Mirum Pharmaceuticals, Inc.

EU Risk Management Plan for Livmarli (Maralixibat Chloride)

RMP Version number	0.9
Data lock point:	17 September 2020
Date of final signoff	12 October 2022
Rationale for submitting an updated RMP:	Not applicable
Summary of significant changes in this RMP:	Not applicable
QPPV name:	Claudia Serafim
On behalf of QPPV:	[redacted]

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
EPAR	European Public Assessment Report
GGT	gamma-glutamyl transferase
GI	gastrointestinal
IBAT	ileal bile acid transporter
IV	intravenous
NOAEL	no-observed-adverse-effect level
PFIC	progressive familial intrahepatic cholestasis
PND	postnatal day
PT	prothrombin time
RMP	Risk Management Plan
SLC10A2	solute carrier family 10 member 2
SmPC	Summary of Product Characteristics

Part I: Product Overview

Table Part I.1 – Product Overview

Active substance (INN or common name)	Maralixibat chloride
Pharmacotherapeutic group (ATC Code)	Bile and liver therapy, other drugs for bile therapy (A05AX04)
Marketing Authorisation Applicant	Mirum Pharmaceuticals International B.V.
Medicinal product to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Livmarli®
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: 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 (formerly known as SHP625, LUM001, and SD-5613) 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: Contains maralixibat drug substance (Maralixibat chloride) and excipients, including propylene glycol, sucralose, grape flavour, disodium ethylenediaminetetraacetic acid (EDTA) dihydrate, and purified water. For each excipient, the projected daily intake of the excipient at the highest proposed clinical dose of Maralixibat is well below the acceptable daily intake of the substance established for foods. Maralixibat was designed to be minimally absorbed after oral administration by virtue of its large molecular weight (~710 Da) and the presence of a positively charged quaternary nitrogen atom.
Hyperlink to the Product Information	See Module 1.3.1 for Prescribing Information provided in the Summary of Product Characteristics
Indication	Current: The indication for maralixibat is for the "Treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older."
	Proposed: Not applicable.

Dosage	Current: Mirum is proposing a dose of 400 µg/kg once daily for cholestatic disease in patients with ALGS. Dosing is proposed to begin at 200 µg/kg once daily as the starting dose before (up to 30 minutes) or with a meal, in the morning, followed by an increase to the proposed marketed dose of 400 µg/kg once daily after 1 week, in the absence of safety or tolerability concerns that would preclude dose increase. The doses described in this document are of Maralixibat chloride but are presented as "maralixibat." For example, 400 µg/kg Maralixibat chloride is equivalent to 380 µg/kg maralixibat but will be referred to as 400 µg/kg maralixibat throughout this document.
	Proposed: Not applicable.
Pharmaceutical form and strength	Current: Maralixibat is available as a ready-to-use oral solution (10 mg/mL).
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring?	Yes

Part II: Safety Specification

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

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 multicenter observational study (Kamath et al. 2020), the SD 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.

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 2 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. Module 2.4 discusses the in vitro; in vivo; safety pharmacology; absorption, distribution, metabolism, and excretion (ADME); pharmacokinetic; and 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 (IV) 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 (aPTT) 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 IV 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 1000 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 1000 mg/kg/day in females. Four deaths (1 female at 500 mg/kg/day and 3 females at 1000 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 1000-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 (DART) 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 2000-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/fetal development studies with doses up to 1000 and 250 mg/kg/day, respectively, demonstrated no observed adverse effects on fetal 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 or carcinogenic potential. In the juvenile rat, maralixibat was well tolerated when administered during neonatal development.

Part II: Module SIII - Clinical Trial Exposure

Alagille Syndrome Programme

Maralixibat (also known as SD-5613, LUM001, or SHP625) has been studied in over 1600 participants, including over 180 paediatric or adult participants with cholestatic liver disease. Over 120 paediatric participants have been exposed to maralixibat. Some of these participants have reached over 5 years of total maralixibat exposure.

The clinical program in patients with ALGS includes five completed Phase 2 studies in paediatric participants with ALGS (LUM001-301, -302, -303, -304, -305), one ongoing Phase 2 study in paediatric participants with ALGS or PFIC (MRX-800), one ongoing Phase 2 study in infants with ALGS or PFIC (MRX-801), and an ongoing expanded-access program for patients with ALGS.

Given that the safety profile of maralixibat in ALGS was based upon an analysis conducted on the five 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 1. Exposure data in years and months for the ALGS indication are presented in Table 2 and Table 3, respectively.

Cumulative exposure by age, sex, and racial group is presented in Table 4 and Table 5 for the ALGS indication.

Table 1: 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 4week (Weeks 18–22) randomised, placebo-controlled withdrawal period.

[a] 12 participants were exposed to placebo in LUM001-301. 11 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] 6 participants were exposed to placebo in LUM001-302. 5 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] 16 participants are exposed to both maralixibat and placebo in LUM001-304, and they are counted for both maralixibat and placebo.

Source: Data on file at Mirum.

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

Table 2: 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.
Source: Data on file at Mirum.

Table 3: 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.
Source: Data on file at Mirum.

Table 4: 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.
Source: Data on file at Mirum.

Table 5: Cumulative Exposure to Maralixibat in Participants with Alagille Syndrome by Racial Group – Safety Population (Received Maralixibat)

Study Race	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).

Source: Data on file at Mirum.

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

As of September 2020, a total 86 paediatric participants have received maralixibat in completed studies of ALGS.

As shown in Table 5, there is limited exposure to date among diverse ethnicities. It is not anticipated that there would be any meaningful differences in the safety of maralixibat across different ethnicities.

Maralixibat has not been studied in the elderly, in participants with renal impairment or end-stage renal disease requiring haemodialysis, or in participants with end-stage liver failure or advanced cirrhosis; these patients are not expected to receive maralixibat.

Maralixibat has also not been studied in pregnant or lactating women.

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

In the completed pivotal clinical study (LUM001-304) as well as the completed supporting studies (LUM001-301, -302, -303, -305), the primary exclusion criteria included hypersensitivity to maralixibat or any of its excipients, current or sequelae from chronic diarrhoea, presence of other liver disease or history of or planned transplant, history of or current alcohol or substance abuse, abnormal liver function tests at screening, and subjects with a history of or current atopic dermatitis or other noncholestatic diseases associated with pruritus (see Table 6).

Table 6: Exclusion Criteria in Pivotal Clinical Study LUM001-304

Exclusion Criterion	Reason for Exclusion	Missing Information Y/N	Rationale
Chronic diarrhoea requiring ongoing intravenous fluid or nutritional intervention	Maralixibat has been associated with GI effects and could exacerbate this condition.	N	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.	N	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.	N	It is not anticipated that maralixibat will be used in this population.
Decompensated cirrhosis (ALT >15 x 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.	N	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.	N	It is not anticipated that maralixibat will be used in this population.
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.	N	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.	N	Use in this population is not predicted to be associated with additional risks of clinical significance.

Exclusion Criterion	Reason for Exclusion	Missing Information Y/N	Rationale
Known diagnosis of HIV infection	Condition could confound results with maralixibat.	N	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.	N	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.	N	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.	N	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.	N	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	N	Use in this population is not predicted to be associated with additional risks of clinical significance.
Known hypersensitivity to maralixibat or any of its components	To prevent allergic reactions	N	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.	N	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.	N	Not applicable

Exclusion Criterion	Reason for Exclusion	Missing Information Y/N	Rationale
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.	N	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.	N	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.
Source: LUM001-304 protocol.

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

The clinical programme has excluded pregnant or breastfeeding women. In addition, to date, patients with renal impairment or end-stage renal disease requiring haemodialysis, end-stage liver failure or advanced cirrhosis, or immune or cardiac impairment (other than those associated with ALGS) have also been excluded from clinical trial participation; therefore, data in these populations are not available. Maralixibat has not been studied in the elderly.

The exposure of special populations in the clinical development programmes is displayed in Table 7.

Table 7: 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 comorbidities: Patients with severe hepatic failure (end--stage liver disease or advanced cirrhosis) Patients with renal impairment or end-stage renal disease requiring haemodialysis Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Cardiovascular anomalies are present in more than 90% of patients with ALGS. Involvement of the pulmonary outflow tract is the most common type of congenital heart disease, with some form of peripheral pulmonary stenosis (PPS) affecting at least two-thirds of cases (Turnpenny and Ellard 2012). Patients with comorbid cardiovascular impairment as part of the diagnosis of ALGS were included in the clinical development program. Patients with mild, moderate, and severe hepatic impairment as defined by NCI-ODWG criteria (Synold et al. 2007) were also included in the clinical development program, see SmPC Sections 4.2 and 5.2. The remaining comorbidities have not been included in the clinical development programme.
Paediatric population	The current clinical development programme for maralixibat has been focused on rare cholestatic liver diseases, primarily in the paediatric patient population, which includes 86 patients in ALGS studies.
Population with relevant different ethnic origin	The current global programme has been conducted in primarily White participants in those studies where race was available or collected. To date, 6 Black/African American participants and 2 Asian participants have been treated in the ALGS studies. Race information was not collected in Study LUM001-304. No participants known to be of Latino/Hispanic origin have been treated in ALGS studies to date.
Subpopulations carrying relevant genetic polymorphisms	No data available; no relevant polymorphisms have yet been identified

ALGS=Alagille syndrome.

Part II: Module SV - Post-Authorisation Experience

As of the data lock point of this RMP, maralixibat is an investigational product. Maralixibat is not approved in any country, and it has not been withdrawn from any market. There has been no marketing experience with this drug to date.

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

Based on the mechanism of action, maralixibat is not anticipated to show a potential for drug abuse or dependence; hence, there is no anticipated potential for misuse for illegal purposes.

Part II: Module SVII - Identified and Potential Risks

Mirum Pharmaceuticals performed a review and analysis of adverse event (AE) data from clinical studies included in the Marketing Authorization Application (MAA) evaluating maralixibat for the treatment of patients with ALGS. Safety data were reviewed from a pooled population (Integrated Summary of Safety population) comprising five Phase 2 studies in ALGS (Studies LUM001-301, LUM001-302, LUM001-303, LUM001-304, and LUM001-305). The database cutoff date for data to be included in this adverse drug reaction (ADR) analysis is 17 September 2020.

Based on the nonclinical and clinical research available to date, 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. Hepatotoxicity is considered an important potential risk for maralixibat.

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 gastrointestinal (GI)-related AEs 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 diarrhea or abdominal pain were serious, no treatment-related events of diarrhea 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 characterization 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 etiologies 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

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 characterization.

Continued surveillance of hepatic safety is recommended in the product information, and evaluation is planned via additional pharmacovigilance measures to further characterize 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.

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

Not applicable.

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

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

Important Potential Risk: 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.

Evidence source(s) and strength of evidence:

Laboratory data showed elevations in transaminases in some ALGS participants during treatment; 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, 6 (7.1%) participants discontinued the trial due to ALT increases that were all assessed as related or possibly related to study drug. However, it is a difficult population to assess because of wide variability in the severity of the underlying disease and the preexistence or development of advanced liver disease. Due to the small overall sample size in the clinical studies in ALGS participants, further evaluation is needed.

Characterization of the risk:

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 post-marketing in the LEAP study (MRX-310), MRX-800, and MRX-801.

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 by Kamath et al. (2020) 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), that this increase is associated with increased age, and that there was no significant difference in such elevations with or without maralixibat treatment.

No dose-relationship has been seen in patients with ALGS 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.

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 prior to start and during treatment with maralixibat. Additionally, close monitoring is advised for patients with end-stage liver disease or (progression to) decompensation.

Impact on the risk-benefit balance of the product:

Elevations in transaminases have been seen in the ALGS development programme for maralixibat that may be a sign of hepatotoxicity. However, due to the underlying disease affecting the liver and since the population is very limited, more data are needed to conclude whether there is a hepatotoxicity risk with maralixibat. If the risk will be confirmed, this will have an impact on the benefit/risk of the product; accordingly, it is considered important and, as such, included in the RMP as an important potential risk. Further characterization for the potential risk of hepatotoxicity via the proposed LEAP study (MRX-310; Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome) and within the ongoing Studies MRX-800 and MRX-801 is expected to provide additional data that may help in the clarification of the nature of the hepatic findings in patients with ALGS being treated with maralixibat. 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 favorable for patients with ALGS.

Public health impact:

The indication for use of maralixibat in the post-market setting includes ALGS in children 2 months of age and older wherein elevations of liver enzymes in this specific population is common. The estimate of events of hepatotoxicity or elevated liver enzymes in patients treated with maralixibat is anticipated to be similar to the background rate of these events in patients not treated with maralixibat.

SVII.3.2. Presentation of the Missing Information

Carcinogenic Potential

There were higher incidences of bronchiolo-alveolar adenoma and carcinoma in male RasTG mice administered 25 mg/kg/day maralixibat compared with concurrent study vehicle controls. However, the incidences of these findings were still within the range of those observed in historical controls of this mouse strain, and while the implication of this finding for human risk assessment is unknown, it cannot be ruled out that these findings are maralixibat-related. 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. No gastrointestinal cancers have been observed in humans to date for 5 years. Based on this situation, “carcinogenic potential” is considered as Missing Information. A 2-year rat carcinogenicity study is ongoing, with final report expected in late 2023.

Part II: Module SVIII - Summary of the Safety Concerns

Table 8: List of Safety Concerns

List of Safety Concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity
Missing information	Carcinogenic potential

Part III: Pharmacovigilance Plan (including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Specific adverse reaction follow-up questionnaires:

None.

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional Pharmacovigilance Activities

Hepatotoxicity	
Additional pharmacovigilance activities	**MRX-310 SUMMARY:** Study short name and title: MRX-310: Long-term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome (LEAP) Rationale and study objectives: The objective of this prospective, interventional cohort study is to evaluate the long--term safety and clinical outcomes of Livmarli in patients with ALGS. To assess liver safety, liver functions tests will be collected routinely in participants. Therefore, this study will provide data to further characterize the important potential risk of Hepatotoxicity. Study Design: Prospective, interventional cohort study Study Population: Patients with ALGS Milestones: Feasibility assessment submission: within 3 months of EC decision Protocol submission within 6 months of EC decision Interim results: Yearly reporting/ annual reassessment 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
	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 multicenter, 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 characterize the important potential risk of Hepatotoxicity. Study Design: Open-label, interventional follow-up study

	Study Population Patients with ALGS and PFIC Milestones: Start date of collection (FPI): 16 Jan 2020 End date of collection (LPO): Q1 2024 Final report of study results (Final CSR): Q3 2024
	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 multicenter, 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 characterize the important potential risk of Hepatotoxicity. Study Design: Open-label, interventional follow-up Study population: Patients with ALGS or PFIC Milestones: Start date of collection (FPI):09 Sep 2021 Last date of collection (LPO): Q3 2023 Final report of study results (final CSR): Planned Dec 2023
Carcinogenic Potential	
Additional pharmacovigilance activities	**MRXNC-006 SUMMARY:** Short name and title: MRXNC-006: A 104-week oral gavage carcinogenicity study of maralixibat in Sprague Dawley Rats. Rationale and objectives: The primary objective of this study is to evaluate the toxicity and carcinogenic potential of the test article, maralixibat, when administered daily via oral gavage to rats for at least 104 weeks. Study Design: Standard 2-yr rat carcinogenicity bioassay design in male and female rats with 3 dose levels of maralixibat and a vehicle control group Study population: Sprague Dawley Rats

	Milestones This study was initiated in Q4 2020 and is ongoing at the time of this report. The analysis will be performed upon study completion. Final study report submission: Oct 2023

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
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-310 (LEAP): Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome. Planned	The objective of this prospective, interventional cohort study is to evaluate the long-term safety and clinical outcomes of Livmarli in patients with ALGS.	Hepatotoxicity	Feasibility assessment submission Protocol Submission Interim results	Within 3 months of EC decision Within 6 months of EC decision Yearly reporting/ 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
Category 3 – Required additional pharmacovigilance activities				
MRXNC-006: A 104-week oral gavage carcinogenicity study of maralixibat in Sprague Dawley Rats. Ongoing	To evaluate the toxicity and carcinogenic potential of the test article, maralixibat, when administered daily via oral gavage to rats for at least 104 weeks.	Carcinogenic potential	Final study report submission	October 2023

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
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 Ongoing	To evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS and PFIC.	Hepatotoxicity	Start date of collection (FPI) End date of collection (LPO): Final report of study results (final CSR):	16 Jan 2020 Planned Q1 2024 Planned Q3 2024
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 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	Start date of collection (FPI) End date of collection (LPO): Final report of study results (final CSR):	09 Sep 2021 Planned Q3 2023 Planned Dec 2023

Part IV: Plans for Post-Authorisation Efficacy Studies

None

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

Part V.1 Routine Risk Minimisation Measures

Safety concern	Routine risk minimization activities
Carcinogenic potential	***Routine risk communication*:** SmPC section 5.3 ***Routine risk minimisation activities recommending specific clinical measures to address the risk*:** None ***Other routine risk minimisation measures beyond the Product Information:*** Medical prescription
Hepatotoxicity	***Routine risk communication*:** SmPC section 4.4, Package leaflet 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. If tolerability issues persist, lower doses may be considered. Escalation back to target dose can be attempted as tolerated. ***Other routine risk minimisation measures beyond the Product Information:*** Medical prescription

Part V.2 Additional Risk Minimisation Measures

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

Part V.3 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimization Measure	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk measures:** SmPC section 4.4, Package Leaflet section 2 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** MRX-310 (LEAP): Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome. (Planned Study Initiation: 2022) Submission of yearly updates on any new information concerning the safety and efficacy of maralixibat. 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 (Ongoing) 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 (Ongoing)
Carcinogenic Potential	**Routine Risk Measures:** SmPC section 5.3 **Additional risk minimization measures:** No risk minimization measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MRXNC-006: A 104-week oral gavage carcinogenicity study of maralixibat in Sprague Dawley Rats. (Ongoing) Report completion: October 2023

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for Livmarli (Maralixibat Chloride)

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

The Livmarli 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 RMP.

I. The medicine and what it is used for

Livmarli is authorized for the "treatment of cholestastic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older." (see the SmPC for the full indication). It contains maralixibat chloride as the active substance, and it is given as ready-to-use oral solution.

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 minimize such risks and the proposed studies for learning more about Livmarli's risks, are outlined below:

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, including a package leaflet;

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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report 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 Safety Concerns

List of Safety Concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity
Missing information	Carcinogenic potential

II.B Summary of Important Risks

Hepatotoxicity	
Evidence linking the risk to the medicine	Laboratory data showed elevations in transaminases in some ALGS participants during treatment; 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, 6 (7.1%) participants discontinued the trial due to ALT increases that were all assessed as related or possibly related to study drug. However, it is a difficult population to assess because of wide variability in the severity of the underlying disease and the preexistence or development of advanced liver disease. Due to the small overall sample size in the clinical studies in ALGS participants, further evaluation is needed.
Risk factors and Risk Groups	Currently, there are no risk factors and risk groups that have been observed to be at risk for hepatotoxicity with maralixibat treatment. The natural history comparison by Kamath et al. (2020) 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), that this increase is associated with increased age, and that there was no significant difference in such elevations with or without maralixibat treatment. No dose-relationship has been seen in patients with ALGS 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 minimization activities: ***Routine risk measures*:** SmPC section 4.4, Package leaflet section 2 ***Additional risk minimisation measures:*** No risk minimisation measures
Additional pharmacovigilance activities	***Additional pharmacovigilance activities*:** MRX-310 (LEAP): Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome. Submission of yearly updates on any new information concerning the safety and efficacy of maralixibat. 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. 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.

Carcinogenic potential	
Risk minimization measures	Routine risk minimization activities: ***Routine risk measures*:** SmPC section 5.3 ***Additional risk minimisation measures:*** No risk minimisation measures
Additional pharmacovigilance activities	***Additional pharmacovigilance activities*:** MRXNC-006: A 104-week oral gavage carcinogenicity study of maralixibat in Sprague Dawley Rats.

II.C Post-Authorisation Development Plan

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

The following studies are conditions of the marketing authorisation:

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
MRX-310 (LEAP): Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome. (Planned)	The objective of this prospective, interventional cohort study is to evaluate the long-term safety and clinical outcomes of Livmarli in patients with ALGS.	Hepatotoxicity	Feasibility assessment submission Protocol Submission Interim results	Within 3 months of EC decision Within 6 months of EC decision Yearly reporting/ 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

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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
MRXNC-006: A 104-week oral gavage carcinogenicity study of maralixibat in Sprague Dawley Rats. (Ongoing)	To evaluate the toxicity and carcinogenic potential of the test article, maralixibat, when administered daily via oral gavage to rats for at least 104 weeks.	Carcinogenic potential	Final study report submission	October 2023
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 (Ongoing)	To evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS and PFIC .	Hepatotoxicity	Start date of collection (FPI) End date of collection (LPO): Final report of study results (final CSR):	16 Jan 2020 Planned Q1 2024 Planned Q3 2024
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 (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	Start date of collection (FPI) End date of collection (LPO): Final report of study results (final CSR):	09 Sep 2021 Planned Q3 2023 Planned Dec 2023

Part VII: Annexes

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Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

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

Not applicable.