.2)	11 (35.5)	19 (29.7)	11 (23.4)	15 (32.6)	26 (28.0)
13 to 18 years	3 (21.4)	1 (5.9)	4 (12.9)	3 (9.1)	1 (3.2)	4 (6.3)	4 (8.5)	2 (4.3)	6 (6.5)
Sex, n (%)									
Male	7 (50.0)	6 (35.3)	13 (41.9)	17 (51.5)	13 (41.9)	30 (46.9)	20 (42.6)	22 (47.8)	42 (45.2)
Female	7 (50.0)	11 (64.7)	18 (58.1)	16 (48.5)	18 (58.1)	34 (53.1)	27 (57.4)	24 (52.2)	51 (54.8)
Race, n (%)									
American Indian or Alaska Native	3 (21.4)	3 (17.6)	6 (19.4)	3 (9.1)	4 (12.9)	7 (10.9)	3 (6.4)	4 (8.7)	7 (7.5)
Asian	0	0	0	3 (9.1)	0	3 (4.7)	3 (6.4)	0	3 (3.2)
Black or African American	1 (7.1)	2 (11.8)	3 (9.7)	1 (3.0)	2 (6.5)	3 (4.7)	1 (2.1)	2 (4.3)	3 (3.2)

Variable Statistics or Category	Primary Cohort			PFIC Cohort			Full Cohort		
	Maralixibat (N=14)	Placebo (N=17)	Overall (N=31)	Maralixibat (N=33)	Placebo (N=31)	Overall (N=64)	Maralixibat (N=47)	Placebo (N=46)	Overall (N=93)
White	9 (64.3)	9 (52.9)	18 (58.1)	24 (72.7)	19 (61.3)	43 (67.2)	36 (76.6)	34 (73.9)	70 (75.3)
More than one race	1 (7.1)	2 (11.8)	3 (9.7)	2 (6.1)	4 (12.9)	6 (9.4)	3 (6.4)	4 (8.7)	7 (7.5)
Not Reported	0	1 (5.9)	1 (3.2)	0	2 (6.5)	2 (3.1)	1 (2.1)	2 (4.3)	3 (3.2)
Ethnicity, n (%)									
Hispanic or Latino	9 (64.3)	7 (41.2)	16 (51.6)	16 (48.5)	13 (41.9)	29 (45.3)	18 (38.3)	17 (37.0)	35 (37.6)
Not Hispanic or Latino	5 (35.7)	9 (52.9)	14 (45.2)	17 (51.5)	16 (51.6)	33 (51.6)	28 (59.6)	27 (58.7)	55 (59.1)
Not Reported	0	1 (5.9)	1 (3.2)	0	2 (6.5)	2 (3.1)	1 (2.1)	2 (4.3)	3 (3.2)
Region, n (%)									
Asia	0	0	0	2 (6.1)	0	2 (3.1)	2 (4.3)	0	2 (2.2)
Europe	3 (21.4)	5 (29.4)	8 (25.8)	7 (21.2)	7 (22.6)	14 (21.9)	14 (29.8)	10 (21.7)	24 (25.8)
Middle East	1 (7.1)	0	1 (3.2)	5 (15.2)	5 (16.1)	10 (15.6)	7 (14.9)	9 (19.6)	16 (17.2)
North America	6 (42.9)	9 (52.9)	15 (48.4)	9 (27.3)	12 (38.7)	21 (32.8)	13 (27.7)	19 (41.3)	32 (34.4)
South and Central America	4 (28.6)	3 (17.6)	7 (22.6)	10 (30.3)	7 (22.6)	17 (26.6)	11 (23.4)	8 (17.4)	19 (20.4)
PFIC type (genotype), n (%)									
PFIC2 (*ABCB11*)	14 (100.0)	17 (100.0)	31 (100.0)	14 (42.4)	17 (54.8)	31 (48.8)	23 (48.9)	22 (47.8)	45 (48.4)
nt-PFIC2	14 (100.0)	17 (100.0)	31 (100.0)	14 (42.4)	17 (54.8)	31 (48.8)	18 (38.3)	18 (39.1)	36 (38.7)
BSEP1	2 (14.3)	6 (35.5)	8 (25.8)	2 (6.1)	6 (19.4)	8 (12.5)	4 (8.5)	6 (13.0)	10 (10.8)
BSEP2	12 (85.7)	11 (64.7)	23 (74.2)	12 (36.4)	11 (35.5)	23 (35.9)	14 (29.8)	12 (26.1)	26 (28.0)
t-PFIC2 (*BSEP3*)	0	0	0	0	0	0	5 (10.6)	4 (8.7)	9 (9.7)
PFIC1 (*ATP8B1*)	0	0	0	7 (21.2)	6 (19.4)	13 (20.3)	9 (19.1)	8 (17.4)	17 (18.3)

Variable Statistics or Category	Primary Cohort			PFIC Cohort			Full Cohort		
	Maralixibat (N=14)	Placebo (N=17)	Overall (N=31)	Maralixibat (N=33)	Placebo (N=31)	Overall (N=64)	Maralixibat (N=47)	Placebo (N=46)	Overall (N=93)
PFIC3 (*ABCB4*)	0	0	0	4 (12.1)	5 (16.1)	9 (14.1)	4 (8.5)	5 (10.9)	9 (9.7)
PFIC4 (*TJP2*)	0	0	0	6 (18.2)	1 (3.2)	7 (10.9)	6 (12.8)	2 (4.3)	8 (8.6)
PFIC6 (*MYO5B*)	0	0	0	2 (6.1)	2 (6.5)	4 (6.3)	2 (4.3)	2 (4.3)	4 (4.3)
Heterozygous variant [c]	0	0	0	0	0	0	0	2 (4.3)	2 (2.2)
No variant found	0	0	0	0	0	0	3 (6.4)	5 (10.9)	8 (8.6)

BSEP=bile salt excretion pump; max=maximum; min=minimum; N=total number of participants; nt-PFIC2=nontruncating progressive familial intrahepatic cholestasis 2; PFIC=progressive familial intrahepatic cholestasis; SD=standard deviation; SE=standard error of the mean; Q1=25th percentile; Q3=75th percentile; t-PFIC2=truncating progressive familial intrahepatic cholestasis 2.

[a] Age at baseline visit.

[b] nt-PFIC2=partial loss of BSEP function; t-PFIC2=complete loss of BSEP function. Only applicable for PFIC2 participants, with exception of 1 nt-PFIC2 participant with heterozygosis *ABCB11* mutation; Not applicable for all other participants.

[c] One participant had heterozygous ABCB11 mutation, and another had heterozygous *ATP8B1* mutation.

Source: Tables 14.1.3 and 14.1.4

Part II: Module SIV Populations Not Studied in Clinical Trials

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

The important exclusion criteria discussed in this section were selected from the exclusion criteria introduced in the pivotal Study LUM001-304 in patients with ALGS (Table SIV.1) and in the pivotal Study MRX-502 in patients with PFIC (Table SIV.2).

Table SIV.1: Exclusion Criteria in Pivotal Clinical Study LUM001-304 in ALGS Clinical Development Programme

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?	Rationale
Chronic diarrhoea requiring ongoing intravenous fluid or nutritional intervention	Maralixibat has been associated with GI effects and could exacerbate this condition.	No	It can be anticipated that use in these patients may increase the risk of diarrhoea. Based on the known safety profile of maralixibat, diarrhoea is considered to be an identified risk for maralixibat.
Surgical interruption of the enterohepatic circulation	Surgical interruption may negate the effects of maralixibat, which inhibits ASBT resulting in blocking of enterohepatic recirculation of bile acids.	No	It is not anticipated that maralixibat will be used in this population.
Previous liver transplant	Maralixibat is intended for use in patients with compromised native liver function.	No	It is not anticipated that maralixibat will be used in this population.
Decompensated cirrhosis (ALT >15 × ULN, INR >1.5 [unresponsive to vitamin K therapy], albumin <3.0 g/dL, history or presence of clinically significant ascites, variceal haemorrhage, and/or encephalopathy)	These conditions could confound results with maralixibat.	No	It is not anticipated that maralixibat will be used in this population.
History or presence of other concomitant liver disease	Maralixibat is intended for use in ALGS; other liver conditions could confound results.	No	It is not anticipated that maralixibat will be used in this population.

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?	Rationale
History or presence of any other disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, including bile salt metabolism in the intestine (e.g., inflammatory bowel disease)	These conditions could confound results with maralixibat; maralixibat has been associated with GI effects.	No	It is not anticipated that maralixibat will be used in this population.
History or presence of gallstones or kidney stones	Condition could confound results with maralixibat.	No	Use in this population is not predicted to be associated with additional risks of clinical significance.
Known diagnosis of HIV infection	Condition could confound results with maralixibat.	No	It is not anticipated that maralixibat will be used in this population.
Cancers, except for in situ carcinoma, or cancers treated at least 5 years prior to screening with no evidence of recurrence	Condition could confound results with maralixibat.	No	It is not anticipated that maralixibat will be used in this population.
Recent medical history or current status that suggests that the subject may be unable to complete the study	Condition could confound results with maralixibat.	No	Not applicable
Any female who is pregnant or lactating or who is planning to become pregnant during the study period	Maralixibat has not been studied in pregnant or lactating participants.	No	It is not anticipated that maralixibat will be used in this population.
Known history of alcohol or substance abuse	Abuse of either substance may affect the liver, which could confound results with maralixibat.	No	It is not anticipated that maralixibat will be used in this population.
Administration of bile acid or lipid binding resins within 28 days prior to screening and throughout the trial	Use could confound interpretation of results with maralixibat due to overlapping mechanisms of action	No	Use in this population is not predicted to be associated with additional risks of clinical significance.

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?	Rationale
Known hypersensitivity to maralixibat or any of its components	To prevent allergic reactions	No	It is not anticipated that maralixibat will be used in this population.
Receipt of investigational drug, biologic, or medical device within 28 days prior to screening, or 5 half-lives of the study agent, whichever is longer	Condition could confound results with maralixibat.	No	Not applicable
History of non-adherence to medical regimens, unreliability, mental instability or incompetence that could compromise the validity of informed consent or lead to nonadherence with the study protocol based upon investigator judgment	Condition could confound results with maralixibat.	No	Not applicable
Any other conditions or abnormalities that, in the opinion of the investigator or sponsor medical monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study	Condition could confound results with maralixibat.	No	It is not anticipated that maralixibat will be used in this population.
Subjects weighing over 50 kg at screening	There was no notable change from baseline in mean total sBA concentration among obese subjects in Study SHP625-101.	No	Use in this population is not predicted to be associated with additional risks of clinical significance.

ALGS=Alagille syndrome; ASBT=apical sodium-dependent bile acid transporter; GI=gastrointestinal; HIV=human immunodeficiency virus; INR=International normalised ratio; sBA=serum bile acid; ULN=upper limit of normal.

Table SIV.2: Important Exclusion Criteria from Pivotal Clinical Study MRX-502 in Patients with Progressive Familial Intrahepatic Cholestasis

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?	Rationale
Current or recent history (<1 year) of atopic dermatitis or other non-cholestatic disease associated with pruritus	This criterion was established to minimise the potential confounding factors for the evaluation of efficacy and safety of maralixibat.	No	The safety profile of maralixibat is not expected to differ in patients with atopic dermatitis or other condition associated with pruritus.
Chronic diarrhoea requiring intravenous fluid or nutritional intervention for the diarrhoea and/or its sequelae	Maralixibat has been associated with GI effects and could exacerbate this condition.	No	It can be anticipated that use in these patients may increase the risk of diarrhoea. Based on the known safety profile of maralixibat, diarrhoea is considered to be an identified risk for maralixibat.
Previous or need for imminent liver transplant	Maralixibat is intended for use in patients with compromised native liver function.	No	It is not anticipated that maralixibat will be used in this population.
Decompensated cirrhosis (INR >1.5 and/or albumin <30 g/L, history or presence of clinically significant ascites, and/or variceal haemorrhage, and/or encephalopathy) ALT or TSB >15 × ULN at screening	These conditions could confound results with maralixibat.	No	It is not anticipated that maralixibat will be used in this population.
Presence of other liver disease	Maralixibat is intended for use in PFIC; other liver conditions could confound results.	No	It is not anticipated that maralixibat will be used in this population.

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?	Rationale
Possible malignant liver mass on imaging Any prior cancer diagnosis (except for in situ carcinoma)	Condition could confound results with maralixibat.	No	It is not anticipated that maralixibat will be used in this population.

ALT=alanine aminotransferase; GI=gastrointestinal; INR=international normalised ratio; PFIC2=progressive familial intrahepatic cholestasis type 2; TSB=total serum bilirubin; 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 adverse reactions that are uncommon, 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 Programs

Table SIV.3: 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	
Patients with relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Maralixibat is minimally absorbed and plasma concentrations are often below the limit of detection (0.25 ng/mL). In the course of its development for cholestatic diseases, maralixibat has been assessed in patients with varying degree of hepatic impairment, with no indication of an effect on plasma drug levels. However, the pharmacokinetics of maralixibat have not been systematically investigated in patients classified according to the Child-Pugh classification. Patients with end-stage liver failure or cirrhosis have not been specifically investigated. Maralixibat has not been specifically studied in individuals with renal impairment but such patients were not excluded from the development programme. The very low renal clearance of maralixibat (<1% in urine) indicates a very low risk of increased plasma exposures in subjects with renal impairment. Cardiovascular anomalies are present in more than 90% of patients with ALGS. Involvement of the

Type of Special Population	Exposure
	pulmonary outflow tract is the most common type of congenital heart disease, with some form of peripheral pulmonary stenosis, affecting at least two-thirds of cases (Turnpenny and Ellard 2012). Patients with co-morbid cardiovascular impairment as part of the diagnosis of ALGS were included in the clinical development programme. PFIC patients with cardiovascular impairment or immunocompromised patients were not excluded from the clinical development programme but such patients were not specifically investigated.
Population with relevant different ethnic origin	Participants of different race or ethnic origin were included in the clinical development programme for maralixibat in ALGS (refer to Table SIII.6) and PFIC patients (refer to Table SIII.10).
Subpopulations carrying relevant genetic polymorphisms	Refer to Table SIII.10, showing subject exposure in PFIC participants by their disease genotype.

ALGS=Alagille syndrome; PFIC=progressive familial intrahepatic cholestasis.

Part II: Module SV Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

The estimated post-marketing exposure to LIVMARLI in the EU/EEA is based on the number of unique shipments to locations for commercial LIVMARLI with the assumption that a unique location equates to a unique patient.

The estimated post-marketing exposure to LIVMARLI in the United States and Canada is based on Mirum Specialty Pharmacy unique patient commercial dispense level details.

SV.1.2 Exposure

Since the International Birth Date for maralixibat (29 September 2021) until 28 September 2023, LIVMARLI was prescribed and dispensed to an estimated 446 patients in the post-marketing setting (Table SIV.1).

Table SV.1: Cumulative Patient Exposure to LIVMARLI in Post-Marketing Setting

Region/Country	Estimated Number of Patients
EU/EEA	**94**
France	46
Germany	48
Non-EU/EEA	**352**
Canada	11
United States	341
Total	**446**

EEA=European Economic Area; EU=European Union.

Additionally, maralixibat has been provided to patients with ALGS and PFIC within the early access programmes, conducted in the EU/EEA (Austria, Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Slovenia, and Spain), Australia, Canada, China, Colombia, Israel, Russia, Singapore, Switzerland, Taiwan, United Arab Emirates, United Kingdom, and United States.

Table SV.2 shows the overall number of patients enrolled in the early access programmes as of 28 September 2023.

Table SV.2: Cumulative Enrolment in the Early Access Programmes for Maralixibat

Indication	No. of Enrolled Patients
ALGS	272
PFIC	21
Other indications	11
Total	**304**

ALGS=Alagille syndrome; PFIC=progressive familial intrahepatic cholestasis

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

Potential for Misuse for Illegal Purposes

Based on the mechanism of action, maralixibat is not anticipated to have a potential for misuse for illegal purposes.

Part II: Module SVII Identified and Potential Risks

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

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The identified risks (ADRs) associated with the use of maralixibat in the indication of ALGS are diarrhoea and abdominal pain; neither is considered an important safety concern at this time. With data from up to 4 years on treatment, these effects are not shown to increase with increased dosing or time on treatment, and they typically resolve in less than a week, which demonstrates that these effects are transient in nature.

Hepatotoxicity is the only important potential risk for maralixibat.

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 GI-related adverse events observed with maralixibat—diarrhoea and abdominal pain—are mechanism-based due to elevated bile acid concentrations in the colon and, therefore, are not unexpected. They are considered to have minimal clinical impact on patients in relation to the severity of the indications treated.

Consistent with the previous clinical programme of hypercholesterolaemia in adults, the most commonly reported ADRs in the current clinical programme of cholestatic liver diseases are abdominal cramping/pain and diarrhoea/loose stools. No treatment-related events of diarrhoea or abdominal pain were serious, no treatment-related events of diarrhoea were severe (i.e., Grade ≥3), and only one patient (1.2% of the ALGS safety population, N=86) had a treatment-related event of Grade ≥3 abdominal pain. Additionally, these events were transient (median duration 2 days for diarrhoea, 1 day for abdominal pain) and resolved for the majority of participants while remaining on treatment. No events of abdominal pain or diarrhoea resulted in discontinuation of maralixibat in the clinical studies comprising the current development programme.

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

The above GI risks, diarrhoea and abdominal pain, require no further characterisation and will be followed up via routine pharmacovigilance—namely, through signal detection and adverse reaction reporting. Risk-minimisation measures recommended in the product information (SmPC) are considered part of standard clinical practice and are as follows:

- From Section 4.4: *"Diarrhoea has been reported as a very common adverse reaction when taking maralixibat (section 4.8). Diarrhoea may lead to dehydration. Patients should be monitored regularly to ensure adequate hydration during episodes of diarrhoea."*
- From Section 4.8: "*If diarrhoea and/or abdominal pain persist and no other aetiologies are found, reducing the dose or interrupting treatment should be considered. Dehydration should be monitored and treated promptly. If dosing*

with Livmarli is interrupted, Livmarli can be restarted as tolerated when diarrhoea or abdominal pain improve (Section 4.2).”

In addition, the following guidance is provided to patients and caregivers in the Package leaflet (Section 2):

- *Talk to your doctor if your diarrhoea gets worse while taking Livmarli. If you get diarrhoea, drink plenty of liquids so you do not become dehydrated.*

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Potential Risk: Hepatotoxicity

Risk-Benefit Impact: Data from the long-term extension studies in participants with ALGS shows that ALT increased was the most commonly reported event (6 participants; 7.1%) that led to discontinuation of maralixibat. Events were considered related or possibly related to maralixibat; however, the large underlying intrapatient ALT variability observed in the natural history of ALGS (Kamath et al. 2020), is an alternative explanation. Given the limited data in the target population, the potential risk of hepatotoxicity requires further characterisation.

Continued surveillance of hepatic safety is recommended in the product information, and evaluation is planned via additional pharmacovigilance measures to further characterise this risk. If confirmed, hepatoxicity will have an impact on the benefit/risk ratio. Therefore, hepatotoxicity is included as an important potential risk in the RMP.

Missing Information: Carcinogenic Potential

Risk-Benefit Impact: The higher incidence of bronchiolo-alveolar adenoma and carcinoma was observed in male RasTG mice administered 25 mg/kg/day maralixibat within the nonclinical programme compared with concurrent study vehicle controls. While the incidences of these findings were still within the range of those observed in historical controls of this mouse strain, in rat repeat-dose toxicity studies, GI mucosal epithelial alterations (e.g., crowding/proliferation of crypt cells) were observed that may theoretically indicate a risk of future carcinogenic transformation. The implication of this finding for human risk assessment is unknown and as such, it cannot be ruled out that these findings are related to maralixibat. Therefore, carcinogenic potential of maralixibat is considered as missing information and requires further investigation.

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

The clinical studies conducted in PFIC participants did not identify any safety concerns specifically associated with the use of maralixibat. However, the long-term safety of maralixibat in ALGS and PFIC patients and the long-term safety of chronic exposure to propylene glycol in PFIC patients from 3 months to 5 years of age represent new areas of missing information (refer to SVII.3.2) , while medication errors resulting from erroneous dosing represents important potential risk in PFIC population.

The missing information of carcinogenic potential was removed from the list of safety concerns, following the results of the completed PASS MRXNC-006 (refer to Part II: Module SII) and outcome of the procedure EMEA/H/C/005857/II/0009.

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

Important Potential Risk 1: Hepatotoxicity

Potential mechanisms:

No mechanism of action for maralixibat to potentially cause hepatoxic effects is currently known. There is currently no evidence that maralixibat causes bilirubin elevations in patients with ALGS or PFIC.

Evidence source(s) and strength of evidence:

Increased ALT and AST activity was observed in some patients receiving maralixibat treatment. Considering a close temporal relationship, a positive de-challenge and re-challenge for some of the received cases, a causal relationship between maralixibat and ALT/AST increased is at least a reasonable possibility.

Laboratory data showed elevations in transaminases in some ALGS participants during treatment in the clinical trials; most of the values were considered non-serious. Serious adverse events or autoimmune hepatitis (1 participant) and chronic hepatic failure (1 participant) were reported. However, involvement of the underlying disease cannot be excluded. During the long-term extension trials in ALGS, 6 (7.1%) participants discontinued the trial due to ALT increases that were all assessed as related or possibly related to study drug.

In the pivotal Study MRX-502 in PFIC participants, numerically, there were more maralixibat-treated participants who had adverse events of elevated transaminases in comparison to the placebo-treated participants. However, abnormal liver enzymes vary by PFIC type and approximately 70% of patients with PFIC1 and 95% of patience with PFIC2 have abnormal ALT levels at baseline (Sakita et al. 2018). Fluctuating liver enzymes are expected in patients with PFIC.

ALGS and PFIC patients are difficult populations to assess because of wide variability in the severity of the underlying disease, the pre-existence or development of advanced liver disease, and the wide intra-patient variability in ALT that is observed in the natural history.. Due to the small overall sample size and the paucity of placebo-controlled data in the clinical studies in ALGS and PFIC participants, further evaluation is needed.

Characterisation of the risk:

Clinical trials

ALGS participants

A group of paediatric hepatologists adjudicated 27 suspected cases within the maralixibat development programme for ALGS treatment. The group reached the conclusion that of the 27 cases, 6 were considered possibly and 1 probably related to the study drug. One case was considered as probably drug-associated liver injury. They assessed 24 of 27 cases as of low concern and 3 as of medium concern.

In addition, during the long-term extension trials, 6 participants (7.1%) discontinued the trial due to ALT increases that were all assessed as related or possibly related to drug.

However, due to the overall small sample size of the clinical studies and the underlying disease also potentially affecting liver function parameters, a final conclusion cannot be

drawn and further evaluation is needed. Hepatotoxicity will be further evaluated in post-marketing experience in Studies MRX-803 (former MRX-311), MRX-800, and MRX-801.

PFIC participants

In the full cohort of Study MRX-502, 8 maralixibat participants (17%) and 3 placebo participants (6.5%) had elevated transaminases events. Therefore numerically, there were more maralixibat-treated participants who had adverse events of elevated transaminases in comparison to the placebo-treated participants. However, a review of objective transaminase laboratory data for all cohorts of Study MRX-502 (i.e., primary, PFIC, and full cohort) demonstrated no clinically meaningful differences between maralixibat and placebo for change from baseline at any time point. For the PFIC cohort, a mixed model repeated measures analysis also showed no clinically or statistically significant differences in ALT or AST levels between maralixibat and placebo.

None of the events of elevated transaminases were considered serious, all were mild or moderate in severity, most events of elevated transaminases were not considered treatment related, and no events of elevated transaminases led to discontinuation of study drug.

Six of 8 participants with transaminase increased had no change in dose, and majority of the events (4 of 6) resolved with continued dosing in all but 2 participants. These 2 participants had dose interruptions or reductions with subsequent rechallenge to full dose of study drug without resolution or worsening of the event and without clinical sequalae, supporting a negative dechallenge.

There were no trends noted in terms of latency or timing of event relative to the first dose of maralixibat. No dose-response relationship was observed.

There have been no drug-induced liver injury events observed to date in Studies MRX-502 or MRX-503.

Post-authorisation experience

Increased ALT and AST activity was observed in some patients receiving maralixibat treatment. Considering a close temporal relationship, a positive de-challenge and re-challenge for some of the received cases, a causal relationship between maralixibat and ALT/AST increased is at least a reasonable possibility.

The general characterisation of this risks did not change with the information collected from the post-marketing sources.

Risk factors and risk groups:

Currently, there are no risk factors or groups that have been observed to be at risk for hepatotoxicity with maralixibat treatment.

The natural history comparison demonstrated that elevation of ALT is common in the ALGS population (varying from 56% lower to 129% higher for 95% of the time in a given individual) (Kamath et al. 2020), that this increase is associated with increased age, and that there was no significant difference in such elevations with or without maralixibat treatment.

Abnormal liver enzymes vary by PFIC type and approximately 70% of patients with PFIC1 and 95% of patience with PFIC2 have abnormal ALT levels at baseline (Sakita et al. 2018). Fluctuating liver enzymes are expected in patients with PFIC.

No dose-relationship has been seen in patients with ALGS or PFIC who experienced elevated transaminases while on treatment with maralixibat. No additive or synergistic effects with

other drugs are known to occur with the introduction of maralixibat treatment.

The safety of LIVMARLI has not been established in patients with decompensated cirrhosis.

Preventability:

Currently, there are no data on predictability of hepatotoxicity or factors that could increase the risk of hepatotoxicity with administration of maralixibat. However, early detection of elevations of liver enzymes could mitigate occurrence of hepatotoxicity.

Therefore, liver function should be monitored in patients with ALGS and PFIC prior to start and during treatment with maralixibat. Additionally, close monitoring is advised for patients with ALGS and PFIC with end-stage liver disease or (progression to) decompensation.

LIVMARLI is contraindicated in patients with prior or active liver decompensation events (e.g., variceal haemorrhage, ascites, hepatic encephalopathy).

Impact on the risk-benefit balance of the product:

Elevations in transaminases have been observed in ALGS and PFIC development programs for maralixibat, which may be related to underlying liver disease or other factors. Increased ALT and AST activity was observed in some patients receiving maralixibat treatment. Considering a close temporal relationship, a positive de-challenge and re-challenge for some of the received cases, a causal relationship between maralixibat and ALT/AST increased is at least a reasonable possibility. Nonetheless, further investigation is needed to determine whether maralixibat poses a hepatotoxicity risk.

Further characterisation for the potential risk of hepatotoxicity via the proposed Study MRX-803 (in ALGS and PFIC patients) and within the ongoing Studies MRX-800, MRX-801 (in ALGS and PFIC patients), and MRX-503 (in PFIC patients) is expected to provide additional data that may help in the clarification of the nature of the hepatic findings in patients with ALGS and PFIC treated with maralixibat (refer to Part III.2). The data are expected to allow a more thorough analysis to determine whether maralixibat is hepatotoxic. With the current data on efficacy, the benefit-risk balance is considered to be favourable for patients with ALGS and PFIC.

Public health impact:

The elevations of liver enzymes in patients with ALGS and PFIC are common. Approximately 70% of patients with PFIC1 and 95% of patients with PFIC2 have abnormal ALT levels at baseline (Sakita et al. 2018).

The estimate of events of hepatotoxicity or elevated liver enzymes in patients with ALGS and PFIC treated with maralixibat is anticipated to be similar to the background rate of these events in patients not treated with maralixibat.

Considering the overall low incidence of ALGS and PFIC in general population, any impact of this risk on the public health is considered negligible.

Important Potential Risk 2: Medication Error Resulting from Erroneous Dosing (PFIC Patients)

Potential mechanisms:

LIVMARLI medicinal product consists of a multidose bottle, co-packed with three, repeat-use syringes of different sizes (0.5 ml, 1 ml, and 3 mL). The dosing of LIVMARLI oral solution is based on patient's weight. The individual dose volume and the correct syringe are presented in the dosing schedule within the method of administration.

Evidence source(s) and strength of evidence:

Administration of LIVMARLI is associated with a potential for medication errors resulting from erroneous dosing in patients with PFIC, potentially leading to overdose or other undesirable clinical outcomes associated with incorrect dosing. Patients with PFIC require higher doses of LIVMARLI than patients with ALGS and as such are at higher risk for potential undesirable clinical outcomes associated with overdose due to dosing medication errors. No reports of undesirable clinical outcomes due to dosing medication errors were collected to date for LIVMARLI in the clinical trials or in the post-marketing setting.

Characterisation of the risk:

The frequency of dosing medication errors leading to any undesirable clinical outcomes has not yet been established.

Sporadic cases of asymptomatic, accidental overdose have been reported in association with LIVMARLI oral solution in the clinical trials and the post-marketing setting. However, no reports suggestive of undesirable clinical outcomes resulting from the medication error were collected to date.

Additionally, LIVMARLI oral solution contains propylene glycol, which may be harmful if given in excessive amount, especially to small children, which are the target population for LIVMARLI (refer also to SVII.3.2). No reports of propylene glycol harmful effect associated with medication error were reported to date for LIVMARLI.

Risk factors and risk groups:

Patients with PFIC require higher doses of LIVMARLI than patients with ALGS and as such are at higher risk for potential undesirable clinical outcomes associated with overdose due to dosing medication errors.

Additionally, patients at higher risk for toxicity associated with propylene glycol include infants and small children, those with renal or hepatic impairment, epilepsy, and burn patients receiving extensive dermal applications of propylene glycol-containing products (Lim et al. 2014) (refer also to SVII.3.2).

Preventability:

Special attention should be paid to accurate calculation of the LIVMARLI dose and clear communication of dosing instructions to caregivers and patients to minimise the risk of medication errors and overdoses.

The additional risk minimisation measures in place for this risk are detailed in Part V.2.

Impact on the risk-benefit balance of the product:

While the overall number of medication errors leading to harm is small, the actual impact on individual patients or the healthcare system can be high (European Medicines Agency 2024).

LIVMARLI has an increased potential for medication errors resulting from erroneous dosing in PFIC patients. Considering the routine and additional risk minimisation measures in place and the nature of medication errors reported from the clinical trials and post-marketing experience to date, the impact of this potential risk on the benefit-risk balance of LIVMARLI is acceptable.

Public health impact:

The impact of this risk on the public health is considered negligible in light of the rarity of PFIC indication.

SVII.3.2 Presentation of the Missing Information

Missing Information 1: Long-Term Safety

Evidence source:

Given the rare nature of the indication and the limited population eligible for clinical studies, there are limited data on the long-term exposure to maralixibat from the clinical development programme in ALGS and PFIC patients.

Population in need of further characterisation:

The long-term safety data in all age groups and disease genotypes of patients with ALGS and PFIC need to be collected post approval. A planned category 2 MRX-803 (former MRX-311) study and the ongoing category 3 studies MRX-800, MRX-801, and MRX-503 will further characterise the long-term safety of maralixibat in these patient populations (refer to Part III.2).

Missing Information 2: Long-Term Safety of Chronic Exposure to Propylene Glycol in PFIC Patients from 3 Months to 5 Years of Age

Evidence source:

Propylene glycol is a generally safe excipient and the commercial formulation of LIVMARLI was developed to adhere to the current conservative safety limit for propylene glycol, recognised as safe in humans down to 1 month of age, i.e., 50 mg/kg/day (EMA/CHMP/334655/2013).

The adverse effects associated with propylene glycol per the literature include central nervous system toxicity, hyperosmolarity, haemolysis, cardiac arrhythmia, seizures, agitation, and lactic acidosis (Lim et al. 2014).

Since LIVMARLI is administered to PFIC patients in doses higher than in ALGS patients and it is intended for the long-term use, the impact of prolonged exposure to propylene glycol in patients from 3 months to 5 years of age is unknown.

Anticipated risk/consequence of the missing information and population in need of further characterisation:

Since propylene glycol can accumulate with higher doses and/or prolonged use, the outcome of prolonged exposure to LIVMARLI is unknown and will be further investigated within a planned category 2 study MRX-803 (former MRX-311) (refer to Part III.2).

Patients at risk for toxicity associated with propylene glycol include infants and small children, those with renal or hepatic impairment, epilepsy, and burn patients receiving extensive dermal applications of propylene glycol-containing products (Lim et al. 2014).

Part II: Module SVIII Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity Medication error resulting from erroneous dosing (PFIC patients)
Missing information	Long-term safety Long-term safety of chronic exposure to propylene glycol in PFIC patients from 3 months to 5 years of age

PFIC=progressive familial intrahepatic cholestasis

Part III Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

The pharmacovigilance plan does not include any routine pharmacovigilance activities beyond signal management and reporting of adverse reactions.

III.2 Additional Pharmacovigilance Activities

Study MRX-803 (Former MRX-311) Summary

Study Short Name and Title:

MRX-803 (former MRX-311): "Long-term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome and Progressive Familial Intrahepatic Cholestasis"

Rationale and Study Objectives:

The objectives of this low-intervention clinical study are to:

- evaluate the long-term safety
- evaluate the long-term efficacy (impact on liver-related events/clinical outcomes, growth and development).
- List of Addressed Safety Concerns:

  Hepatotoxicity

  Medication errors resulting from erroneous dosing (PFIC patients)

  Long-term safety

  Long-term safety of chronic exposure to propylene glycol in PFIC patients

Study Design:

Prospective, low-intervention clinical study

Study Population:

Patients with ALGS and PFIC

Milestones:

Submission of feasibility assessment (PFIC cohort): within 3 months of European Commission decision

Protocol submission within 6 months of European Commission decision

Statistical analysis plan (SAP) submission: within 6 months of study start

Interim report: Within 5 years from study start

Interim results: Yearly reporting with annual reassessment

Submission of Yearly Updates on any New Information Concerning the Safety and Efficacy of Maralixibat

In order to ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with ALGS, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of maralixibat.

Study MRX-800 Summary

Study Short Name and Title:

MRX-800: "A Long-Term Safety Study of Maralixibat, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study (MERGE)"

Rationale and Study Objectives:

The objective of this multicentre, open-label, interventional follow-up study is to evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS and PFIC. Evaluation of the long-term effects of maralixibat on total serum bilirubin and time to liver-associated outcomes are secondary objectives of this study.

To assess liver safety, liver functions tests will be collected routinely in participants.

- List of Addressed Safety Concerns:

  Hepatotoxicity

  Long-term safety

Study Design:

Open-label, interventional follow-up study

Study Population

Patients with ALGS and PFIC

Milestones:

End date of collection (last patient out [LPO]): Q3 2024

Final report of study results (final clinical study report [CSR]): Q1 2025

Study MRX-801 Summary

Study Short Name and Title:

MRX-801: "Open-Label, Phase 2 Study to Evaluate the Safety and Tolerability of Maralixibat in the Treatment of Infants with Cholestatic Liver Diseases Including Progressive Familial Intrahepatic Cholestasis and Alagille Syndrome (RISE)"

Rationale and Study Objectives:

The objective of this multicentre, open-label, interventional follow-up study is to assess the safety and tolerability of maralixibat in infants <12 months of age with cholestatic liver disease due to ALGS or PFIC. Evaluation of the effect of maralixibat on liver enzymes (ALT, AST) and bilirubin are secondary objectives of this study.

To assess liver safety, liver functions tests will be collected routinely in participants.

- List of Addressed Safety Concerns:

  Hepatotoxicity

  Long-term safety

Study Design:

Open-label, interventional follow-up

Study Population:

Patients with ALGS and PFIC

Milestones:

End date of collection (LPO): Q4 2024

Final report of study results (final CSR): Q2 2025

Study MRX-503 Summary

Short Name and Title:

MRX-503: "An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)"

Rationale and Objectives:

The primary objective of the study is to evaluate the long-term safety and tolerability of maralixibat. Additionally, the long-term efficacy of maralixibat will be investigated, including the maintenance of severity and frequency of pruritus as well as serum bile acids over time and growth in the primary cohort.

To assess liver safety, liver functions tests will be collected routinely in participants.

- List of Addressed Safety Concerns:

  Hepatotoxicity

  Long-term safety

Study Design:

Open-label, multicentre interventional study

Study population:

Patients with PFIC

Milestones

End date of collection (LPO): Q4 2024

Final report of study results (final CSR): Q2 2025

Retrospective Study Summary

Short Name and Title:

MRX-502, MRX-503, MRX-800, MRX-801: "A retrospective study to compare impact of maralixibat treatment on long-term clinical outcomes against historical control in the patients with PFIC"

Rationale and Objectives:

The primary objective of this retrospective study is to evaluate the long-term effects on liver-related events and clinical outcomes in patients with PFIC from studies MRX-502, MRX-503, MRX-800, and MRX-801 against historical control.

- List of Addressed Safety Concerns:

  Hepatotoxicity

  Long-term safety

Study Design:

Retrospective analysis

Study population:

Patients with PFIC

Milestones

Final report of study results (final CSR): Q2 2025

The details on the pharmacovigilance plan and study protocols are provided in Annex 2 and Annex 3, respectively.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.3: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
MRX-803 (former MRX-311): "Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome and Progressive Familial Hepatic Cholestasis" Low-intervention clinical study Planned	The objectives are to: • evaluate the long term safety evaluate the long-term efficacy (impact on liver related events/clinical outcomes, growth and development)	Hepatotoxicity Medication error resulting from erroneous dosing (PFIC patients) Long-term safety Long-term safety of chronic exposure to propylene glycol in PFIC patients	Submission of feasibility assessment (PFIC cohort)	Within 3 months of EC decision
			Protocol submission	Within 6 months of EC decision

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
			SAP submission	Within 6 months of study start
			Interim report	Within 5 years from study start
			Interim results	Yearly reporting with annual reassessment
Submission of yearly updates on any new information concerning the safety and efficacy of maralixibat.	In order to ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with ALGS.	Hepatotoxicity	Annual report	First report as part of the Annual Reassessment

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
Category 3 – Required additional pharmacovigilance activities				
MRX-800: "A Long-Term Safety Study of Maralixibat, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study (MERGE)" Ongoing	To evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS and PFIC.	Hepatotoxicity Long-term safety	End date of collection (LPO):	Q3 2024
			Final report of study results (final CSR):	Q1 2025
MRX-801: "Open-Label, Phase 2 Study to Evaluate the Safety and Tolerability of Maralixibat in the Treatment of Infants with Cholestatic Liver Diseases Including Progressive Familial Intrahepatic Cholestasis and Alagille Syndrome (RISE)" Ongoing	To assess the safety and tolerability of maralixibat in infants <12 months of age with cholestatic liver disease due to ALGS or PFIC	Hepatotoxicity Long-term safety	End date of collection (LPO):	Q4 2024
			Final report of study results (final CSR):	Q2 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
MRX-503: "An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)" Ongoing	Primary objective: To evaluate the long-term safety and tolerability of maralixibat. Secondary objective: To evaluate the long-term efficacy of maralixibat, including the maintenance of severity and frequency of pruritus as well as serum bile acids (over time and growth in the primary cohort	Hepatotoxicity Long-term safety	End date of collection (LPO)	Q4 2024
			Final report of study results (final CSR):	Q2 2025
MRX-502, MRX-503, MRX-800, MRX-801: "A retrospective study to compare impact of maralixibat treatment on long-term clinical outcomes against historical control in the patients with PFIC"	Primary objective: To evaluate the long-term effects on liver related events and clinical outcomes	Hepatotoxicity Long-term safety	Final report of study results (final CSR):	Q2 2025

ALGS=Alagille syndrome; CSR=clinical study report; EC=European Commission; LPO=last patient out; PFIC=progressive familial intrahepatic cholestasis; Q=quarter; SAP=statistical analysis plan.

Part IV Plans for Post-Authorisation Efficacy Studies

None.

Part V Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Hepatotoxicity	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: For patients with liver function test elevations, monitoring per standard practice is recommended. Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Medication errors resulting from erroneous dosing (PFIC patients)	Routine risk communication: SmPC section 4.2 PL section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Long-term safety	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: Restricted medical prescription

Long-term safety of chronic exposure to propylene glycol in PFIC patients	Routine risk communication: SmPC sections 4.2, 4.4, 4.6, and 4.9 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription

PFIC=progressive familial intrahepatic cholestasis; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Educational Materials

Dosing Guide

Objective(s):

To provide an aide to the prescribing physicians and pharmacists outside of the Product Information to guide the patients with PFIC regarding dose, total volume per dose, and the required syringe to be used for LIVMARLI administration.

- List of Addressed Safety Concerns:

  Medication error resulting from erroneous dosing (PFIC patients)

Rationale for the Additional Risk Minimisation Activity:

The dose of LIVMARLI oral solution is established on the basis of patient's weight. This dosing guide was developed to provide an aide outside of the Product Information for the prescribing physicians and/or the pharmacists to guide the patients about the correct dose of LIVMARLI.

Target Audience and Planned Distribution Path:

The target audience for the dosing guide are the prescribing physicians and/or the pharmacists dispensing the drug.

The exact distribution path will be agreed by the national competent authorities in the EU.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

The effectiveness of this risk minimisation measure will be evaluated by routine pharmacovigilance activities, namely by analysis of medication errors resulting from erroneous dosing and their undesirable clinical outcomes in the post-marketing setting in PFIC patients and an outcome of the evaluation will be provided in each Periodic Safety Update Report (PSUR).

Criteria for Success: Stable cumulative reporting rate and nature of reported medication errors.

Patient Booklet

Objective(s):

To provide the patients and/or the caregivers with a record of the prescribed dose of LIVMARLI in order to minimise the dosing errors due to incorrectly calculated dose.

- List of Addressed Safety Concerns:

  Medication error resulting from erroneous dosing (PFIC patients)

Rationale for the Additional Risk Minimisation Activity:

The patient booklet is designed for the patients to have a record of patient's weight, calculated dose and volume, and the syringe size to be used for LIMARLI administration in order to prevent medication errors due to incorrectly calculated dose.

The dated record will be made by the prescribing physician at the time of LIVMARLI prescription.

Target Audience and Planned Distribution Path:

The target audience for this patient booklet are patients with PFIC and/or their caregivers.

The patient booklet will be provided to patients/caregivers by their prescribing physician, while prescribing LIVMARLI (or renewing the prescription).

The exact distribution path will be agreed by the national competent authorities in the EU.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

The effectiveness of this risk minimisation measure will be evaluated by routine pharmacovigilance activities, namely by analysis of medication errors resulting from erroneous dosing and their undesirable clinical outcomes in the post-marketing setting in PFIC patients and an outcome of the evaluation will be provided in each PSUR.

Criteria for Success: Stable cumulative reporting rate and nature of reported medication errors.

V.3 Summary of Risk Minimisation Measures

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimisation Measures by Safety Concern

Safety Concern	Risk Minimisation Measure	Pharmacovigilance Activities
Hepatotoxicity	Routine risk minimisation measures: SmPC section 4.4 PL section 2 For patients with liver function test elevations, monitoring per standard practice is recommended. Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: MRX-803 (former MRX-311) Submission of yearly updates on any new information concerning the safety and efficacy of maralixibat MRX-800 (final CSR: Q1 2025) MRX-801 (final CSR: Q2 2025) MRX-503 (final CSR: Q2 2025) MRX-502, MRX-503, MRX-800, MRX-801 (final CSR: Q2 2025)
Medication error resulting from erroneous dosing (PFIC population)	Routine risk minimisation measures: SmPC section 4.2 PL section 3 Restricted medical prescription Additional risk minimisation measures: Educational materials: – Dosing guide – Patient booklet	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: MRX-803 (former MRX-311)
Long-term safety	Routine risk minimisation measures: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measure	Pharmacovigilance Activities
		MRX-803 (former MRX-311) MRX-800 (final CSR: Q1 2025) MRX-801 (final CSR: Q2 2025) MRX-503 (final CSR: Q2 2025) MRX-502, MRX-503, MRX-800, MRX-801 (final CSR: Q2 2025)
Long-term safety of chronic exposure to propylene glycol in PFIC patients	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.6, and 4.9 PL section 2 Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: MRX-803 (former MRX-311)

CSR=clinical study report; PFIC=progressive familial intrahepatic cholestasis; PL=Package Leaflet; Q=quarter; SmPC=Summary of Product Characteristics.

Part VI Summary of the Risk Management Plan

Summary of risk management plan for Livmarli (maralixibat chloride)

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

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

This summary of the RMP of Livmarli 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 are part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Livmarli is authorised for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older and for the treatment of progressive familial intrahepatic cholestasis (PFIC) patients 3 months of age and older (see the SmPC for the full indication). It contains maralixibat chloride as the active substance and it is given by the oral route.

Further information about the evaluation of Livmarli's benefits can be found in Livmarli's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Livmarli, together with measures to minimise such risks and the proposed studies for learning more about Livmarli'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 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 the case of Livmarli, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

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

II.A List of Important Risks and Missing Information

Important risks of Livmarli 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 Livmarli. 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	None
Important potential risks	Hepatotoxicity Medication error resulting from erroneous dosing (PFIC patients)
Missing information	Long-term safety Long-term safety on chronic exposure to propylene glycol in PFIC patients

PFIC=progressive familial intrahepatic cholestasis

II.B Summary of Important Risks

Important potential risk: Hepatotoxicity	
Evidence linking the risk to the medicine	Increased ALT and AST activity was observed in some patients receiving maralixibat in the clinical trials and post-marketing experience. Considering a close temporal relationship, a positive de-challenge and re-challenge for some of the received cases, a causal relationship between maralixibat and ALT/AST increased is at least a reasonable possibility. Laboratory data showed elevations in transaminases in some ALGS participants during treatment in the clinical trials; most of the values were considered non-serious. Serious adverse events or autoimmune hepatitis (1 participant) and chronic hepatic failure (1 participant) were reported. However, involvement of the underlying disease cannot be excluded. During the long term extension trials with ALGS, 6 (7.1%) participants discontinued the trial due to ALT increases that were all assessed as related or possibly related to study drug. In the pivotal Study MRX 502 in PFIC participants, numerically, there were more maralixibat treated participants who had adverse events of elevated transaminases in comparison to the placebo treated participants. However, abnormal liver enzymes vary

	by PFIC type and approximately 70% of patients with PFIC1 and 95% of patience with PFIC2 have abnormal ALT levels at baseline (Sakita et al. 2018). Fluctuating liver enzymes are expected in patients with PFIC. ALGS and PFIC are difficult population to assess because of wide variability in the severity of the underlying disease and the pre-existence or development of advanced liver disease. Due to the small overall sample size and the paucity of placebo-controlled data in the clinical studies in ALGS and PFIC participants, further evaluation is needed.
Risk factors and risk groups	Currently, there are no risk factors or groups that have been observed to be at risk for hepatotoxicity with maralixibat treatment. The natural history comparison demonstrated that elevation of ALT is common in the ALGS population (varying from 56% lower to 129% higher for 95% of the time in a given individual) (Kamath et al. 2020), that this increase is associated with increased age, and that there was no significant difference in such elevations with or without maralixibat treatment. Abnormal liver enzymes vary by PFIC type and approximately 70% of patients with PFIC1 and 95% of patience with PFIC2 have abnormal ALT levels at baseline (Sakita et al. 2018). Fluctuating liver enzymes are expected in patients with PFIC. No dose-relationship has been seen in patients with ALGS and PFIC who experienced elevated transaminases while on treatment with maralixibat. No additive or synergistic effects with other drugs are known to occur with the introduction of maralixibat treatment.
Risk minimization measures	Routine risk minimisation measures: SmPC section 4.4, PL section 2 For patients with liver function test elevations, monitoring per standard practice is recommended. Restricted medical prescription Additional risk minimisation measures: None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: MRX-803 (former MRX-311) Submission of yearly updates on any new information concerning the safety and efficacy of maralixibat. MRX-800 MRX-801 MRX-503 MRX-502, MRX-503, MRX-800, MRX-801 See section II.C of this summary for an overview of the post-authorisation development plan.

ALGS=Alagille syndrome; ALT=alanine aminotransferase; AST = aspartate aminotransferase; PFIC=progressive familial intrahepatic cholestasis; PL=package leaflet; SmPC=summary of product characteristics

Kamath BM, Ye W, Goodrich NP, Loomes KM, Romero R et al. Outcomes of Childhood Cholestasis in Alagille Syndrome: Results of a Multicenter Observational Study. Hepatol Commun. 2020; 4(3): 387-398.

Sakita FM, Sawe HR, Mwafongo V, Mfinanga JA, Runyon MS et al. The Burden and Outcomes of Abdominal Pain among Children Presenting to an Emergency Department of a Tertiary Hospital in Tanzania: A Descriptive Cohort Study. Emerg Med Int. 2018; 2018: 3982648.

Important potential risk: Medication error resulting from erroneous dosing (PFIC patients)	
Evidence linking the risk to the medicine	Administration of Livmarli is associated with a potential for medication errors resulting from erroneous dosing in patients with PFIC, potentially leading to overdose or other undesirable clinical outcomes associated with incorrect dosing. Patients with PFIC require higher doses of Livmarli than patients with ALGS and as such are at higher risk for potential undesirable clinical outcomes associated with overdose due to dosing medication errors. No reports of undesirable clinical outcomes due to dosing medication errors were collected to date for Livmarli in the clinical trials or in the post-marketing setting.

Risk factors and risk groups	Patients with PFIC require higher doses of Livmarli than patients with ALGS and as such are at higher risk of potential undesirable clinical outcomes associated with overdose due to dosing medication errors. Additionally, patients at higher risk for toxicity associated with propylene glycol include infants and small children, those with renal or hepatic impairment, epilepsy, and burn patients receiving extensive dermal applications of propylene glycol containing products (Lim et al. 2014).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 PL section 3 Restricted medical prescription Additional risk minimisation measures: Educational materials: – Dosing guide – Patient booklet
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MRX-803 (former MRX-311) See section II.C of this summary for an overview of the post-authorisation development plan.

ALGS=Alagille syndrome; PFIC=progressive familial intrahepatic cholestasis; PL=package leaflet; SmPC=summary of product characteristics

Lim TY, Poole RL, Pageler NM. Propylene glycol toxicity in children. J Pediatr Pharmacol Ther. 2014; 19(4): 277-282.

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MRX-803 (former MRX-311) MRX-800 MRX-801 MRX-503 MRX-502, MRX-503, MRX-800, MRX-801 See section II.C of this summary for an overview

	of the post-authorisation development plan.

Missing information: Long- term safety of chronic exposure to propylene glycol in PFIC patients	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.6, and 4.9 PL section 2 Restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MRX-803 (former MRX-311) See section II.C of this summary for an overview of the post-authorisation development plan.

PFIC=progressive familial intrahepatic cholestasis; PL=package leaflet; SmPC=summary of product characteristics

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

The following studies are specific obligations in the context of a marketing authorisation under exceptional circumstances:

Study MRX-803 (former MRX-311)

Purpose of the study: The objectives of this low-intervention clinical study are to evaluate the long-term safety and to evaluate the long-term efficacy (impact on liver related events/clinical outcomes, growth and development).

Submission of yearly updates on any new information concerning the safety and efficacy of maralixibat

Purpose of the study: To ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with ALGS.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study MRX-800

Purpose of the study: The objective of this multicentre, open-label, interventional follow-up study is to evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS and PFIC. Evaluation of the long-term effects of maralixibat on total serum bilirubin and time to liver-associated outcomes are secondary objectives of this study.

To assess liver safety, liver functions tests will be collected routinely in participants.

Therefore, this study will provide data to further characterise the important potential risk of hepatotoxicity and the long-term safety in ALGS and PFIC patients.

Study MRX-801

Purpose of the study: The objective of this multicentre, open-label, interventional follow-up study is to assess the safety and tolerability of maralixibat in infants <12 months of age with cholestatic liver disease due to ALGS or PFIC. Evaluation of the effect of maralixibat on liver enzymes (ALT, AST) and bilirubin are secondary objectives of this study.

To assess liver safety, liver functions tests will be collected routinely in participants.

Therefore, this study will provide data to further characterise the important potential risk of hepatotoxicity and the long-term safety in ALGS and PFIC patients.

Study MRX-503

Purpose of the study: The objectives of this study are to evaluate the long-term safety and tolerability of maralixibat in the treatment of PFIC patients. Additionally, the long-term efficacy of maralixibat will be investigated, including the maintenance of severity and frequency of pruritus as well as serum bile acids over time and growth in the primary cohort.

To assess liver safety, liver functions tests will be collected routinely in participants.

MRX-502, MRX-503, MRX-800, MRX-801 Studies

Purpose of the study: The objective of this retrospective study is to evaluate the long-term effects on liver related events and clinical outcomes.

Part VII: Annexes

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Draft Key Messages of the Additional Risk Minimisation Measures

Prior to the use of LIVMARLI in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at providing the prescribing physicians, patients with progressive familial intrahepatic cholestasis, and their caregivers with an aide facilitating the correct individual dose volume of LIVMARLI.

The MAH shall ensure that in each Member State where LIVMARLI is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use LIVMARLI have access to/are provided with the following educational package:

- dosing guide
- patient booklet.

- The **dosing guide** shall contain the following key elements:
    - Information on the dosing schedule per patient's weight and on the maximum recommended dose.
    - Information on the required syringe size, indicated by different colours.

- The **patient booklet** shall contain the following key elements:
    - Placeholders for a record of patient's weight, calculated dose and volume, and the syringe size for the LIVMARLI prescribed dose as well as record date.

Annex 7 - Other Supporting Data (Including Referenced Material)

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