13 October 2022
EMA/864249/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Livmarli

International non-proprietary name: maralixibat chloride

Procedure No. EMEA/H/C/005857/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
7αC4	7 alpha-hydroxy-4-cholesten-3-one
AAS	Atomic absorption spectrometry
ADME	Absorption, distribution, metabolism, and elimination
AE	Adverse event
AESI	Adverse event of special interest
ALGS	Alagille syndrome
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
ASBT	Apical sodium-bile acid transporter
ASM	Active substance manufacturer
ASMF	Active substance master file = drug master file
AUC_{last}	Area under the curve from time 0 to the last measurable concentration
BET	Bacterial endotoxins
CE	Conformité Européene
CEP	Certificate of Suitability of the EP
CFU	Colony forming units
C_{max}	Maximum concentration observed
CMS	Concerned member state
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical quality attribute
CSR	Clinical study report
CR	Child resistant
CRS	Chemical Reference Substance (official standard)
CSS	Clinician scratch scale
CYP	Cytochrome P450
DSC	Differential scanning calorimetry
DCC	Data coordinating centre
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DVS	Dynamic vapor sorption
EAIR	Exposure-adjusted incidence rate
EAP	Expanded access programme
EDQM	European Directorate for the Quality of Medicines
EDTA	Disodium edetate dihydrate
EFS	Event-free survival
ET	Early termination
fBA	Faecal bile acid
FDA	US Food and Drug Administration
FDSC	Fixed drug substance concentration
FDV	Fixed dosing volume
FSV	Fat-soluble vitamin
GC	Gas chromatography
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HD	High dose
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HRQoL	Health-related quality of life
ICH	International Council for Harmonization
ICP-OES	Inductively coupled plasma optical emission spectrometry
IPC	In-process control
IR	Infrared
ItchRO(Obs)	Itch reported outcome (observer)
ItchRO(Pt)	Itch reported outcome (patient)
ITT	Intent-to-treat

Abbreviation	Definition
IU	International units
JAG1	Jagged 1
KF	Karl Fischer
KPP	Key process parameter
LC/MS/MS	Liquid Chromatography with tandem Mass Spectrometry
LC-NMR	Liquid chromatography/nuclear magnetic resonance
LD	Low dose
LDL	Low-density lipoprotein
LDPE	Low density polyethylene
LLOQ	Lower limit of quantitation
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification
Lp-X	Lipoprotein-X
LS	Least squares
LTE	Long-term extension
MAH	Marketing authorisation holder
MD	Mid dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed model repeated measures
MRX-MRX-MRX	Participants randomised to maralixibat during the randomised withdrawal period of Study LUM001-304
MRX-PBO-MRX	Participants randomised to placebo during the randomised withdrawal period of Study LUM001-304
MS	Mass spectrometry
ND	Not detected
NDA	New drug application
NLS	Native liver survival
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOR	Normal operating range
NOTCH2	Neurogenic locus notch homolog protein 2
NT	Not tested
ntPFIC	Nontruncating progressive familial intrahepatic cholestasis
OOS	Out of Specifications
OL	Open label
OVAT	One Variable at a Time
PAR	Proven acceptable range
PBC	Primary biliary cholangitis
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamic
PDE	Permitted daily exposure
PE	Polyethylene
PEBD	Partial external biliary diversion
PedsQL	Pediatric Quality of Life Inventory
PET	Polyethylene terephthalate
PFIC	Progressive familial intrahepatic cholestasis
Ph. Eur.	European pharmacopoeia
PIP	Paediatric investigation plan
PK	Pharmacokinetic
PP	Polypropylene
PPQ	Process performance qualification
PSC	Primary sclerosing cholangitis
PVC	Poly vinyl chloride
QoL	Quality of life
QOS	Quality overall summary
REDCap	Research electronic data capture
RH	Relative humidity

Abbreviation	Definition
RMS	Reference member state
RRT	Relative retention time
RSD	Relative standard deviation
RWD	Randomised withdrawal
SAP	Statistical analysis plan
sBA	Serum bile acid
SBD	Surgical biliary diversion
SCXRD	Single crystal x-ray data
SD	Standard deviation
SE	Standard error of the mean
SmPC	Summary of Product Characteristics
SIP	Sterilisation in Place
TGA	Thermo-gravimetric analysis
TLC	Thin layer chromatography
TTC	Threshold of Toxicological Concern
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
UV	Ultraviolet
XRD	X-ray diffraction
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mirum Pharmaceuticals International B.V. submitted on 8 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Livmarli, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 January 2021.

Livmarli was designated as an orphan medicinal product EU/3/13/1214 on 18 December 2013 in the following condition: Treatment of Alagille syndrome.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Livmarli as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/livmarli

The applicant applied for the following indication: Livmarli is indicated for the treatment of cholestatic liver disease in patients with Alagille syndrome (ALGS) 1 year of age and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0133/2021 on the agreement of a paediatric investigation plan (PIP).

The PIP was completed and PDCO issued an opinion on compliance for the PIP P/0133/2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

1.5.2. New active substance status

The applicant requested the active substance maralixibat chloride contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
27 June 2019	EMEA/H/SA/4117/1/2019/PA/PED/II	Ewa Balkowiec-Iskra, Kolbeinn Gudmundsson
27 June 2019	EMEA/H/SA/4117/2/2019/PA/PED/III	Kolbeinn Gudmundsson, Serena Marchetti
17 October 2019	EMEA/H/SA/4117/2/FU/1/2019/PA/PED/I	Alexandre Moreau, Stephan Lehr

The Protocol assistance pertained to the following quality and clinical aspects:

- Suitability of the proposed maralixibat liquid formulations for use in paediatric patients. The proposed starting materials and their specifications for the synthesis of maralixibat drug substance. The proposed commercial specifications for maralixibat drug substance. The proposed specifications for the grape flavour excipient. The proposed commercial specifications for maralixibat drug product (test parameters).
- Whether the totality of the available clinical data including studies LUM001-301 (and its extension, LUM001-305), LUM001-302 (and its extension LUM001-303) and LUM001-304 in Alagille Syndrome (ALGS), could form the basis to support the benefit/risk assessment of maralixibat for the treatment of ALGS, and if MRX-308 study results could be submitted post authorisation to confirm a clinically relevant effect of maralixibat in ALGS.
- Design of proposed study MRX-308, a double-blind, placebo-controlled, randomised drug withdrawal study in paediatric subjects with ALGS between ≥12 months and <18 years of age with the primary endpoint mean change in the average morning itch reported outcome observer [ItchRO(Obs)] severity score between the start and end of the randomised drug withdrawal period.
- At a discussion meeting the observed placebo effect and implications for study design, the rationale for dose selection, the itching scale validity and clinically significant change, and the proposed indication were further discussed.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Thalia Marie Estrup Blicher

The application was received by the EMA on	08 September 2021
The procedure started on	30 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 December 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	03 January 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	04 January 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	11 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 January 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2022
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses	17 June 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 June 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	06 September 2022
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	20 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	29 September 2022

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Livmarli	13 October 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	13 October 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Alagille syndrome (ALGS) is an inherited multi-organ disease of variable severity with its first description in the year 1969 by the French hepatologist Daniel Alagille. ALGS is an autosomal dominant disease with variable expressivity, caused by heterozygous mutations in either JAG1 or NOTCH2. The vast majority of cases are due to JAG1 mutations accounting for 94%, and NOTCH2 mutations in additional 2-4%. Sixty percent of patients harbour de novo mutations (i.e., sporadic). The remaining 40% inherit their mutation from a typically mildly affected parent. The Notch pathway is involved in cell fate determination and plays a crucial role in normal development, and the JAG1 is highly expressed in organs that are typically affected in patients with ALGS.

The proposed treatment is aimed at one of the most prominent features of the disease which is cholestasis caused by paucity of biliary ducts, and which itself manifests as cholestasis with scleral icterus, conjugated hyperbilirubinaemia, and potentially hepatomegaly. The increased level of bile acids in the serum usually causes severe pruritus.

2.1.2. Epidemiology and risk factors

ALGS is a rare disease. The prevalence of ALGS is estimated to be 1 in 70,000 (estimation vary from 1:30000 to 1:100000). Chronic obstructive cholestasis is present in 75% to 100% of patients with ALGS (Kamath et al. 2018).

In most cases, the liver dysfunction in ALGS is the earliest and more serious feature of this genetic condition, characterised by severe chronic intrahepatic cholestasis that often develops in the first 3 months of life.

2.1.3. Biologic features, aetiology and pathogenesis

In ALGS, Notch signalling impairment due to JAGGED1 or NOTCH2 mutations may affect the development of intrahepatic bile ducts leading to bile duct paucity and cholestasis (Kamath et al. 2003; Kamath et al. 2012). In this condition, bile ducts are abnormally narrow, malformed, and reduced in number, which leads to retention of toxic bile acids in the liver and elevated serum bile acids (sBAs), that are associated with pruritus, the most burdensome symptom in ALGS (Kamath et al. 2018). In addition, high bile acid levels in the liver lead to a decrease in the cholesterol conversion to bile acid resulting in elevations in systemic cholesterol levels (Nemes 2016). Excess of cholesterol can lead to a build-up of cholesterol under the surface of the skin, known as xanthomas. Cholestasis typically also presents with growth impairment and chronic fatigue.

The cholestatic liver disease in ALGS, even in the absence of liver cirrhosis include severe and unremitting pruritus, xanthomas (disfiguring and sometimes disabling subcutaneous lipid deposits, chronic fatigue and growth failure (although this could also be related to the cardiac disease manifestations). In addition, fat-soluble vitamin (FSV) malabsorption and increased risk of bone fractures due to trabeculae malformation can also be present as a direct consequence of the bile-duct related disease manifestation. Collectively, all cholestasis-related symptoms result in poor HRQoL. In this regard, the cholestasis-related pruritus of ALGS is thought to be among the most severe of all liver

diseases, resulting in cutaneous mutilation and disrupted sleep and school activities. Children with cholestasis and ALGS often also have disfiguring xanthomas.

2.1.4. Clinical presentation and prognosis

The diagnosis of ALGS is usually made early in life due to either hepatic/bile-duct or heart-related manifestations of the disease, finally by genetic testing.

The seven main features of the disease are thought to be cardiac defects (more than 90% of the patients, with pulmonary artery stenosis, tetralogy of Fallot, septal defects, aortic stenosis and coarctation), the hepatic manifestations (almost 100%; characterised with cholestasis, hyperbilirubinaemia, pruritus, xanthomas, and finally end-stage liver disease), renal abnormalities (about 40%, renal dysplasia, glomerular mesangiolipidosis, renal tubular acidosis), skeletal abnormalities (30-90%; butterfly vertebrae, hemivertebrae, pathological fractures of long bones), ophthalmologic manifestations (above 80%, posterior embryotoxon), dysmorphic facies (prominent, broad forehead, deep-set eyes with hypertelorism, prominent ears, triangular face, broad nasal bridge), and finally vascular abnormalities (>15).

Further features also include short stature, failure to thrive, developmental delay and immunodeficiency.

Key features associated with cholestasis in ALGS are:

1. Severe and unremitting cholestatic pruritus (80% at 2 years of age) that is among the most severe of all liver diseases and results in cutaneous mutilation and disrupted sleep and school activities (Kamath et al. 2015; Kamath et al. 2018)
2. Hypercholesterolaemia (81% - 83% in ALGS patients with cholestasis; Kamath et al. 2018)
3. Xanthomas (between 30% and 42%), that can be disfiguring and/or disabling (Kamath et al. 2018)
4. Chronic fatigue (between 65% and 85% in cholestatic patients in general, though specific prevalence data in ALGS is lacking; Swain 2006)
5. Growth failure (between 50% and 87% in ALGS patients; Kamath et al. 2018)
6. Significantly diminished quality of life (HRQoL) (Kamath et al. 2018).

Notably, there are likely multiple potential contributing factors to poor growth and fatigue, such as malabsorption of fat-soluble vitamins (FSV) and lipids (as a result of poor bile flow), growth hormone insensitivity, impaired ability of the liver to metabolise nutrients in the setting of bile flow abnormalities, and hepatic inflammation (Bucuvalas 1993; Wasserman 1999; Rovner 2002; Kamath 2020).

Fat-soluble vitamin (FSV) malabsorption and increased risk of bone fractures due to trabeculae malformation can also be present as a direct consequence of the bile-duct related disease manifestation. Elevated bilirubin and liver function parameters are typical manifestations of ALGS. Bilirubin (particularly, direct/conjugated) is one of the key components of cholestasis. Increased liver function parameters are the indicators of liver damage, that takes place due to accumulation of toxic bile acids.

2.1.5. Management

There are no pharmacological therapies approved to treat cholestasis in ALGS. Off label oral treatments used in children with ALGS with cholestasis are described in Table 2. In general, the clinical

burden of cholestasis in ALGS is so severe that even in the absence of end-stage liver disease, it is a leading indication for liver transplantation (Lykavieris et al. 2001; Englert et al. 2006; Kamath et al. 2012; Vandriel et al., in press).

Table 1 Oral Treatments Utilised in Patients with ALGS to Manage Symptoms associated with Cholestasis

Drug Indication	Drug Class or Mechanism	Agent (examples)
Cholestasis	Bile acids	Ursodeoxycholic acid[b]
Pruritus	PXR agonist[a]	Rifampicin
	CAR agonist[a]	Phenobarbital
	Selective serotonin reuptake inhibitors	Fluoxetine
		Sertraline
	Binding Resins	Cholestyramine[b]
	Antihistamines	Cetirizine Hydrochloride
		Dexchlorpheniramine maleate
	Opiate Antagonists	Naltrexone
		Naloxone
	Serotonin Antagonists	Ondansetron
Xanthomas	Lipid-lowering agents	Atorvastatin
Hypercholesterolaemia	Lipid-lowering agents	Atorvastatin
Chronic fatigue	No therapy	NA
Growth and Nutritional deficiency	Nutritional support	Peptamen
	Liposoluble vitamin supplementation	Retinol, Tocopherol, Calciferol
	Pituitary and hypothalamic hormones	Desmopressin
		Mecasermine
		Somatropin

ALGS=Alagille syndrome; NA=not applicable

[a] PXR and CAR agonists are hypothesised to mitigate cholestatic pruritus through upregulation of metabolic pathways involved in bile metabolism.

[b] Also have lipid-lowering effects.

A majority of patients, however, require surgical intervention, that include surgical biliary diversion (SBD) (partial internal biliary diversion and ileal exclusion) and liver transplantation. SBD has been reported to have variable success rates.

The majority of patients receive a liver transplant by adulthood (Kamath et al. 2020; Vandriel et al. 2020) and more than half of these transplantations is for persistent pruritus (Vandriel et al., in press). Importantly, the clinical burden of cholestasis, including pruritus, outweighs reasons for transplantation of cirrhosis and manifestations of portal hypertension (see Table below).

Table 2 Reasons for Liver Transplantation in the Global Alagille Alliance

Liver Transplantation Indication		% (n/N)
Persistent cholestasis		48 (158/328)
Complications of persistent cholestasis	Intractable pruritus	69 (161/235)
	Growth failure	54 (127/235)
	Xanthomas	49 (116/235)
	Metabolic bone disease	7 (16/235)
	Fat soluble vitamin deficiency	2 (3/235)
	≥1 complication of persistent cholestasis	71 (235/328)
Cirrhosis		3 (11/328)
Manifestations of portal hypertension	Ascites	20 (19/97)
	≥1 GI varices requiring intervention	16 (16/97)
	Not specified	65 (63/97)
	≥1 complication of portal hypertension	30 (97/328)
Other		7 (24/328)

Given the lack of approved pharmacotherapy for cholestatic pruritus, the invasive nature of surgical treatment options, and patients' short- and long-term morbidity and mortality, there remains a high unmet medical need for pharmacological treatment that is safe and efficacious in easing disease burden.

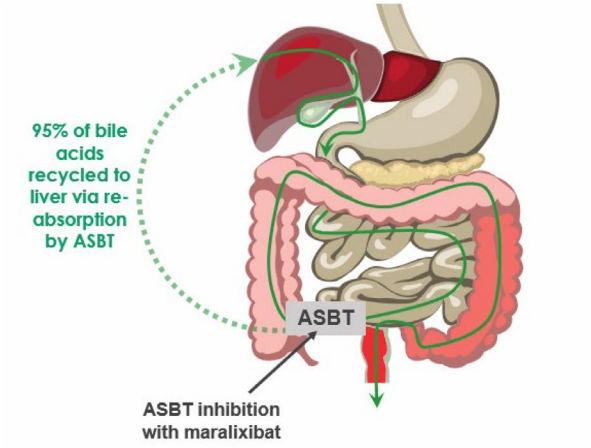
2.2. About the product

Mode of action: Maralixibat chloride (formerly known as SD-5613, SHP625, and LUM001; hereafter referred to as maralixibat) is an inhibitor of the ASBT.

This transmembrane protein transporter, localised on the luminal surface of ileal enterocytes, is present in the terminal 25% of the small intestine and mediates uptake of conjugated bile acids across the brush border membrane of the enterocyte.

Maralixibat is a potent, highly selective ASBT inhibitor (IC50 = 0.3 nM) as demonstrated in cell-based assays. Maralixibat is minimally absorbed due to its large molecular weight (710 Da) and the presence of a positively charged quaternary nitrogen atom, therefore maximizing the local exposure of the molecule to its target and minimizing unnecessary systemic exposure.

Maralixibat-mediated blockade of intestinal reabsorption of bile acids by ASBT interrupts the enterohepatic circulation, thereby increasing fBA excretion and lowering sBA levels (see the following figure).



ASBT = apical sodium-dependent bile acid transporter.

Figure 1 Interruption of Enterohepatic Circulation of Bile Acids by Maralixibat

The proposed commercial formulation is an oral solution that will be measured for dosing on a weight basis and be taken once or twice daily. It is supplied as a 9.5 mg/mL ready-to-use fixed concentration of maralixibat free base solution (equivalent to 10 mg/mL maralixibat chloride).

The proposed dosing regimen is a starting dose of 190 µg/kg maralixibat (free base) once daily and should be increased to 380 µg/kg maralixibat once daily after one week.

The initially targeted indication was "treatment of cholestatic liver disease in patients with Alagille syndrome (ALGS) 1 year of age and older". Later during the procedure, the indication was adapted to treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older.

2.3. Type of application and aspects on development

Maralixibat was originally developed for the treatment of cholestatic diseases by Lumena Pharmaceuticals, Inc., Shire Human Genetic Therapies, Inc. Ownership of the maralixibat development programme was transferred to Mirum Pharmaceuticals, Inc. in December 2018. Maralixibat was previously studied in healthy volunteers as well as adults and adolescents with elevated cholesterol, and adults with Primary Biliary Cholangitis (PBC), and Primary Sclerosing Cholangitis (PSC). Indications of hypercholesterolaemia, PSC and PBC are no longer being pursued.

Table 3 Development and Sponsorship for Maralixibat

Date	**Sponsors**	**Targeted Diseases**
15 June 1999	G.D. Seale & Co.	Primary hypercholesterolaemia
5 June 2003	Pharmacia & Upjohn Company	
15 July 2005	Pfizer Global Research & Development	
26 April 2013 to	Lumena Pharmaceuticals, Inc.	Cholestatic diseases (ALGS, PFIC, PBC, and PSC)
February 2015 to	Shire Human Genetic Therapies, Inc.	
18 December 2018	Mirum Pharmaceuticals, Inc.	
7 August 2020	Mirum Pharmaceuticals, Inc.	BA

ALGS = Alagille syndrome; BA = biliary atresia; IND = Investigational New Drug; PBC = primary biliary cholangitis; PFIC = progressive familial intrahepatic cholestasis; PSC = primary sclerosing cholangitis.

The applicant is currently developing maralixibat for the treatment of ALGS, PFIC, and biliary atresia.

Due to its key role in bile acid intestinal re-uptake, the ASBT is considered an adequate target for pharmacological interruption of bile acid enterohepatic circulation, especially considering, that ASBT is upregulated in patients with cholestasis. By blocking ASBT, maralixibat reduces systemic uptake of bile acids and improves cholestatic pruritus.

The maralixibat clinical development programme in children with cholestatic liver diseases includes 5 completed studies in participants with ALGS (LUM001-301, -302, -303, -304, and -305), 3 studies in participants with PFIC (LUM001-501 [completed], MRX-502, and MRX-503), a long-term study that includes participants with ALGS and PFIC who had completed previous maralixibat studies (MRX-800), and an infant study for participants with ALGS and PFIC younger than 1 year of age (MRX-801). In addition, 1 study (MRX-701) in participants with biliary atresia was initiated.

For the proposed indication there is currently no regulatory guidance document available.

The quality development programme of maralixibat was discussed at a Protocol Assistance meeting which the applicant applied for in June 2019.

A final advice letter was submitted to the applicant October 2019.

The following issues, were discussed:

- Issues related to starting materials for the synthesis of the drug substance, one of which was not agreed with.

- Issues related to the proposed specifications for drug substance, drug product and the grape flavour excipient, which were generally considered acceptable. Some conditions were given for the acceptability of especially the drug product.

The clinical development for the product was discussed in an advice which was applied for in March 2019. At that time the targeted indication was "treatment of Alagille Syndrome". A Scientific Advice oral hearing took place in June 2019, and the final advice letter was adopted by CHMP in the same month. The following issues were discussed:

- The proposal of the applicant to conduct study MRX-308 post-authorisation in order to confirm a clinically relevant effect of maralixibat in ALGS. This approach was considered critical at the time, due to the fact that other studies had not shown significant improvements in itch scores, and the randomised withdrawal design as pivotal evidence was considered to be problematic. Given these caveats, it was strongly advised to both redesign and complete study 308 prior to submission of the MAA. Advice was given to conduct a conventional placebo-controlled trial with an at least 12 week duration.

- Agreement with the proposed study design of study MRX-308. The answer is, in principle included in the above. The intention of the applicant at that time was, to initiate study MRX-308 in Q4-2019. Study MRX-308 was proposed as a 30-week study, including a 6-week randomised, double-blind treatment withdrawal period to evaluate the efficacy and safety of maralixibat in paediatric subjects with ALGS ($\geqslant$12 months and <18 years of age). The main reason for not accepting the design of the trial was related to the assumption that effects after a withdrawal of a compound (when all patients have "adjusted" to its effects already), must be regarded differently from evaluating the effects of a compound that is newly introduced (which more closely resembles what will happen in clinical practice).

Since the 13 June 2019 meeting, new evidence has prompted the applicant to seek full approval in the first instance and the applicant has submitted an application for the indication "treatment of cholestatic liver disease in patients with ALGS 1 year of age and older" without mentioning the conduct of study MRX-308. The conduct of study MRX-308 has obviously been abandoned. The reasons for this decision is given as follows by the applicant:

First, 2 large population-based studies have been published, shedding a new light on the natural history of ALGS (Kamath et al. 2020; Vandriel et al. 2020). These studies demonstrated the progressive and deleterious liver involvement in ALGS. Most patients with ALGS either die or undergo liver transplantation in the first 2 decades of life.

Second, the applicant has obtained longer follow-up data from Studies LUM001-304 and LUM001-303 and new long-term data from Study LUM001-305, which are provided in this MAA , along with a new natural history comparison where 84 maralixibat-treated patients with ALGS are compared with patients from the GALA clinical research database. The long-term studies have shown consistent and durable clinical improvements as well as a positive impact on long-term EFS when compared with a natural-history cohort.

The applicant has also had a pre-submission meeting with the Rapporteur and Co-Rapporteur in May 2021, during which the following aspects were discussed:

- The suitability of the database proposed for submission and for assessment, which was in principle confirmed.

- The problems mentioned with the assessment of withdrawal effects (as compared to de-novo treatment comparisons), similar to the concern raised in the Scientific Advice procedure.

- Comparability of the GALA population to the study population within the development programme was considered to be of utmost importance

- Justification of the proposed dose and dosing schedule.

During the procedure the initially targeted indication "treatment of cholestatic liver disease in patients with Alagille syndrome (ALGS) 1 year of age and older" was adapted to "treatment of cholestasis in patients with Alagille syndrome (ALGS) 2 months of age and older" and then further modified to "treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older" (the finally approved indication).

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the inherent weaknesses identified to be present within the development programme, and the conclusion that it was therefore unclear whether the unmet medical need can be met, and the public interest/need to correctly conclude on efficacy and/or positive benefit risk was rated higher than the possibility for early approval.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as oral solution containing 9.5 mg/mL of maralixibat (as maralixibat chloride).

Other ingredients are: propylene glycol (E1520), disodium edetate, sucralose, grape flavour and purified water.

The product is available in an amber-coloured PET bottle with a preinstalled LDPE adapter and a HDPE child-resistant closure with a foam liner as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of maralixibat chloride is 1-[[4-[[4-[(4*R*,5*R*)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azabicyclo[2.2.2]octan-1-ium, chloride corresponding to the molecular formula $C_{40}H_{56}ClN_3O_4S$. It has a relative molecular mass of 710.42 g/mol and the following structure:

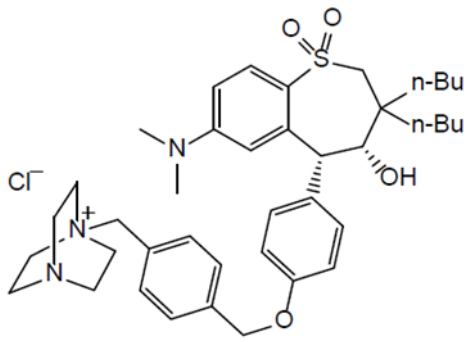


Figure 2 Active Substance Structure

The chemical structure of maralixibat chloride was elucidated by a combination of mass spectrometry, ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, ultraviolet spectrometry, Fourier-transform infrared spectroscopy, specific optical rotation and elemental analysis. The solid-state properties of the active substance were determined by thermogravimetric analysis, differential scanning calorimetry, X-ray powder diffraction and dynamic vapor sorption analysis. The absolute stereochemistry of maralixibat was assigned based on single crystal X-ray data.

The active substance is a white to light yellow, slightly hygroscopic solid which is soluble in water, methanol and propylene glycol. The solubility of maralixibat chloride is low in some organic solvents (acetonitrile, acetone) and in others the active substance is insoluble (tetrahydrofuran, toluene, heptane). Maralixibat chloride is a Class III compound according to the Biopharmaceutical Classification System with high solubility and low permeability.

Maralixibat chloride exhibits stereoisomerism due to the presence of two chiral centres. It is a single stereoisomer in the *R*, *R*-configuration. The desired stereoisomer is stable during manufacture of the active substance. Currently, the two chiral centres originate from a starting material, but the applicant has committed to redefine the starting material (see more detailed discussion in the next chapter). The chiral purity is controlled by chiral HPLC in the starting material specification and is also routinely controlled in the active substance specification.

Polymorphism has been observed for the active substance. The active substance manufactured is the thermodynamically stable polymorphic form.

2.4.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the dossier and it was considered satisfactory. The active substance is obtained from a single manufacturer.

Starting from the initially proposed starting material, maralixibat chloride is synthesised in three main steps.

During the procedure, a Major Objection was raised on the designation of a starting material. The designation of this complex chiral molecule as active substance starting material was not considered in line with regulatory requirements. The applicant has already initiated work to establish the active substance manufacturing process at an additional manufacturing site beginning with the introduction of a new starting material. The manufacturing process to the new intermediate is adequately described in the dossier. The re-designed starting material is acceptable.

In order not to delay patients' access to this orphan medicinal product with unmet medical need for a severe disease and based on the data available from batches from the new (additional) manufacturer and the comparability with batch data from the current process, it has been agreed that the applicant will introduce the additional manufacturer and all the relevant data related the new starting material by submission of a variation no later than December 2023 (see recommendations).

The two other starting materials used in the manufacture of the active substance are well-defined with acceptable specifications. Following a question from the CHMP, the applicant has agreed to strengthen the control strategy for a solvent used (see recommendations).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Following a question from the CHMP, the applicant has agreed to improve the specification for the solvent mixture used for washing of one of the intermediates by developing a test method for assay and potential impurities testing (see recommendations).

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in double low-density polyethylene bags placed within a high-density polyethylene container. The primary packaging complies with Regulation EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), polymorphic form (XRPD), assay (HPLC), impurities (HPLC, GC-MS), chiral purity (HPLC), water content (Ph. Eur.), chloride identity (Ph. Eur.), residual solvents (GC HS) and residue on ignition (Ph. Eur.).

The proposed active substance specifications limits, tests, and methods are acceptable. Acceptance criteria have been established and justified in accordance with guideline ICH Q6A. The acceptance criteria of stated impurities have been justified based on general ICH thresholds. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by non-clinical studies. All necessary tests have been included in the specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay, chiral purity and impurities testing has been presented.

Batch analysis data on 6 batches of the active substance manufactured at commercial scale are provided. Additionally, batch analysis data from stability and relevant clinical and toxicological batches are provided. The results are within the specifications applied at the time of testing and show that process improvements have led to lower levels of impurities in the active substance.

2.4.2.4. Stability

Stability data from five batches of active substance manufactured at pilot scale (≥ 1/10) or larger relative to the commercial scale have been presented. Two batches of active substance were manufactured at the proposed commercial manufacturer, while three batches were manufactured at a different manufacturer used during development. The batches were stored in a container closure system representative of that intended for the market for up to 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines. In addition, data from 7 supportive stability batches of active used in toxicology and clinical studies and manufactured at a different manufacturer used during development was provided for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (4 ºC / 75% RH). The analytical methods used were the same as for release and were stability indicating. No significant trends were observed, and all tested parameters were within the specifications. The comparison of the stability results for assay, impurities, and water content shows no difference between the two primary stability batches manufactured at the site proposed for commercial manufacture and the primary and supportive stability batches manufactured at the previous manufacturer. Parameters not tested have been appropriately justified by stability data.

Photostability testing following the ICH guideline Q1B was performed on one batch. The active substance in the solid state was found to be relatively stable when exposed to light. In solution, minor degradation was observed.

Stress test studies were conducted with the solid active substance and in solution. Samples were exposed to acidic, basic, oxidative, dry heat and heat/humidity stress conditions. Minor degradation was observed under basic conditions in solution. Under acidic and oxidative conditions, the active substance was found to be unstable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored at controlled room temperature with excursions permitted between 15°C – 30°C and with the storage condition ‘Store in the original package in order to protect from light’.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Livmarli 9.5 mg/mL oral solution presents as 30 mL of clear, colourless to light-yellow solution formulation filled into a 30 mL amber coloured PET bottle with a preinstalled LDPE adapter and a HDPE child-resistant closure with a foam liner.

The oral solution is recommended to be administered using a repeated-use dosing dispenser for oral use. Three sizes of CE marked oral syringes (0.5 mL, 1 mL and 3 mL) are co-packaged in the secondary container closure system.

The aim of formulation development was to develop a liquid formulation for paediatric patients which provided for ease of dosing, patient acceptability and flexibility of dosing allowing weight-based dosing over a broad range of patient weights. Definition of the quality target product profile (QTPP, Table 6) allowed identification of potential critical quality attributes (CQAs: identity, assay, degradation products, propylene assay, disodium edetate dihydrate assay and microbial enumeration/tests for specified microorganisms) which were then investigated during development studies, although not in detail, which is acceptable for an aqueous solution using an active substance with high solubility.

Table 4 QTPP for Livmarli

QTPP Elements	Target	Justification
Route of Administration	Oral	Oral dosage form is selected for maralixibat because the drug target (ASBT) lies on the apical side of the intestinal surface.
Dosage Form	Solution	A solution formulation is selected due to the ease of weight-based dosing through use of a range of volumes and because it is preferred for paediatric patients.
Pharmacokinetics	Immediate Release	Maralixibat chloride is highly soluble and minimally absorbed after oral administration. No contributions from the formulation are needed to enhance availability to the target.
Dosage Strength	Minimum number of strengths	The strength (based on maralixibat free base) is selected so that patients of different ages can receive prescribed doses by adjusting the dosing volume.
Stability	At least 24 months shelf-life at controlled room temperature. At least 45 days in-use period.	Adequate stability to ensure drug safety and efficacy within the in-use period and specified shelf life.
Container Closure System	Suitable container closure system to achieve the target shelf-life and to ensure drug product integrity during storage and shipping and enable ease of use with an appropriate oral syringe (dosing dispenser).	To provide adequate protection for the drug product throughout its shelf life, and ease of use.

QTPP Elements	Target	Justification
Alternative Route of Administration	None	The drug target (ASBT) lies on the apical side of the intestinal surface. The compound is minimally absorbed. Therefore, the oral route is the most appropriate route for drug administration.

The choice of route of administration, dosage form and dosing needs/flexibility as well as the excipients used in the formulation and the administration devices have been adequately discussed.

The thermodynamically stable form of the active substance is used.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. with the exception of the grape flavour. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. Propylene glycol (E1520) is an excipient with a known physiological effect and is thus also listed in section 2 of the SmPC.

The commercial finished product formulation is a fixed active substance concentration with variable administered volumes to achieve the desired weight-based dosing. Different strengths of active substance were investigated, and minor adjustments were made to the composition compared to the fixed-dose volume formulation. In addition to acting as a solvent, propylene glycol also serves a preservative. In this regard an antimicrobial effectiveness test to evaluate the ability of the solution to withstand microbial contamination during use showed that the Ph. Eur. requirements (5.1.3) were only met with propylene glycol. Development of a propylene glycol-free formulation was explored however a stable formulation free of propylene glycol is not readily available for commercial manufacturing. Although the excipients are considered safe for children at the levels used in the formulation, as this product is indicated for chronic use in paediatric patients suffering from a liver disease, the CHMP recommends continuation of development towards a propylene glycol-free formulation (see recommendations). To ensure stability, sodium edetate dihydrate was added to formulation as antioxidant.

The development of the manufacturing process has been adequately described.

The changes made to the formulation during clinical studies are not expected to have an impact on the bioequivalence as the finished product is an aqueous solution with an active ingredient that is highly soluble in water.

The maximum acceptable holding time for the bulk solution was established based on a bulk hold time study.

As the product is administered with an oral syringe, physical characteristics of the liquid formulation (pH, density, viscosity) were studied at different temperatures (5°C to 30°C). While viscosity decreases at lower temperatures, the viscosity of the solution remained low within the studied range ensuring that the solution can be drawn from the bottle consistently and without difficulty.

A deliverable volume study has been conducted to determine the target fill volume in the bottle.

Extractable and leachable studies were performed with the container closure system and results were presented. The container closure system is suitable.

Qualification studies were performed to support the use of the oral syringes for oral administration. These studies include delivered volume accuracy, rinse studies to support reuse, compatibility with the oral solution, and extractables and leachables assessments. The studies demonstrated that the syringes

are suitable for the intended use. Livmarli is administered up to 30 minutes before or with a meal. Mixing Livmarli directly info food or drink prior to administration has not been studied during formulation development and should therefore be avoided as stated in the SmPC.

The primary packaging is an amber-coloured PET bottle with a preinstalled LDPE adapter and a HDPE child-resistant closure with a foam liner. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process for Livmarli consists of three main steps: compounding, primary packaging (solution filling and capping of bottles) and labelling/secondary packaging. The process is considered to be a standard manufacturing process.

Critical process steps have been presented in tabular format in the dossier together with the respective critical process parameters and the applied in process controls. No intermediates are isolated during the finished product manufacture.

The applicant proposes concurrent validation of the finished product manufacturing process as described in Annex 15 of the EU GMP guidelines. Based on the knowledge gained through development and batch history, the risk of concurrent validation from a quality viewpoint is low and the approach is therefore acceptable.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications shown in include appropriate tests for this kind of dosage form: description, identity (HPLC, UV), active substance assay (HPLC), degradation products (HPLC), propylene glycol assay (HPLC), disodium edetate assay (HPLC), uniformity of mass delivered doses from multidose container (Ph. Eur.), deliverable volume (USP), pH (Ph. Eur.), microbial enumeration (Ph. Eur.) and specified microorganism (Ph. Eur).

The finished product specification includes all relevant test parameters for an oral solution and complies in general with Ph. Eur. and the EU/ICH guidelines. All proposed acceptance criteria have been sufficiently justified. Proposed acceptance criteria for description of the solution, assay and impurities has been re-evaluated according to the presented stability data. Limits for impurities are set in line with ICH Q3B.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and supporting data from stability batches demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE, it can be concluded that no specific controls for elemental impurities are required in the finished product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No)

726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for three batches of finished product manufactured at commercial scale with active substance from the commercial manufacturer confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Batch results for batches manufactured with active substance from a previous supplier and for clinical batches were also provided.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Stability data from four batches of finished product manufactured at the commercial manufacturer and stored for up to 24 months for one batch und up to 18 months for three batches under long term conditions (2-8°C and 25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Three of these stability batches were manufactured with active substance from a previous supplier while one batch was manufactured with active substance from the commercial manufacturer. Stability data from three supportive batches is also provided.

Samples were tested for description, maralixibat assay, degradation products, propylene glycol assay, disodium edetate dihydrate assay, weight loss, and microbial quality. The analytical procedures used are stability indicating. All results remained within the specification limits.

Since the product is packaged in a semi-permeable container and in line ICH Q1A(R2), water loss/weight loss at low humidity conditions (25°C / 40% RH and 40°C / 25% RH) was investigated and calculated. The data provided demonstrate that the finished product will not have significant water loss throughout the proposed shelf life if stored at 25°C at the reference relative humidity of 40% RH.

Results from forced degradation studies were provided. Samples were exposed to heat, aqueous acidic, aqueous basic and oxidative conditions. Significant degradation was seen under oxidative conditions and formation of degradation products was observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Significant degradation was observed in a clear flask, but the finished product remained stable when protected in an amber coloured PET bottle.

An in-use stability study was conducted at 30°C in support of the shelf-life after first opening of the bottle. Before starting this study, the medicinal product solution was stored for 8 months at 30°C. Results of the study demonstrated that the product is stable for up to 105 days at 30°C.

Based on available stability data, the proposed shelf-life of 2 years with the precaution 'Store in the original package in order to protect from light' as stated in the SmPC (section 6.3 and 6.4) is acceptable. The product does not require any special temperature storage conditions.

After the first opening of the bottle, the medicinal product must be used within 100 days and stored below 30°C as stated in the SmPC (section 6.3). After that, the bottle and its contents have to be discarded, even if not empty.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A major objection raised during the procedure in relation to the designation of a starting material used to manufacture the active substance has been satisfactorily resolved. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product which pertain to (1) the introduction of an additional manufacturer and all the relevant data related the new starting material, (2) updating of the specification for a solvent mixture used in the manufacture of an active substance intermediate (3) strengthening of the control strategy for a solvent used for crystallisation in the active substance starting material manufacture, (4) extending the in-use shelf life and (5) continuation of development work aiming to develop a propylene glycol-free formulation. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Description of post-authorisation measures
1. The commitment to submit all documents and data regarding the routine commercial production using the new starting material as an appropriate post authorisation measure to be provided no later than December 2023 is accepted and is noted. (Quality)
2. Commitment to submit all relevant information pertaining to the tests and specifications for assay and potential impurities for a solvent mixture used in the active substance manufacturing process as an appropriate post authorisation measure to be provided no later than December 2023 is accepted and is noted. (Quality)

Description of post-authorisation measures
3. Commitment to establish an appropriate control strategy for a solvent originating from starting material manufacture and to submit the data as an appropriate post authorisation measure no later than December 2023 is accepted and is noted. (Quality)
4. A variation application to extend the in-use shelf-life should be provided no later than end of December 2023. Applicant is reminded that the design of the in-use stability study should simulate the intended use as proposed in the SmPC and cover the worst-case time necessary to consume the content. (Quality) 5. As the formulation is for chronic use in paediatric patients, the development towards a propylene glycol-free formulation should be continued since propylene glycol should be avoided if possible at all. (Quality) The post-authorisation measures (recommendations) no. 1 – 3 relate to the active substance and should be submitted together by one grouped type II variation at the end of December 2023. The post-authorisation measure (recommendation) no. 4 relates to the finished product and should be submitted by a separate variation (type IB, B.II.f.1.b.2) at the end of December 2023.

2.5. Non-clinical aspects

2.5.1. Introduction

Nonclinical studies carried out to support the development of maralixibat include *in vitro* and *in vivo* primary pharmacodynamic (PD) and safety pharmacology studies, absorption, distribution, metabolism, and elimination (ADME) studies, single-dose toxicity studies, repeat-dose toxicity studies, chronic toxicity studies in 2 species, genotoxicity studies, reproductive toxicity studies, juvenile toxicity studies, and so far one completed carcinogenicity study.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Maralixibat is considered a potent inhibitor of the human ASBT. *In vitro* proof of concept is considered established.

The ASBT transporter protein is highly conserved across species, with the human and mouse proteins showing 81% identity and 89% similarity at the amino acid level and with human versus monkey (99% similar), dog (93% similar) and rat (89% similar) proteins even more highly conserved and the documented *in vivo* effects of maralixibat across species, including mouse, rat, dog, and monkey, indicate the potency and mechanism of action across the nonclinical species.

The pharmacodynamic effects of maralixibat *in vivo* were investigated in naïve rats, partial bile duct ligated (pBDL) rats as a cholestasis model, dogs and monkeys and *in vivo* primary pharmacology data are in line with the ability of orally administered maralixibat to inhibit the re-uptake of bile acids and to increase the faecal excretion thereof.

In naïve male Wistar rats, oral treatment with maralixibat of up to once daily 2 mg/kg for 4 days resulted in a dose-dependent increase in faecal bile acid (fBA) excretion up to 3.6-fold with an ED_{50} of approximately 0.027 mg/kg/day. In pBDL male Sprague Dawley rats treated orally once daily with up to 10 mg/kg maralixibat statistically significant reductions in sBA and ALT were seen at Day 3, the first time of sampling, and reductions in additional liver injury biomarkers at 7 and 14 days. In Beagle dogs after oral daily treatment with 1 or 4 mg/kg of maralixibat for 14 days statistically significantly dose-dependent increases in fBA excretion (up to 5-6 fold compared to pretreatment) and statistically significant reductions in serum total and HDL-cholesterol were seen. In Cynomolgus monkeys administered oral doses of maralixibat once daily for 7 days, fBA levels were increased by 2- and 5-fold at doses of 5.0 and 20.0 mg/kg, respectively.

2.5.2.2. Secondary pharmacodynamic studies

In a secondary pharmacology screen investigating maralixibat at concentrations of up to 100 nM neither relevant inhibition nor stimulation of any of the investigated 87 molecular targets was identified. Regarding systemic exposure a safety margin of approximately 1,600-fold to the mean plasma free drug C_{max} at a therapeutic dose level in humans results which is considered sufficient. Maralixibat was designed to be poorly absorbed and the drug target, the ASBT, is located on the brush border of the enterocytes. Based on a pharmacokinetic modelling exercise maralixibat could inhibit luminally expressed transporters with affinities in the lower micromolar range or lower. The potential inhibition of OATP2B1 by maralixibat is, mentioned in the SmPC section 4.5.

2.5.2.3. Safety pharmacology programme

The applicant submitted a study report on an *in vitro* hERG channel assay claimed to be GLP compliant. Due to several mishaps occurring during the conduct of the study the data obtained are considered limited. Maralixibat did not inhibit the hERG channel at a nominal concentration of 1 µM statistically significantly different from vehicle control values. A subsequently performed extension of an analytical validation study supports the view that the patch-clamp measurements obtained at the nominal concentration of 1 µM may be considered true.

Cardiovascular safety studies in conscious and in anesthetised dogs, with oral and IV administration, respectively, CNS safety studies in rats with oral and IV administration, respectively, and respiratory safety studies in guinea pigs with IV administration did not reveal concerns regarding cardiovascular, CNS or respiratory safety of maralixibat.

2.5.2.4. Pharmacodynamic drug interactions

Maralixibat is an OATP2B1 inhibitor based on *in vitro* studies. A decrease in the oral absorption of OATP2B1 substrates (e.g. fluvastatin or rosuvastatin) due to OATP2B1 inhibition in the GI tract cannot be ruled out. Therefore, the monitoring of the drug effects of OATP2B1 substrates are advised in SmPC 4.5.

Maralixibat is also an inhibitor of CYP3A4 based on *in vitro* studies. An increase of plasma levels of CYP3A4 substrates (e.g. midazolam, simvastatin) can therefore not be excluded and the SmPC advises caution when such compounds are administered concomitantly.

Maralixibat, being an inhibitor of bile acid absorption, has not been fully evaluated with regard to the interaction potential with the bile acid Ursodeoxycholic acid (UDCA). Therefore, the SmPc advises to monitor patients that are concomitantly treated with this compound.

Maralixibat is minimally absorbed, is not significantly metabolised, and is not a substrate of active substance drug transporters; therefore, other concomitant medicinal products are not expected to affect the disposition of maralixibat. Maralixibat is not expected to inhibit or induce other cytochrome P450 in patients; therefore, maralixibat is not predicted to affect the disposition of concomitant medicinal products through those mechanisms.

2.5.3. Pharmacokinetics

Methods of analysis

Maralixibat has been in development for more than two decades. The applicant (Mirum) sponsored new general toxicity studies in rodents. Embryofetal development was evaluated in rabbit in a study in 2001. For these two studies, no separate bioanalytical report was provided, however that as well as ISR was not required at the time of study conduct. Moreover, both studies include a QA statement documenting audit of bioanalytical raw data and toxicokinetics draft reports.

The bioanalytical programme appears to be and have been in good control with robust bioanalytical methods and documented stability of maralixibat in plasma.

Validation studies were provided for determination of maralixibat in plasma of TgrasH2 and CD-1 mice, rats (juvenile and adult), rabbits and dogs. Plasma concentrations of maralixibat were measured by liquid chromatography with tandem mass spectrometry (LC/MS/MS). Plasma concentrations of radiolabeled maralixibat were analysed using liquid scintillation counting (LSC). High performance liquid chromatography (HPLC) was also developed and validated for quantifying maralixibat concentrations in diet admix formulations and water.

Maralixibat showed indications of adherence to surface materials in several studies. The extend is unknown. This may result in some discrepancies between intended and applied dose. However, the relevance for the safety assessment is considered low.

Absorption

Absorption after single or repeated dose oral administration was investigated mice, juvenile and adult rats, (pregnant) rabbits, dogs, guinea pigs and cynomolgus monkeys in a multitude of studies. Due to a limited relevance, results in guinea pigs and cynomolgus monkeys are not discussed in the following.

Absorption after single dose

Single dose bioavailability was evaluated in mouse (50, 150 mg/kg), rat (1- 2000 mg/kg), rabbit (50, 150 mg/kg) and dog (1-1000). Bioavailability was below 1% in all species and tested doses. A study in femoral artery and portal vein cannulated rats showed that first pass effect was not the cause of the low bioavailability as it only accounted for 7.88% of the administered dose as determined from AUC after intravenous and intraportal infusion. A similar study design was used in dog (studies M3098258 and M3098260), where first pass effect and/or biliary excretion actually was shown to affect the bioavailability by up to 79%.

Absorption in dog was evaluated both after oral gavage and oral capsule. The capsule formulation increased T_{max}, however bioavailability was still below 1%. In an acute toxicity study, dogs were dosed 50, 200, 400, 600, 800 or 1,000 mg/kg maralixibat as an oral capsule (SA4948). Emesis increased with dose and bioavailability decreased with dose (range 0.08 to 0.02%).

Absorption after repeat dose

An extensive amount of repeat-dose pharmacokinetic studies was conducted to evaluate the absorption of maralixibat in all relevant species including pregnant rabbits and juvenile rats. Low

bioavailability was observed in all species except the youngest juvenile rats. Low bioavailability is also evident in humans including children.

Repeat dose in mouse

Repeat-dose TK of maralixibat in mice was evaluated in 9 studies of 2 to 26 weeks duration. 5 studies were using oral gavage and 4 were using dietary admix. The dose-range for oral gavage was 2.5 to 2.000 mg/kg/day and for dietary admix 5 to 10.000 mg/kg/day. Bioavailability was less than 1% for oral gavage and generally even lower for dietary admix. Females showed higher exposure than males in the final 26 weeks carcinogenicity study in rasH2 mice at doses 7.5 and 25 mg/kg/day on Day 1 (MRX-NC-002). Other studies show the same tendency at doses up to 250 mg/kg/day (M8562M-SHP625 and M7614M-SHP625). High accumulation was evident in some dosing groups in study MRX-NC-002.

Repeat dose in rat

Repeat-dose TK in rat was evaluated in 10 studies of 2 to 13 weeks duration in adult rats. 8 studies were using oral gavage and 2 were using dietary admix. The dose range for oral gavage was 1-1.500 mg/kg/day and for dietary admix 150 to 2.000 mg/kg/day. Bioavailability was less than 1% for oral gavage and generally even lower for dietary admix, typically less than 0.1%. No obvious sex differences were observed, and slight accumulation was only seen at very high doses in female animals.

In the recent 13-week study sponsored by Mirum (MRX-NC-004), the following was concluded:

No appreciable sex differences observed. The values for C_{max} were 1.06, 9.76 and 43.1 ng/mL on Day 1 and 1.16, 17.4 and 48.9 ng/mL on Day 91 for the 10, 300 and 1,000 mg/kg/day doses, respectively. The values for AUC0-24hr were 8.70, 129 and 609 ng·hr/mL on Day 1 and 12.2, 129 and 627 ng·hr/mL on Day 91 for the 10, 300 and 1,000 mg/kg/day doses, respectively.

As dose increased, Cmax and AUC0-24hr also increased, though at a less than dose proportional manner from the 10 to 300 mg/kg/day oral dose. The increase was dose proportional from the 300 to 1,000 mg/kg/day dose. The accumulation ratio was 1.40, 1.38 and 1.03 for the 10, 300 and 1,000 mg/kg/day doses, respectively, which suggests that accumulation is low following repeated doses.

Toxicokinetics was evaluated in juvenile rat from PND7 to PND 21 (MRX-NC-001) and from PND21 to PND63 (13-4397). The highest exposures were documented in the youngest rat pups on PND 7 and decreased significantly on PND 14 and 20. Bioavailability was approximately 17% on PND 7, but decreased to <1% by PND 20. This decrease in bioavailability over the course of the experiment was likely due to decreasing permeability of the maturing GI tract in the rat pups during the early neonatal period.

In the older juvenile rats, C_{max} and AUC0-24hr values were similar or greater on PND 56 compared to PND 21. There was some accumulation observed in female rats (accumulation ratio between 1.6 and 1.8) after repeated doses, which may be in part due to the higher doses administered compared to the doses administered to male rats (25-, 50-, 100-, or 200-mg/kg/day dose to males and females were administered either a 125-, 250-, 500-, or 1,000-mg/kg/day dose).

Toxicokinetics after dietary admix was evaluated in pregnant rats in two studies; SA5043 (50, 250 and 1000 mg/kg/day) and EX5034 (250, 750 and 2,000 mg/kg/day). Exposure was documented; however, bioavailability was in the range of 0.04 to 0.25%.

Repeat dose in rabbit

Repeat-dose TK in pregnant rabbit was evaluated in two studies (EX5033 and SA5061) covering the dose range of 25 to 500 mg/kg/day. In both studies rabbits were dosed from GD7 to GD18 and the

bioavailability of maralixibat was < 0.1% across all dose ranges and days of sampling. Exposure was too low on GD7 for the lower doses to conclude anything on dose proportionality, however exposure was much higher on GD18 than on GD7 for the doses 100 and 250 mg/kg/day. Exposure was higher than dose proportional on GD18 in study SA5061 reaching 766 ng/mL*h for the highest dose of 250 mg/kg/day. It should be noted that rabbits receiving 500 mg/kg/day in the DRF study (EX5033) did not survive to GD18.

Repeat dose in dog

Repeat-dose TK in dog was evaluated in studies of up to 1-year duration. In general, bioavailability was less than 0.2% across the whole dose range of 1 to 600 mg/kg/day. Dogs suffered from emesis, hence toxicokinetics may be less reliable, as the fact that many samples were below LLOQ, also show. The highest $AUC_{0\text{-}24h}$ and C_{max} was reached on Day 176 at 100 mg/kg/day in the 1-year toxicity study (455 ng/mL*h and 113 ng/mL, respectively). Similar range of exposure was obtained in the 13-week toxicity study at the same dose level (SA4991). Accumulation was observed at higher doses (100 and 300). No sex differences in exposure were observed in any study. Exposure increased with increasing dose, however dose proportionality evaluation is deemed unreliable due to the large variability and many samples being >LLOQ. In the 1-year study doses up to 20 mg/kg/day was relatively well tolerated, providing AUC0-24h and C_{max} of 57.7 ng/mL*h and 18.5 ng/mL, respectively (SA4987). Plasma concentrations in patients are often below LLOQ of 0.25 ng/mL.

Distribution

Distribution was investigated in (pigmented) rats and dogs by the use of [3H] and [14C] labelled maralixibat.

Tissue to plasma ratios of tissues in the gastrointestinal tract was in the range of 100 to 6000 in the rat after 5 mg/kg of 14C-maralixibat (study M2098359). Levels of ng equivalents/g in tissues of the gastrointestinal tract was largely in a similar range between rat and dog after oral doses of 5 mg or 7.5 mg/kg of 3H-maralixibat, however levels in female rats were lower than in male.

Due to maralixibat's low bioavailability, distribution to other tissues is low, although maralixibat was also found in the liver and pancreas of the rat at levels approximately 10 times higher than plasma. Maralixibat was detected in many other tissues in low amounts, but at the last time point of 168 hours, the highest concentration was still in the small intestine, hence no retention in specific organs was observed. No binding to skin was detected (non- or pigmented skin).

Other tissues than gastrointestinal were not evaluated in the dog.

Plasma protein binding was determined with [^{14}C]maralixibat for mouse, rat, guinea pig, rabbit, dog monkey and human (M3099225), covering the concentration range of 0.25 to 25.0. µg/mL. Plasma protein binding was high (99 - 84%) and concentration independent in all species tested. Partitioning of 0.250, 2.50 and 25 µg/mL maralixibat into red blood cells of rats (20 – 43%), dogs (22 – 38%) and humans (33 – 45%) was determined by the use of [^{14}C]maralixibat in vitro. Partitioning into blood cells appears to be dose dependent over the concentration range tested. Results of in vivo studies showed, that maralixibat does not preferentially distribute into red blood cells (*in vitro*: M3099280; *in vivo*: M3099009, M3098328 and M3098330).

Regarding the volume of distribution, the applicant refers to studies with IV administration performed in mice, rats, guinea pigs, dogs and monkeys

In mice and dogs, the apparent volume of distribution at steady-state (Vss,0.622 and 0.257 L/kg, respectively) after intravenous application was lower than total body water/ total extracellular fluid indicating that maralixibat did not penetrate extensively into tissues. For rats and monkeys, the apparent Vss (0.73 and 0.599/0.296 ml/kg. resp.) and the volume of distribution (Vz) following

intravenous application were slightly higher than the volume of total extracellular water. Furthermore, the applicant claims that the volume of distribution and the volume of distribution at steady state for guinea pigs were slightly higher than the volume of the total extracellular/ body water without providing a reference. Since studies in guinea pigs are limited to studies on excretion and local tolerance, this missing information is considered to be of low relevance.

No information is provided regarding a potential transfer of maralixibat into the milk or the developing fetus. This appears to be acceptable in the light of the low bioavailability and the resulting low plasmatic levels anticipated in human use.

Metabolism

In vitro

Metabolism was investigated *in vitro* and *in vivo*. In vitro metabolism studies were performed in liver microsomes of rat, dog, cynomolgus monkeys and human using [^{14}C]maralixibat. Several metabolites have been identified. Studies with subsequent HPLRC identified potential sex differences in rats only. 4 potential metabolites were detected in males and 3 in females. Metabolism rate was low (12.3 % in males and 2.4 % in females). In dogs, at least 7 potential metabolites were identified. The metabolism rate was slightly higher (21%) compared to rats. Microsomes obtained from Cynomolgus monkeys showed the highest similarities to metabolism in humans. Metabolism rate was higher (74% and 69% in Cynomolgus monkeys and humans, respectively) compared to rats and dog. In both species, at least 8 potential metabolites were identified. By subsequent LC/MM/MS and LC-MR detection, 6 potential metabolites (M1-M6) were detected. These metabolites included the N-demethylation metabolites of maralixibat (M1 and M2) and the hydroxylation metabolites of maralixibat (M3 and M6), as well as the N-demethylation and hydroxylation metabolites M4 and M5. Based on this data the applicant has proposed an overview on potential metabolic pathways in liver microsomes. In the light of the low bioavailability and the rather local mode of action the relevance of the discrepancies between human and the species involved in toxicity testing is of minor relevance.

In vivo

A potential pre-systemic metabolism was investigated in mice, rats, rabbits and (female) dogs. Maralixibat was mainly detected in the faeces. In mice one minor degradation product was identified in the faeces (N-demethylated maralixibat; M1) and in rabbits three (M1 (N-demethylated maralixibat); M2 (N-di-demethylated maralixibat) and M3 (monohydroxylated maralixibat)). In rats and dogs, maralixibat appears to be stable. Systemic metabolism was investigated in rats and dogs following intravenous administration. In rats, sex-related difference in the metabolism were noted. In female rats, only 2.07% of the dose was metabolised compared to 55.0% in male rats. In dogs the majority of the dose was excreted in the faeces as parent compound (65.1%) with a smaller amount excreted as metabolite M3 and one other minor degradation product/metabolite M1 (total metabolites = 8.95%). No apparent sex-related difference in metabolism was noted. Keeping in mind maralixibat's low bioavailability in all species including humans, potential differences in the metabolic patterns of the species involved in toxicity testing has to be considered of minor relevance. The omission of studies of Phase II metabolism and induction/inhibition of CYPs is considered acceptable. From pharmacokinetic point of view toxicity testing in mice, rats, dogs and rabbits is therefore adequate.

Excretion

Excretion of maralixibat following single dose administration was investigated in mice (oral, study M3000146), rats (oral, study M2000269, and intravenous, study M2000112), guinea pigs (intravenous, study M2000113), rabbits (oral, study M3099010), and dogs (oral and intravenous, studies M2098132, M3098330 and M2000114). Excretion after oral repeated dose administration was investigated in mice, rats and dogs (studies M3000146, M2000269, M2000114, respectively). Maralixibat was mainly

excreted via faeces (71.9 – 96.4%). Only very low amounts could be detected in urine (0.1 to 9.63%). Adequate recovery was obtained in all these studies for the conclusions to be considered valid (72.5 to 96.6%).

Comparisons with published data (Davies and Morries 1993) showed that the clearance was lower than the hepatic blood flow in mice, rats, dogs and monkeys. It can, therefore, be concluded that, following intravenous administration the excretion of maralixibat is not limited by the hepatic blood flow. The applicant claims the same for the guinea pig without providing published evidence.

Pharmacokinetic drug interactions

No robust pharmacokinetic drug interaction studies were submitted within the non-clinical part of the dossier. The applicant claims completeness of the investigations concerning this point and refers to the clinical part of the dossier. There are no objections against the applicant´s approach to place this aspect in the clinical part (For further information on this aspect, please, refer to the clinical part of this report).

2.5.4. Toxicology

The non-clinical toxicology programme submitted by the applicant is considered to be in general in line with the respective guidelines.

The batches of maralixibat used for the toxicology programme were synthesised using the same synthetic route as that used for clinical study batches and that planned for commercial batches, with impurity profiles representative of the clinical API.

The nonclinical PK data indicate that maralixibat is minimally absorbed after oral administration. Since systemic exposure following oral administration of maralixibat is low, findings from IV administration are not likely to be clinically relevant.

Toxicology studies with maralixibat (salt form) were conducted in mice, rats, dogs, rabbits, and monkeys. For the main nonclinical toxicity assessment, Sprague-Dawley rats and beagle dogs were used, and those were also the strains used for key ADME studies in rats and dogs. Various formulations of maralixibat API were used, i.e. a simple aqueous solution of maralixibat API in water for oral gavage of small animals, dietary admix formulations were used for some repeat-dose toxicity studies and maralixibat API in capsules was utilised for dosing of dogs.

2.5.4.1. Single dose toxicity

Single dose toxicity studies were performed in the rat and in the dog with oral and with IV administration of maralixibat.
In the oral study in rats doses of 0, 1000, and 2000 mg/kg of maralixibat were administered via gavage. The minor maralixibat-related adverse effects observed, which were reversible within one week, included stool alterations and salivation.

In the rat study using the IV route doses of 0, 0.06, 0.6 and 6.0 mg/kg were administered. Transient clinical signs beginning 10-15 min post-dose were observed at the high dose only, were transient and included ataxia, reduced activity, reduced body tone, tremors and dilated pupils.

In the GLP compliant oral single dose toxicity study in Beagle dogs doses of 0, 50, 200, 400, 600, 800, or 1,000 mg/kg were administered. Emesis was observed at doses of ≥ 50 mg/kg and was considered severe at doses of ≥ 400 mg/kg. Stool abnormalities were observed at doses of ≥ 200 mg/kg. Exposure

values were rather similar in the 400 to 1000 mg dose groups, possibly due to either emesis or saturation of absorption.

In the single dose toxicity study in Beagle dogs with IV administration doses of 0, 1, 2.5 and 5 mg/kg of maralixibat, transient clinical neurological signs of lethargy, tremors or muscle stiffness were noted at the highest dose. As the exposure (C_{max}) is more than 70,000 times higher than the C_{max} reported for humans receiving about 3 times the clinically intended maximum therapeutic oral dose for two weeks, the neurological signs seen in the dog are considered of no clinical relevance.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies were performed in mice for up to 13 weeks, in rats for up to 26 weeks, in dogs for up to one year and in the monkey for 2 weeks. The duration of the chronic repeated dose toxicity studies is in line with ICH M3. The route of administration was the oral route, the route of administration in humans. A total of 27 repeated dose studies were performed. A part of them aimed at finding an appropriate dose for carcinogenicity studies in mice. In mice and rats, a part of the studies was conducted using gavage and another part was conducted using dietary admixture. Bioavailability of maralixibat in the repeated dose studies was generally below 1%.

Mouse

The three GLP compliant repeated dose toxicity studies in CD-1 mice were conducted with treatment durations of 13 weeks. In two of these studies maralixibat was administered via oral gavage, one via admixture to the diet. Dosages in the studies using gavage were 0, 50, 150, 500, 1000 mg/kg/day and 0, 50 250, 750 mg/kg/day, respectively, in the study using dietary admixture 0, 50, 150 and 750 mg/kg/day were administered. In the studies using gavage deaths were mostly attributed to gavage errors/aspiration or respiratory distress due gaseous distended abdomen especially in high dose groups. The latter effect is considered to be possibly related to a change in the intestinal microenvironment due to administration of maralixibat. Reduction in bodyweight/- gains have been seen predominantly in male animals and at higher dosages. A consistent finding in the studies is prolongation of coagulation parameters (PT, aPTT) in males starting from the lowest dose of 50 mg/kg/day of maralixibat (gavage or admix). The applicant considers this effect likely to be caused by vitamin K deficiency. In the mouse repeated dose toxicity studies no bleeding events were reported. Increases in cecum and/or colon weights are reported in both genders in all studies and they are possibly related to the oral administration of poorly absorbable material. Increases in faecal bile acid excretion, the expected main pharmacological effect of maralixibat, were seen in all of these studies. In the studies using gavage, increases in serum cholesterol/HDL are reported at the highest administered doses. These effects, although not expected as a direct pharmacological effect of maralixibat, according to the applicant increases of serum cholesterol in rodents treated with certain cholesterol-lowering drugs (like the statins) have previously been described and are thought to be related to strong induction of HMG-CoA reductase.

The NOAEL in the mouse gavage study SA4954, the study of the two gavage studies with more parameters investigated, is considered to be the MD of 150 mg/kg/day. Mean combined C_{max} was 71.7 ng/mL and $AUC_{0\text{-}24hr}$ was 529 hr•ng/mL. In humans after administration of once daily doses of 100 mg maralixibat for 14 days, mean C_{max} was 1.146 ng/mL and mean $AUC_{0\text{-}24}$ was 4.614 ng•h/mL were reported. As this dosage in humans is about three times the clinically maximally intended one, assuming dose linearity, exposure based safety factors between NOAEL in this study and the maximum clinical dose of at least 136 (C_{max}, male animals) and 310 (AUC female animals) result. The NOAEL in the mouse study SA5005 with admixture to diet is considered to equal the HD of 750 mg/kg/day. A mean gender-combined C_{max} of 21.9 ng/mL and $AUC_{0\text{-}24hr}$ of 453 ng•h/mL were reported which would

under the same assumption result in exposure based safety factors of at least 55 (outlier-eliminated C_{max} in male animals) and 279 (outlier eliminated $AUC_{0\text{-}24hr}$ in male animals) result. Considering the toxicological effects reported in the repeated dose toxicity studies with maralixibat in mice these exposure based safety factors are considered sufficient.

Rat

Six GLP-compliant repeated dose toxicity studies in rats were performed with a treatment duration of 13 weeks/3 months. In five of the 13 week studies maralixibat was administered orally via gavage, in the remaining one and in the 26 week GLP compliant study via dietary admix. Three of the gavage studies and one of the dietary admix 13 week studies included recovery periods of 4 weeks. The maximum dosages in the gavage studies ranged from 150 mg/kg/day to 1500 mg/kg/day. In two of these studies males received up to two thirds lower dosages than females. In the dietary admix study of 13 weeks duration the highest dose level was 1500 mg/kg/day. In the 26 week dietary admix study the dose levels were initially 0 (males + females), 30 (males only), 150 (males + females), 500 (females only), 750 (males only), and 2000 (females only) mg/kg/day of maralixibat. Due to high mortalities in HD groups, the dose in HD males was lowered around week 12 from 750 to 300 mg/kg/day and in the group of HD females around week 12 from 2000 to 1500 mg/kg/day of maralixibat.
In general, in the studies with administration of maralixibat via oral gavage a considerable number of deaths were attributed to aspiration of dosing solution. In all but two repeated dose toxicity studies in rats, especially in male animals, prolongation of coagulation parameters with bleeding events at higher dosages were seen. The lowest dose at which prolongation of PT and aPTT was already seen, was 5 mg/kg/day of maralixibat (study SA4865) and at 500 mg/kg/day (study SA5006) fatal bleeding events occurred in male animals. When investigated, the prolonged coagulation times showed reversibility. The applicant considers secondary to loss of bile acids induced vitamin K deficiency a likely cause for the prolongation of coagulation times/bleeding events. Prolongation in coagulation time was only considered an adverse effect by the applicant if it was associated with bleeding event. This is not endorsed, as increasing PT and APTT precedes the bleeding event and the increasing values should therefore be considered an adverse effect in itself. However, as vitamin K deficiency and prolonged coagulation time appears to be rodent specific and not a problem at clinically relevant doses in dog, monkey or human, the issue will not be further pursued.

Another phenomenon/clinical observation associated with maralixibat treatment is the discolouration of papers placed under the cages or unusual urine colour. In one study this was already seen at a dose as low as 5 mg/kg/day and studies hint that this phenomenon is more prominent in MD than in HD animals. The applicant was unable to identify the cause of this staining and states that repeated urinalyses have excluded urinary blood. In the same two studies, in which no prolongation of coagulation parameters was reported (studies R7834 and MRX-NC-004) no such staining of cage papers was reported. Moderate decreases in body weight gains were seen repeatedly in males, whereas in females only at higher dosages.

An effect on liver were detected in rats (and to a lesser extent in dogs), as decreased liver weight, decreases in serum cholesterol, HDL, triglycerides but also changes in ALT/AST and proteins (albumin and globulins). It is considered plausible, that a change in hepatic activity with respect to bile acid and lipid metabolism potentially could affect related parameter i.e. cholesterol, HDL, triglyceride.
Faecal bile acid excretion increased consistently already starting at the lowest doses tested (5 mg/kg/day; e.g. in study SA4865 at this dosage already up to 10-fold increase compared to control). Slight increases of serum phosphorus were considered secondary to the changes in serum protein levels. Slightly increased serum sodium and/or chloride occurred at all levels and were attributed to possibly increased permeability of the intestinal tract following exposure to increased concentrations of bile acids.

Increasing weight of the intestinal segments in mice and rats was found and was accepted to be a result of poor absorption of large amounts of orally administered material. Increased urine calcium levels were attributed to caecal enlargement, which has been associated with increased intestinal absorption and renal excretion of calcium.

Microscopic changes in cecum, colon and rectum of mucus depletion of goblet cell, oedema in lamina propria, non-suppurative inflammation and mucosal epithelial alterations e.g. crowding of crypt cells with thickening of mucosa, was shown to be a result of increasing levels of luminal fBA. Even though increasing fBA levels is a pharmacological effect of maralixibat and most GI microscopical changes were reversed at treatment discontinuation, highlighting these changes is considered relevant, as abdominal pain and diarrhoea were observed as common adverse reactions in human patients. A potential risk of carcinogenic transformation of the GI mucosal epithelial alterations (e.g. crowding/proliferation of crypt cells) should be excluded histologically when 2-year rat CARC data are available (see section 2.5.4.4).

Due to fatal bleeding events in HD animals in the GLP compliant pivotal repeated dose toxicity study in rats with the longest maralixibat treatment duration of 26 weeks (Study SA4988), the dose of the MD animals is considered being the NOAEL, which is 150 mg/kg/day in male rats and 500 mg/kg/day in female rats. The exposure in male rats at this NOAEL was 5.42 ng/mL (C_{max}) and 108 ng•h/mL (AUC) and in female animals 13.5 ng/mL (C_{max}) and 241 ng•h/mL (AUC). In humans after administration of once daily doses of 100 mg maralixibat for 14 days, mean C_{max} was 1.146 ng/mL and mean AUC_{0-24} was 4.614 ng•h/mL were reported. As this dosage in humans is about three times the clinically maximally intended one, assuming dose linearity, exposure-based safety factors between NOAEL in this study and the maximum clinical dose of at least 13 (C_{max}, male animals, 150 mg/kg/day) and 70 (AUC male animals, 150 mg/kg/day) result. Considering that the main toxicological and dose limiting effect reported in this and the other repeated dose toxicity studies with maralixibat in rats is the prolongation of coagulation factors leading to bleeding events in higher doses and that this is an effect not observed in humans, these exposure-based safety factors are considered sufficient. As the bioavailability of maralixibat is very low (in general below 1%) the use of doses instead of systemic exposure for calculation of safety margins is acceptable as well. According to a table provided by the applicant, it appears that high safety margins to human doses exists, which is also the case in most of the studies conducted. However, it should be noted that safety margins were only calculated for selected repeat-dose studies in which a NOAEL was determined. In a number of the studies, no NOAEL could be determined. The primary toxicity observed in mice and rats, were prolongation of coagulation time. Changes in coagulation parameters were detected at doses as low as 5 mg/kg in rats (HED = 0.8 mg/kg*), which do not provide much of a safety margin to the human dose of 0.38 mg/kg. As also discussed, the prolonged coagulation appears to be rodent specific and not a notable problem in dog, monkey or human patients. With the warning in SmPC section 4.4 „Assessment of fat-soluble vitamin (FSV) levels (Vitamins A, D, E) and international normalised ratio (INR) are recommended for all patients prior to initiating Livmarli, with monitoring per standard clinical practice. " this issue is considered appropriately reflected in the SmPC.

Dog

Repeated dose toxicity studies of 2 weeks (EX4798), 4 weeks (SA4877, SA4945), 13 weeks (SA4991) and 6 to 12 months (SA4987) have been performed in beagle dogs. Maralixibat was given in an oral gelatin capsule up to 600 mg/kg/day (13 week study SA4991). With the exception of the 2 week study all studies were performed GLP compliant. All studies were accompanied by toxicokinetic evaluation. Recovery groups were included in the 4-week studies (SA4877, SA4945) and the 6 to 12 month study (SA4987).

In dogs, the tolerable dose was limited by exaggerated emesis as demonstrated in the 4 week study (SA4945). In this study, the high dose study group (600 mg/kg/day) was withdrawn due to exaggerated emesis. A maralixibat associated increase in emesis was observed at doses of 100 mg/kg/day and above. In addition, in some cases slight decreases in body weights or body weight gains were observed. To a lesser extend as compared to rats, an increase in coagulation time was observed. Significant changes were observed in the combined 6 to 12 month repeated dose toxicity study at the highest dose group of 100 mg/kg/day. The applicant associates this finding with a vitamin K deficiency, which is considered acceptable.

Several other findings were associated with the pharmacodynamic activity such as a decreased plasma or liver cholesterol / HDL / triglyceride concentration or an increased faecal bile salt excretion, which are clearly caused by the pharmacodynamic activity of maralixibat. Some findings in the field of clinical chemistry such as total protein, albumin, globulin (and their respective ratio), [Cl^-] and [Na^+] concentration, which reached significance in the 6 to 12 month study in some dose groups are less clear associated with the pharmacodynamic activity but overall reversible and of low magnitude and, therefore, of low physiological relevance. Significant changes of liver enzyme concentrations in serum (increased aspartate aminotransferase, decreased alkaline phosphatase) in all dosing groups were considered also to be associated with the pharmacodynamic activity of maralixibat.

The applicant believes that the combination of changes in serum phosphorus and ALP along with the increased urinary excretion of phosphorus suggests that decreased serum ALP values may be related to a decreased osteoblastic activity. The conclusion appears to be reasonable, however, a sound conclusion cannot be drawn.

Two treatment-related histological changes (decreased eosinophilia in the fundic parietal cell and pyloric stomach cell cytoplasmic vacuolisation) were observed in the stomach at the Week 53 sacrifice. Decreased eosinophilia in the fundic parietal cell was noted in 100 mg/kg animals and pyloric stomach cell cytoplasmic vacuolisation was noted in 5, 20 and 100 mg/kg animals. These lesions remained present at the Week 61 (8-week reversal post 1 year of dosing) sacrifice but were considered to be incidental and of no further relevance.

The NOAEL in dogs based on the pivotal study with a duration of 1 year is 20 mg/kg/day. An approximation using exposure in humans and dogs would result in safety factors between 38 to 48 times. This is considered sufficient.

Monkey

In addition, one non-pivotal repeated dose toxicity study in cynomolgus monkey was submitted, which was performed more than 20 years ago. This study would be considered a breach of the principles of 3R nowadays. Furthermore, it should be noted that, the death of one monkey was caused by a dosing error (rupture of the oesophagus), which is hardly acceptable in non-human primates. The only noteworthy finding was an increased spleen weight and decreased colon weight.

2.5.4.3. Genotoxicity

Maralixibat was negative in *in vitro* Ames tests, chromosome aberration assays in CHO cells and in an oral *in vivo* micronucleus test performed in rats. Exposure was not determined in the micronucleus test, however, there were signs of toxicity and excess mortality in the high dose animals indicating sufficient exposure of animals. Based on the provided studies, maralixibat is not considered to be genotoxic *in vitro* and *in vivo*.

2.5.4.4. Carcinogenicity

Carcinogenicity was determined in rat and mouse carcinogenicity studies. One incomplete study evaluating carcinogenicity of maralixibat when administered to rats in the diet for at least 104 weeks was provided. Due to deprioritisation of the programme by a previous sponsor, microscopic evaluation of tissues was discontinued, and tissues were discarded, thus the full investigation of carcinogenicity potential from this study was not available. A further 2-year carcinogenicity in rats was started in 4Q of 2020. The provided study design is considered adequate. Results of the planned carcinogenicity should be provided as soon as data become available. There were higher incidences of bronchiolo-alveolar adenoma and carcinoma in Tg rasH2 male mice administered 25 mg/kg/day maralixibat.

Bronchiolo-alveolar adenomas were statistically significant for incidence and trend, as was the combined incidence of bronchiolo-alveolar adenoma and bronchiolo-alveolar carcinoma. The applicant argues that lung tumours (bronchiolo-alveolar adenoma and carcinoma) are the most common spontaneous neoplasms reported in Tg rasH2 mice and their incidences in males administered 25 mg/kg/day maralixibat in this study (24% and 4%, respectively) are within published control ranges (Paranjpe et al., 2019). It is agreed that lung tumours are common background tumours in this mouse strain. However, Paranjpe et al reported a range for single adenoma of 0 - 24%/study (years 2004 – 2018) and an average of 8.98%. This indicates that lung adenoma incidences reported here are in the upper range of published background findings and higher than the average reported by Paranjpe et al. In addition, historical background findings of control mice of the test facility were presented. The incidence for bronchiolo-alveolar adenoma in male mice was above the historical control range of the test facility (24% vs 16% upper range, respectively), while bronchiolo-alveolar carcinoma was within historical control ranges (4% vs 12.5% upper range, respectively). It is discussed by the applicant that bronchiolo-alveolar adenomas and carcinomas occurred without multiplicity as single tumours and without evidence of a continuum of progression from bronchiolo-alveolar hyperplasia to adenoma to carcinoma. Despite this it cannot completely be ruled out that lung tumour findings in male mice are maralixibat-related. In addition, a potential risk of carcinogenic transformation of the GI mucosal epithelial alterations (e.g. crowding/proliferation of crypt cells) observed in rat repeat-dose toxicity studies should be excluded histologically when 2-year rat carcinogenicity data are available. Thus, a definite conclusion of carcinogenic potential of maralixibat will need be drawn after review of data from the ongoing rat carcinogenicity study, which will be provided by October 2023 as outlined in the RMP.

2.5.4.5. Reproductive and developmental toxicity

A full range of reproductive and juvenile toxicity studies were submitted.

Possible drug related effects on male and female fertility / reproductive capacity, prenatal, postnatal, and juvenile development were investigated in rats, while rabbits served as second species for evaluation of adverse effects on embryofetal development.

Many of the pivotal studies were preceded by DRF studies. All pivotal studies were conducted in accordance with current guidelines and GLP regulations. Regarding the juvenile toxicity studies, the treatment period covers a human age range from birth to adolescence.

For the reproductive toxicity studies performed in rats, the sponsor selected dietary administration over gastric intubation (gavage) based on his experience with negative effects of aspiration of liquid formulations in studies conducted previously. However, it was shown later during drug development that gavage administration was principally possible even in juvenile rats. Unfortunately, no measure was taken to prevent access of offspring to the maternal diet in the PPND study, where adverse effects on pups' body weights were considered due to consuming the maternal diet at the time when the offspring start to eat on their own.

Toxicokinetic evaluations were done in almost all studies. The obtained values were qui variable and contamination of control samples were observed in the PPND and juvenile toxicity studies. According to the applicant, an extensive investigation was conducted, and the most likely explanation is that contamination occurred to the blood samples after collection from the animals. The applied LC-MS/MS method is very sensitive (subnanomolar) and even detects very small levels of contamination e.g. through airborne aerosols. This is agreed.

Toxic effects in adult rats generally resembled those observed in the repeated dose toxicity studies conducted in this species. While male fertility was not affected at all up to the highest dose tested (750 mg/kg/d), in female rats, doses of 500 mg/kg/d and above reduced ovulation rate resulting in a decreased number of corpora lutea and implantation sites, respectively.

Embryofetal development was not affected in either rats or rabbits, despite maternal toxicity (body weight loss) in the latter species. In addition, there were no adverse effects on prenatal and postnatal development including sexual maturation and reproductive capacity as well as learning and memory abilities noted in the offspring of dams exposed to maralixibat during gestation and lactation.
While treatment of juvenile rats following weaning did not adversely affect their viability, mortality / moribundity was noted in all treatment groups in juvenile rats treated from PND 7 to 21. In the DRF study doses ≥ 500 mg/kg/day were associated with drug-related mortality in 4 females. In the pivotal study doses up to 250 mg/kg/day induced no article-related mortality. In this study mortality was considered due to septicemia in 3 rats and gavage error in another one in the HD group, whereas the cause of deaths could not be identified for 5 rats each in the LD and MD group, respectively.

In contrast to other nonclinical studies with maralixibat, relatively large systemic exposures were seen in juvenile rats treated from PND 7 to PND 21. Plasma AUCs did not significantly increase with increases in dose, indicating saturation of absorption at the lowest dose; thus, estimated oral bioavailability was also highest (approximately 17%) at the lowest dose on the first day of dosing. Estimated bioavailability by the end of the study on PND 21 was similar to that seen in adult animals, likely due to rapid maturation of the GI tract in rats between PNDs 7 and 21. Despite these high plasma exposures, maralixibat did not induce major signs of toxicity at doses up to 250 mg/kg/d in both sexes.
According to the applicant, the clinical significance of increased bioavailability on PND 7 rats is likely low. Rat pups at PND 7 are generally representative of a preterm infant in terms of whole animal development, while 10-day-old rats correspond to human term neonates and 21-day-old rats to an infant / toddler aged 2 years. Regarding the GI tract, the newborn rat possesses a very immature system with barely differentiated tissues presenting only a minimal barrier to macromolecules (reviewed in Walthall et al. 2005). This is in contrast to a human full-term newborn who possesses a much more mature GI tract that becomes impermeable to macromolecules within days after birth in response to oral feeding (reviewed in Neal-Kluever et al. 2019).

Given the relative maturity of the human GI tract already at birth and the fact that maralixibat is indicated for treatment of children aged 2 months and older, no major risk for the paediatric population is anticipated.

2.5.4.6. Local tolerance

Local tolerance was investigated in guinea pig on dermal sensitisation potential after intradermal and topical administration and in rabbits on dermal and eye irritation. Potential local effects on colonic or rectal mucosa were investigated in female rats. The relevance of the studies in guinea pig on dermal sensitisation potential after intradermal and topical administration and in rabbits on dermal and eye irritation appears to be questionable. However, based on these studies a sensitisation potential of

maralixibat appears to be unlikely. In the eye, maralixibat showed a moderate to mild irritating potential. Potential local effects on colonic or rectal mucosa as found in the main toxicity studies were investigated in female rats further. In these studies, a mucus depletion of colonic goblet cells, oedema of the colonic lamina propria was confirmed. However, this finding was associated with the fasting conditions of the animals. It can be assumed, that these effects were caused by a local irritation caused by an increased bile salt concentration in the faeces. The human relevance appears to be low.

2.5.5. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): maralixibat chloride			
CAS-number (if available): 228113-66-4			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (based on prevalence)	0.0004	µg/L	> 0.01 threshold (N)

The applicant did not provide the full study report for the determination of the n-octanol/water distribution coefficient. Instead, the applicant refers to a summary of the log Kow study. In this case the provided summary report can be accepted as relevant data/information are included. As logD of 1.53 is clearly below the action limit of 4.5 a screening for persistence, bioaccumulation and toxicity is deemed not required.

Maralixibat PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

2.5.6. Discussion on non-clinical aspects

Maralixibat is considered a potent inhibitor of the human ASBT. *In vitro* proof of concept is considered established using cells transfected with the human ASBT.

The ASBT transporter protein is highly conserved across species, with the human and mouse proteins showing 81% identity and 89% similarity at the amino acid level and with human versus monkey (99% similar), dog (93% similar) and rat (89% similar) proteins even more highly conserved and the documented *in vivo* effects of maralixibat across species, including mouse, rat, dog, and monkey, indicate the potency and mechanism of action across the nonclinical species.

The applicant submitted a study report on an *in vitro* hERG channel assay claimed to be GLP compliant. Due to several mishaps occurring during the conduct of the study the data obtained are considered limited. Maralixibat did not inhibit the hERG channel at a nominal concentration of 1 µM statistically significantly different from vehicle control values. A subsequently performed extension of an analytical validation study supports the view that the patch-clamp measurements obtained at the nominal concentration of 1 µM may be considered true.

Cardiovascular safety studies in conscious and in anesthetised dogs, with oral and IV administration, respectively, CNS safety studies in rats with oral and IV administration, respectively, and respiratory safety studies in guinea pigs with IV administration did not reveal concerns regarding cardiovascular, CNS or respiratory safety of maralixibat.

Pharmacokinetics of maralixibat was investigated in numerous studies in mice, adult and juvenile rats, pregnant and non-pregnant rats, pregnant rabbits, guinea pigs, dogs and monkeys. Studies on absorption, distribution, metabolism and excretion were provided. Maralixibat has to be characterised as a substance of very low bioavailability, with a local mode of action. Overall, the study programme appears to be appropriate and complete, justifying from pharmacokinetic point of view the species involved in toxicity testing.

A very comprehensive general toxicity programme was conducted in mice, rats, dogs and monkeys with maralixibat administration by oral gavage, dietary admix and capsules. Generally, bioavailability was low after oral administration (<1%) and the majority of findings in the toxicity studies were therefore related to the pharmacological effect of maralixibat rather than the systemic toxicity. Findings from iv administration in single-dose studies are therefore not likely to be clinically relevant.

Single dose toxicity studies in rats and dogs with oral and with IV administration did not raise safety concerns regarding the intended use in humans.

Repeat-dose toxicity studies were performed in mice, rats, dogs and monkeys. Duration of maralixibat treatments in the GLP-compliant pivotal chronic repeated dose toxicity studies in rats and dogs comply with the requirements for the intended chronic use in humans. Maralixibat is not genotoxic. A 2-year carcinogenicity in rats is ongoing. The provided study design is considered adequate. Results of the ongoing carcinogenicity will be provided by October 2023 as defined in the RMP. In the 26-week carcinogenicity study in transgenic mice reported lung adenoma incidences are in the upper range of published background incidence and higher than the average reported by Paranjpe et al. In addition, the incidence for bronchiolo-alveolar adenoma in male mice was above the historical control range of the test facility (24% vs 16% upper range, respectively), while bronchiolo-alveolar carcinoma was within historical control ranges (4% vs 12.5% upper range, respectively). Whilst it is not expected that lung tumour findings in male mice are maralixibat-related it cannot completely ruled out. A final conclusion of carcinogenic potential of maralixibat in rodents, which is outlined as missing information in the RMP, can only be drawn after review of data from the ongoing rat carcinogenicity study (category 3 study in the RMP).

In line with the proposed indication "Treatment of cholestatic liver disease in patients with Alagille syndrome (ALGS) 2 months of age and older", a full range of reproductive and juvenile toxicity studies were submitted, which do not raise any concerns.

Maralixibat $PEC_{surfacewater}$ value is below the action limit of 0.01 μg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5.

2.5.7. Conclusion on the non-clinical aspects

This marketing authorisation is approvable from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Number	Study Title
PK, ADME, and PD in Healthy Participants	
NB4-02-06-002	A Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Ascending Single Oral Doses of SD-5613 in Healthy, Adult Subjects
NB4-02-06-003	A Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Ascending Multiple Oral Doses of SD-5613 in Healthy Adult Subjects
NB4-02-06-004	A Pharmacokinetic Study of Single Oral Doses of [^{14}C]SD-5613 in Healthy Male Subjects
MRX-102	A Phase 1 Single-Blind, Randomized Study to Assess the Single Dose Pharmacokinetics of a To-Be-Marketed Liquid Formulation of Maralixibat at Different Dose Levels and Fasting Conditions
Studies in Paediatric Participants with Cholestatic Disease	
LUM001-301	ITCH: The Evaluation of the Intestinal Bile Acid Transport (IBAT) Inhibitor LUM001 in the Reduction of Pruritus in Alagille Syndrome, a Cholestatic Liver Disease
LUM001-302	IMAGO: Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Paediatric Patients with Alagille Syndrome
LUM001-303	IMAGINE: Multicenter Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects with Alagille Syndrome
LUM001-304	ICONIC Study: Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome
LUM001-305	IMAGINE II: Multicenter Extension Study to Evaluate the Long-term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects with Alagille Syndrome
LUM001-501	INDIGO STUDY: Open Label Study of the Efficacy and Long Term Safety of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis
Studies in Other Populations	
SHP625-101	A Randomized, Blinded, Placebo-controlled, Phase 1 Study to Assess the Relative Potency of Multiple Oral Doses of LUM001 and SHP626 in Overweight and Obese

Study Number	Study Title
	Adult Subjects as Assessed by Fecal Bile Acid Excretion
NB4-02-06-014	Clinical Study Report for a Randomized, Double-Blind. Placebo-Controlled, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Ascending Multiple, Oral Doses of SD-5613 in Adolescent Subjects with Hypercholesterolemia
LUM001-401	CAMEO Study: A Pilot, Open-label Study to Evaluate the Safety, Tolerability and Efficacy of LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Primary Sclerosing Cholangitis
Clinical Drug-Drug PK Interaction Studies	
NB4-02-06-008	A Randomized, Double-Blind Study Comparing SD-5613/Statin Combination Therapy and Statin Monotherapy in Healthy, Adult Subjects
NB4-01-06-019	Assessment of Pharmacokinetic Drug-Drug Interaction Between SD-5613, Simvastatin and Lovastatin After Oral Administration of Multiple Concomitant Doses in Healthy Volunteers
NB4-02-06-020	Assessment of Pharmacokinetic Drug-Drug Interaction Between Multiple Concomitant Doses of SD-5613 and Atorvastatin Administered Once Daily in the Morning Versus Once Daily in the Evening in Healthy Volunteers
LUM001-201	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Combination with Ursodeoxycholic Acid (UDCA) in Patients with Primary Biliary Cirrhosis

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics

List of in-silico studies on pharmacology of maralixibat.

Study Number	Study Title
MRX-NC-007	Development and Verification of a PBPK Model for Maralixibat Oral Dosing and Its Application to Predict the Drug-Drug Interaction Potential for Competitive and Time-Dependent Inhibition of CYP3A4 Enzyme in Adult Healthy Human Volunteers
MRX-NC-011	Exploratory Dose-Response Analysis of Maralixibat and Serum Bile Acid

With the Day 120 response document an interim report of the ongoing study in children below 1 year of age (MRX-801) was submitted.

Note: The doses described in section 3.3 are of maralixibat chloride but are presented as "maralixibat". For example, doses of 140, 280, and 560 µg/kg maralixibat chloride are equivalent to 133, 266, and 532 µg/kg maralixibat free base, respectively, but will be referred to as 140, 280, and 560 µg/kg maralixibat in line with the original documentation submitted.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Methods

Plasma concentrations of maralixibat were determined by validated LC-MS/MS methods. Serum levels of conjugated and unconjugated bile acids were also determined using validated LC-MS/MS methods as well as concentrations of the endogenous biomarker, 7α-hydroxy-cholest-4-en-3-one (C4). The method validations and documentation for sample analysis is accepted and missing information has been provided upon request.

Additional validation results for a couple of biomarkers have been presented, of which the one for bile acids is considered the most important, because this has been used both as PD, as well as efficacy parameter. Satisfactory documentation of linearity of this method has been submitted upon request

Absorption

The applicant has conducted 4 PK studies in order to determine the PK of the compound in healthy adult subjects

- Study MN4-02-06-002 which has investigated the safety and PK of single doses
- Study NB402-06-003, which has investigated multiple (ascending doses)
- Study NB-02-06-004 which was an ADME study with radioactively marked compound given as single dose
- Study MRX-102 which was a single to study with the to-be-marketed liquid formulation.

Despite a sensitive method used for the detection of the compound (LloQ=0.025 ng/ml) hardly any substance could be found in plasma or could derived PK parameters be calculated in appropriate manner. In consequence, it is concluded that the substance is very poorly absorbed, and maximum plasma levels are reached between 1.0 to 3.0 hours. The estimated half-life of the compound in plasma has been determined to be about 4 hours, but this had to be based on the evaluation of high doses (above the therapeutic dose-range proposed for children with PFIC2). The study with the to-be-marketed formulation did not provide different results.

The following table shows "typical" results from these early studies, demonstrating the negligible absorption:

Table 5 Summary of Pharmacokinetic Parameters of Plasma Maralixibat (Single Ascending Doses) (Study NB4-02-06-002)

Dose (mg)	n	Mean (SD) PK Parameters[1]					
		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	AUC_{0-96} (ng•h/mL)	AUC_{0-inf} (ng•h/mL)	T_{max} (h)	$t_{1/2}$ (h)
1	6	0.000	0.000	0.000	NA	NA	NA
2.5	6	0.000	0.000	0.000	NA	NA	NA
5	6	0.000	0.000	0.000	NA	NA	NA
10	6	0.000	0.000	0.000	NA	NA	NA
10F[2]	6	0.454 (0.1594)	0.946 (0.4307)	3.27 (4.2368)	NA	2.000 (1.500, 4.000)	NA
20	6	0.081 (0.1972)	0.161 (0.3944)	0.161 (0.3944)	NA	6.000 (6.000, 6.000)[5]	NA
50	6	0.310 (0.4133)	0.600 (0.8516)	0.600 (0.8516)	NA	2.000 (1.500, 4.000)[6]	NA
100	6	0.727 (0.3854)	1.668 (0.6418)	1.668 (0.6418)	NA	2.500 (1.000, 4.000)	NA
300	6	2.078 (0.3296)	7.51 (1.9811)	7.510 (1.9811)	7.798 (3.6340)[3]	3.000 (1.500, 3.000)	2.023 (0.4701)[3]
500	6	2.401 (0.3441)	14.191 (7.5991)	14.812 (9.0517)	16.827 (11.7902)[4]	2.500 (2.000, 4.000)	3.791 (3.3742)[4]

In accordance with this, the ADME study did not detect measurable radioactivity in plasma, and more than 99% of the detected radioactivity was detected in faeces, primarily as parent compound (>94%), which three different metabolites having a share of 1%-5%. The radioactivity detected in urine amounted to 0.066%. Although the overall recovery in this study was only about 73%, the results were considered valid, due to the fact that they were in accordance with the previous studies in healthy volunteers showing minimal plasma levels.

Bioavailability/Bioequivalence

Data on absolute bioavailability are, however, not available because no i.v. administration was included in any of the studies. The estimated bioavailability is expected to be less than 1%. The applicant has therefore also not evaluated bioequivalence of the different formulations, which is also based on the fact that the solid dosage forms used were rapidly dissolving pharmaceutical forms, which is altogether considered acceptable.

Influence of food

The applicant has evaluated the influence of food in two studies (Study MRX-102 and Study NB4-02-06-002) with different dose levels (10, 20, and 45 mg). These studies were partially hampered by the low plasma levels detected. Based on the available results, however, it could be concluded that food further reduces the overall low bioavailability of the compound to a relevant extent (60-80%).

The results for the statistical evaluation of study MRX-201 are shown in the following table:

Table 6 Statistical Analysis of Food Effect (Study MRX-102)

Cohort	PK Parameter	N	Geometric LSM (Fed)	Geometric LSM (Fasted)	Fed/Fasted Ratio (%)	90% CI for Geometric LS Mean Fed/Fasted Ratio
Maralixibat 30 mg	AUClast (ng•h/mL)	8	0.51	3.60	14.2	5.80, 34.69
	Cmax (ng/mL)	8	0.45	1.69	26.8	20.22, 35.56
Maralixibat 45 mg	AUClast (ng•h/mL)	9	1.39	4.53	30.7	18.16, 51.92
	Cmax (ng/mL)	9	0.57	1.62	35.2	27.80, 44.64

Abbreviations: AUC = area under concentration-time curve; AUC_{∞} = AUC from time 0 to extrapolated infinity; AUC_{last} = AUC from time 0 to last measurable concentration; CI = confidence interval; C_{max} = maximum observed concentration; LSM = least squares means; N = number of subjects; PK = pharmacokinetics;
Source: MRX-102, Table 14.2.1.3

While in a compound with systemic action, this would lead to the recommendation to administer the compound in the fasted state, the proposed recommendation initially was to administer the compound half an hour before food intake. This is obviously based on theoretical reflections based on PK as well as PD considerations: The highest concentrations would need to be present in the intestine (lower part of the small intestine. Any absorption would be regarded to be untoward with regard to the PD effects, as well as with regard to safety of the compound. While optimality of the proposed 30 minutes window has not been investigated, it takes not only the food effect into account, but also the consideration that inhibition of bile-acid (re-)absorption would be inhibited highest at the time of highest bile acid secretion, which itself depends on the intake of food. Indeed, study NB4-02-06-002 has shown that bile acid absorption inhibition is abolished with prolonged fasting. Therefore, the final recommendation with regard to medication intake in relation to food intake has been determined to allow flexibility either before (up to 30 minutes), or together with food – which includes the mode of intake within clinical trials.

Distribution

The compound, once absorbed, is expected to be highly bound to plasma proteins (>90% *in vitro*) based on the results of the *in vitro* study M3099225. Plasma protein binding was within 84.2% to 97.3% for all species tested and was found to be concentration independent across the concentration range. Protein binding, as well as the distribution of the compound have not been investigated *in vivo*. While distribution could be determined in some of the studies, due to the low plasma concentrations, the estimates are likely to be inaccurate and the missing of such an estimate is acceptable.

Elimination

As seen in the ADME study, the compound is mainly eliminated in the faeces, and hepatic uptake, metabolism and/or renal excretion are not expected to play a relevant role in PK. Approximately 72% of the radioactive dose was detected in faeces compared to <1% in urine.

In 10 healthy fasted subjects (study MRX-102) receiving single doses of 100 mg maralixibat, the estimated terminal half-life (t1/2) was 1,97 h. The estimated clearance of 7700 L/h is unreliable with the extrapolation portion of AUC_{∞} >20% for the majority of participants.

In patients, no elimination parameters could be calculated.

In consequence of the low plasma levels, the applicant has investigated the potential for hepatic metabolism *in vitro* only. The metabolic profile of the compound has been determined *in vitro* with study M4099002, and it was shown that metabolisation appears to be extensive (almost 70% with 60 minutes incubation). More than 10 metabolites were identified (of which none was unique to humans)

However, in face of the minimal absorption, as well as less than 3% of radioactivity detected as metabolites (most of these in faeces), the relevance of the findings appears to be minor.

Although extensive metabolism of the compound was detected and 6 metabolites have been characterised, no further investigation was performed due to the expected small contribution of metabolites to the overall limited total exposure. This is considered acceptable.

Dose proportionality and time dependencies

Dose-proportionality as a method of PK characterisation was also hampered by the fact that the compound is poorly absorbed only. There was indication of increasing concentration/exposure with doses higher than 20 mg, but a clear linear relation could not be demonstrated. No relevant differences were detected between single and multiple doses of the compound, although a formal evaluation of time-dependency was not conducted (but considered acceptable).

Intra- and inter-individual variability

As expected, no numerical determination of the variability of PK parameters was presented, which is, however, also considered acceptable. A high variability of PK parameters is obvious from the data. In the 100 mg dosing group of the food effect study MRX-102, the coefficient of variation for AUC0-inf and Cmax is 73% and 52%, respectively.

Special populations

The applicant has investigated PK in different diseased populations (adults with cholestatic liver diseases, such as PBC and PSC), adolescents with hypercholesterolaemia, and children with Alagille and PFIC. All these investigations were done with sparse sampling, both after single and multiple drug administration, with the time point mainly after 4 hours post drug intake. The doses used in these studies were variable, but usually (based on body weight) lower than those proposed for the ALGS target population. In all these studies, drug concentrations were below LoQ in the majority of patients, and hardly any concentrations were detected being above 1.0 ng/ml. This also clearly applies to the studies in the target population where doses more similar to the proposed doses for marketing were tested (including the ongoing MRX-801 study in children younger than 1 year of age, who are being treated with the proposed dosing regimen; Note: only interim PK results available from this study). Nevertheless, this study confirmed that there is literally no difference in PK between infants and older children with ALGS. A more permeable intestinal barrier may occur in situations where the gastrointestinal system is acute or chronically disturbed (e.g. in inflammatory bowel diseases, or leaky gut syndrome) and could lead to higher exposure of maralixibat. However, much higher systemic exposure has been achieved with MRX in previous human (adults) and non-clinical studies without critical safety findings. These data suggest that even if higher exposure levels are reached in infants, these are likely not to represent a hazard. Furthermore, such patients, and especially those under the age of 1 year, will be closely monitored for safety in the post-authorisation phase (LEAP study) which is a special obligation to this Marketing Authorisation.

The applicant has evaluated the PK in special populations upon request. For hepatically impaired patients, the applicant has made the case that a high percentage of the patients included in the clinical studies had liver impairment according to the NCI-ODWG criteria. However, it is currently not known whether this classification is appropriate in cholestatic liver disease, and Alagille' Syndrome. Due to the missing of data for patients with advanced liver disease (cirrhosis) and signs of decompensation, a respective warning has been included into the PI (SmPC section 4.2).

The missing of such data for renal impairment was considered acceptable based on the minimal plasma concentrations and on animal data.

The applicant has retrospectively evaluated whether demographic factors such as age, gender and race would influence the PK of the compound. While variability with these factors is partially rather high, the plasma levels appear to be grossly independent from the influence of age, sex and race.

Pharmacokinetic interaction studies

The applicant has determined the interaction potential of the compound mainly with *in vitro* investigations, using *in vitro* assays for cytochrome induction, and inhibition, as well as transporter inhibitions. These investigations identified CYP3A4/5 and the transporter OATP2B1 as the only "candidates" for a relevant inhibition by the compound. This is not only based on the (relative to the other CYPs and transporters) lower inhibitory concentrations, but also to the fact that both are also located in the intestinal mucosa, and could cause a PK inhibition at the local, pre-systemic level.

The applicant is presenting 4 *in vivo* studies in order to address the potential for drug-drug interaction. Three of these studies (NB4-02-06-008, NB4-01-06-019, and NB4-02-06-020) were studies with the statins lovastatin, simvastatin, and atorvastatin. These compounds were thought to be substrates of several organic anion transporters, including OATP2B1. At least two of the compounds are also highly dependent on CYP3A4 metabolism (simvastatin and atorvastatin). The results of the study with Atorvastatin are displayed in the following table:

Table 7 Results of a Statistical Comparison of Atorvastatin, ortho-Hydroxyatorvastatin and para-Hydroxyatorvastatin Pharmacokinetic Parameters Following Morning (AM) Administration of Atorvastatin Alone or in Combination with SD-5613

Analyte	Parameter	Least Squares Means [a]				Comparison: Test/Reference [b]		
		Test [c]		Reference [c]				
		N	Mean	N	Mean	Ratio	90% CI	P-value
Atorvastatin	AUC_{0-24} (hr*ng/mL)	19	42.36	23	51.27	0.83	0.77, 0.89	<0.001
	C_{max} (ng/mL)	19	8.44	23	8.88	0.95	0.81, 1.12	0.600
o-hydroxyatorvastatin	AUC_{0-24} (hr*ng/mL)	19	43.17	23	48.25	0.90	0.81, 0.99	0.081
	C_{max} (ng/mL)	19	4.03	23	4.56	0.88	0.73, 1.07	0.271
p-hydroxyatorvastatin	AUC_{0-24} (hr*ng/mL)	13	5.89	17	6.60	0.89	0.69, 1.16	0.449
	C_{max} (ng/mL)	13	0.45	17	0.51	0.88	0.76, 1.02	0.159

Results of ANOVA of natural log transformed pharmacokinetic parameters, using a model accounting for subject and treatment effects.
[a] Least squares means are back transformed to original scale.
[b] Ratio of least squares means and 90% confidence interval for comparison of Test to Reference treatment, and the p-value for treatment effect from the ANOVA model.
[c] Test: SD-5613 5 mg once daily (AM) + Atorvastatin 20 mg once daily (AM); Reference: Atorvastatin 20 mg once daily (AM).
Source: Tables T8.1 to T8.3.

These studies did not detect a potential for a clinically relevant drug-drug interaction. However, all these studies were hampered by the fact that only rather small doses of maralixibat were used. The applicant has provided argumentation with regard to the different IC50s of the compound in relation to inhibition of OATP2B1 and ASBT, however, this did not take into account the concentrations of the active compound expected in the (respective parts of) intestine. Since no adequate data are available, a respective warning has been included in the PI that there is a theoretical risk of interaction with substrates of OATP1B2.

The DDI potential for competitive and mechanism based inhibition of CYP3A4 was further investigated using a PBPK model in SimCyp. The developed PBPK-Model indicates that CYP3A4 inhibition potential is likely low due to low systemic exposure. Modeled population mean increase in AUC and Cmax after the highest dose of 600 mg/kg BID was 10%, calculated with the predicted fuGut of 0.096. In a worst-case scenario calculated for a fuGut of 1, the increase was estimated to be 31%. Sensitivity analysis showed

an increase of Midazolam exposure up to 40%, which might be clinically relevant for DDI regarding CYP3A4 but is regarded as unlikely (Ki was varied 100-fold).

Model development was impaired by the low number of individuals (six subjects) contributing to model verification. Additionally, model development was based on data collected in healthy adults; transferability to a paediatric population with Alagille syndrome is regarded as limited. It is understood that the small number of subjects, large variability and many measurements near the LOQ prevented further model refinement. Goodness-of-fit-plots are missing but not requested because the platform was not qualified for prediction of CYP3A4 interactions. Due to the above mentioned issues, the meaningfulness of the PBPK analyses is considered limited. Therefore, the potential impact of CYP3A4 is also reflected in the PI (SmPC section 4.5).

A further study was presented, not primarily designed as interaction study, which also evaluated the potential for interaction with ursodeoxycholic acid, which is the standard therapy in patients with PBC, in which population this study was conducted as a phase 2 study. With regard to the influence of maralixibat on UDCA kinetics, only inconclusive results were obtained. This study is characterised rather as a PD interaction study (maralixibat potentially preventing absorption of UDCA), rather than a PK interaction study (see below).

In conclusion, while the potential for PK interactions appears also expected to be low based on the low plasma concentrations, a fully conclusive elucidation of the interaction potential on the local level of intestine has not been presented. This is addressed in the product information.

2.6.2.2. Pharmacodynamics

Mechanism of action

Maralixibat (formerly known as SD-5613, SHP625, and LUM001; hereafter referred to as maralixibat) is an inhibitor of the apical sodium–bile acid transporter (ASBT.) This transmembrane protein transporter, localised on the luminal surface of ileal enterocytes, is present in the terminal 25% of the small intestine and mediates uptake of conjugated bile acids across the brush border membrane of the enterocyte. Maralixibat is a potent ASBT inhibitor (IC50 = 0.3 nM) as demonstrated in cell-based assays.

Maralixibat is minimally absorbed due to its large molecular weight (710 Da) and the presence of a positively charged quaternary nitrogen atom, therefore maximizing the local exposure of the molecule to its target and minimizing unnecessary systemic exposure. Maralixibat-mediated blockade of intestinal reabsorption of bile acids by ASBT interrupts the enterohepatic circulation, thereby increasing fBA excretion and lowering sBA levels (see the following figure).

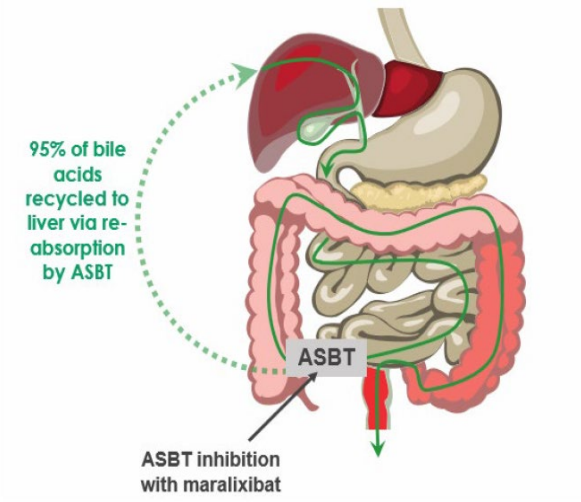


Figure 3 Interruption of Enterohepatic Circulation of Bile Acids by Maralixibat

As obvious, the primary mode of action is by blocking the (re-)absorption of bile acids. The intent is clearly that by blocking the reabsorption, the substance would lead to a decrease of pathologically increased endogenous bile acids in the serum. The use in disorders with a high serum level of bile acids is therefore obvious.

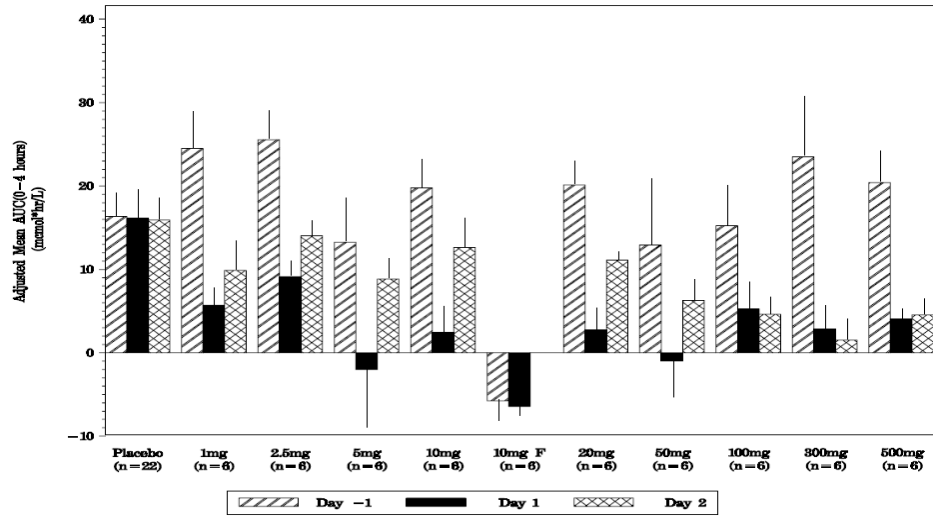
Primary and Secondary pharmacology

Pharmacodynamics in Healthy Adult Participants

Pharmacodynamic effects in humans were already tested in non-diseased subjects in the early studies NB4-02-06-002, NB-02-06-003, and also in Study SHP625-101, which was conducted in obese, but otherwise healthy subjects.

In healthy subjects, a decrease of serum bile acids was seen, which appeared to be dose-dependent with modest correlation and consistent only at doses higher than 2.5-5 mg. The missing clear correlation to the doses administered could potentially be explained by the high influence of food intake as well as the counteracting mechanisms of increase of bile acid synthesis as measured e.g. be biomarkers, such as Serum 7αC4 which was consistently increased. An increase of faecal bile acid excretion was also detected in a clearer dose-dependent manner, and was detected at all doses administered across studies, and without relevant differences between single and multiple administrations, however with high variability between subjects. In addition, a consistent increase in faecal weight was seen, with small increases and a tendency for increased number of bowel movements and liquid stool consistency. In healthy subjects, changes in serum lipid parameters were rather modest, but detectable (e.g. LDL decrease). The studies do provide a clear proof of the concept of reducing serum bile acids by inhibiting the reabsorption within the endogenous bile acid recycling.

In study NB4-02-06-002, a total of 82 subjects received single oral doses of maralixibat ranging from 1 mg to 500 mg or placebo. Profiles of sBA and fBA prior to and following dosing with maralixibat or placebo served as pharmacodynamic markers. The changes of bile acids serum concentrations are shown in the following figure.



Error bars are 1 standard error

Note: One standard error is displayed on the chart.
Note: Baseline adjusted AUC is Area Under the Curve above (that day's) Baseline.
Note: 10 mg F is the fasting 10 mg group.
Note: On Day 1 at Hour 2, subject 802 (10 mg F group), had a sample identified as 'Below Detectable Limit.' For calculation of serum bile acid AUCs, this value was set to 0.00.
Note: As per protocol, no serum total bile acid samples were collected for the fasting 10 mg panel on Day 2.

Figure 4 Baseline Adjusted Serum Total Bile Acids Concentration: Mean AUC (0-4 hours; µmol*hr/L) by Treatment Group and Day (Study NB4-02-06-002)

In study NB4-02-06-003, a total of 167 subjects were treated for 28 days receiving multiple doses of maralixibat ranging from 0.5 mg to 100 mg, or placebo. Profiles of sBA and fBA following dosing with maralixibat or placebo served as pharmacodynamic markers. sBA levels were assessed on Days 1 and 14, and similar to the single ascending dose data, suppression of basal sBA as well as postprandial increases was observed on Day 1. Suppression of sBA increased with increasing doses. In contrast, on Day 14, the effects of higher doses appeared to be attenuated (pooled 10 to 100 mg doses showed greater suppression on Day 1 vs. pooled 1 to 5 mg doses but this was not apparent on Day 14).

Table 8 Summary of Daily Total Faecal Bile Acids Excretion (Multiple Ascending Doses of Maralixibat) (Study NB4-02-06-003)

Dose (mg) or Placebo	N	Mean (SD) Daily Total Fecal Bile Acids Excretion (µmol)	
		Days 9 to 14	Days 23 to 28
Placebo	16	154.58 (161.50)	163.39 (182.13)
0.5	16	266.84 (209.91)	294.94 (173.02)
1.0	8	642.70 (439.36)	780.29 (670.54)
2.5 (qAM)	8	477.95 (403.09)	590.71 (281.49)
5 (qAM)	8	1105.08 (863.17)	848.37 (683.95)
5 (qPM)	16	514.33 (340.23)	593.25 (437.66)
10	8	1236.96 (685.04)	1126.04 (434.47)
20 (qAM)	8	1140.28 (540.62)	1030.58 (370.71)
20 (qAM)	8	665.54 (468.30)	699.77 (511.10)
60	8	973.39 (759.29)	964.54 (683.51)
100	8	2405.71 (843.08)	1718.27 (889.20)

Abbreviations: N = number of subjects; SD = standard deviation; qAM = every morning; qPM = every evening.

Note: The total excretion over the 6-day period is divided by 6 for each subject prior to the calculation of summary statistics.

Note: Subjects who did not produce a sample within a 24-hour collection period have an assigned excretion value of zero and are included in the data.

In study SHP625-101, the pharmacodynamics of maralixibat was assessed in overweight and obese participants (body weight > 63.5 kg and mean body weight 91 kg). Maralixibat at doses of 10 mg once

daily, 20 mg once daily, 50 mg once daily, 100 mg once daily or 50 mg twice daily, or matching placebo, was administered for 7 consecutive days. The primary endpoint was fBA; sBA was included as a secondary endpoint. Mean fBA change from baseline increased in all participants who received maralixibat and increased with increasing total daily dose. The greatest mean change from baseline in total sBA concentration at Day 7 was an increase of 2.571 (2.3099) ng/mL observed in subjects who received placebo. In contrast, no significant change in mean sBA from baseline was demonstrated in this population.

Pharmacodynamics in Paediatric Participants with Cholestatic Disease

PD properties were further evaluated in studies with different disease as the target population, with study NB4-02-06-014 conducted in adolescents with hypercholesterolaemia, study LUM001-401 in patients with PSC, study LUM001-201 in adult patients with PBC, and in various studies in children suffering from Alagille Syndrome (LUM001-301 to LUM001-305).

For patient populations with "modest" cholestasis only, such as patients suffering from PBC or PSC, rather modest decreases of serum bile acids were detected, but in both populations effects were also seen with regard to a reduction of pruritic symptoms, and increase in 7-alpha-C4, as well as for a reduction of LDL-cholesterol. Because these studies were also designed as phase 2 studies, the disease-specific parameters (biomarkers) such as bilirubin and ALP (as well as transaminases) were also investigated, but no relevant effects on these could be detected.

In study NB4-02-06-014 serum bile acids were also partly reduced in adolescent patients with hypercholesterolaemia, although some inconsistencies were found, obviously due to the low doses administered (highest dose 5 mg). There was a clear tendency for lowering of LDL-C, except in the lowest dose group (0.1 mg)

Further studies have been conducted with the compound in patients with hypercholesterolemia, evaluating mainly the effects on lipid parameters. In one of these studies (Study NB4-01-02-035-ASR) pharmacodynamic effects of the compound with regard to bile acid reduction and serum lipids in different diet regimens has been investigated. It could be shown that PD activity increases with increasing caloric content, as well as with increasing fat content, both for (most of) the serum lipids, as well as for serum bile acids. Further studies in this patient population (BATAHC-0524-037 and 038) have investigated whether a "sustained release" mimicking intake of small doses distributed over the day would (in order to assure a more constant blocking of the bile acid transporter) be able to deliver higher changes in serum bile acids and lipid parameters. This was obviously not the case in these studies, which can be considered relevant for the proposed once daily dosing also proposed for the ALGS population.

Finally, in this population, a full factorial design study was conducted in order to see whether combination treatment with statins would make sense. In this study, while modest effects with monotherapy with maralixibat on LDL-C were detected, there was no additional effect when given with atorvastatin.

One study (Study LUM001-501) was presented for the previously proposed indication PFIC2. In this study, the primary outcome parameter was serum bile acid concentrations over time, but this could not achieve statistical significance at the time-point of primary evaluation, also clinical relevance could be questioned. Relevant reductions of sBAs could be shown for this population in the long-term extension study, which, however appeared to be overall flawed with relevant number of patients not responding to treatment excluded in the long-term. Overall, the observed effects appeared to be somewhat smaller in magnitude as compared to what was documented in Alagille's population.

Pharmacodynamics in the target population:

The 5 studies presented in the target population (see also efficacy assessment), children with Alagille Syndrome (LUM001-301, LUM001-302, LUM001-303, LUM001-304, LUM001-305) were treated with maralixibat with various doses. The results of the trials showed a decrease of serum bile acid concentrations, but with some fluctuations between doses and over time. For the final assessment it is referred to the clinical efficacy evaluation.

Secondary pharmacology

The applicant has not conducted any dedicated studies on the potential for effects base on secondary pharmacology. The applicant, however, indicates that e.g. the QT prolongation potential has been evaluated and presents data from the food interaction study MRX-102 which has extensively recorded and analysed ECG data. Study MRX-102 appears to include sufficient data to exclude a potential for QT prolongation, when considered together with the available pre-clinical information, and the safety margins calculated.

PD interactions

The applicant has not conducted any PD interaction studies. However, the study as above with atorvastatin (NB4-00-02-006), as well as the study in patients with PBC (LUM001-201) could also be regarded to represent PD interaction studies.

For atorvastatin, no additional effects on plasma lipids were detected (as seen above, and obviously no indication for PD interaction exists).

For the study in PBC patients, the potential for PK interaction was evaluated, but did not yield conclusive results, potentially due to an incomplete evaluation of UDCA (sparse sampling only, no consideration of endogenous UDCA conjugated and unconjugated UDCA). In similar way, no conclusions appear to be possible when looked at the PD parameters ALP, bilirubin, and liver transaminases. Whether the potential for UDCA interaction has been sufficiently evaluated, however, appears to be questionable. UDCA interaction might be relevant for the target population, in as many patients with ALGS are concomitantly treated with UDCA. An appropriate reminder for this potential interaction has been implemented in the PI (SmPC section 4.5).

In conclusion, the PD properties of the compound have been sufficiently investigated, and overall adequately characterised. By inhibiting bile acid absorption, the compound increases the faecal excretion of bile acids, thereby inducing the potential for gastrointestinal effects (increase stool weight, increased stool frequency and diarrhoea). By blocking (re-)absorption of endogenous bile acids, the compound is able to reduce serum bile acids in healthy subjects, as well as in a variety of disease states, including the severe cholestatic childhood diseases such as ALGS and PFIC. The reduction of the endogenous bile acid pool induces an obvious increase in the production of bile acids, as measured by appropriate biomarkers in healthy volunteers as well as in patients. This mechanism, however, can be considered less relevant in patients with highly pathological serum bile acid levels where levels below (upper limit of) normal are not achieved. In addition, the compound induces a modest improvement in serum lipid parameters (e.g. decrease in LDL-C) which might be based on both the bile acid sequestrant effects, as well as the reactive increase of bile acid production. However, these effects appear not relevant for the target population of ALGS but is nevertheless considered reassuring.

2.6.3. Discussion on clinical pharmacology

The present MAA concerns maralixibat chloride (hereafter maralixibat), an oral inhibitor of the apical sodium-dependent bile acid transporter (ASBT) for the treatment of Alagille's Syndrome (ALGS), a rare

multi-system inherited disease, which includes cholestatic liver disease in children. Maralixibat is a selective ASBT inhibitor small molecule with limited systemic exposure and a molecular weight of 710 Da and harbouring a positively charged quaternary nitrogen atom. Maralixibat inhibits BA reabsorption, thereby increasing faecal bile acid (fBA) excretion and lowering serum bile acid (sBA) levels. The recommended dose is 380 µg/kg of maralixibat once daily with a starting dose of 190 µg/kg once daily to be administered for one week.

The investigations with regard to clinical pharmacology of the compound reflect two basic facts on the compound:

- Maralixibat is very poorly absorbed, and measurable plasma levels are only observed in a minority of subjects, both in healthy subjects, as well as in a variety of disease states.

- Maralixibat has a long history of development with multiple changes of sponsors, and multiple changes of the envisaged target populations. This is reflected in a variety of (diseased) populations included not only in the PK, but also in the PD investigations (with some of the studies presented as PD studies, originally intended as early (Phase 2) development studies.

These facts explain to a relevant part the scope and extent of the studies conducted.

Already early in the development, it was clear that the compound hardly develops measurable plasma concentrations. Therefore, the restricted investigation of the overall PK and the retrospectively addressed factors of the characterisation of PK, such as volume of distribution, the influence of demographic characteristics on PK are acceptable. PD properties with regard to interactions at the local level in the GI tract (with respect to enzymes and transporters playing a role in transmembrane transport or metabolisation) and interactions potentially affecting the target population (e.g. fat-soluble vitamins, UDCA) were not evaluated in full but could be addressed in adequate warning statements included in the PI.

While some dose-finding studies in the target population have been performed, the dosing schedule, including the proposed once daily dosing (regular dose), as well as the intake with or without or timely distance to food intake have not been systematically evaluated and/or deduced from data. The proposed weight-based dosing in children with ALGS 2 months of age and older is acceptable, as already tested in the clinical studies.

Overall, the low levels of plasma concentrations do indeed provide a high level of reassurance that the compound is largely devoid of systemic (off-target) actions which is supported by the results of all investigations conducted both in healthy volunteers, as well as in patients.

The applicant has thoroughly investigated the primary pharmacodynamic targets of IBAT inhibition, which extends from bile acid sequestration (increase in content of bile acids in the faeces) and a reduction of serum bile acids (which only become obvious at higher doses in healthy subjects) to the further consequences of this primary action: increase in faecal weight, stool frequency, and potentially diarrhoea at the local level, induction of bile-acid synthesis in healthy volunteers (as measured by the biomarker 7-alpha-C4), and a modest improvement of the serum lipid profile (LDL reduction, HDL increase, triglyceride decrease). The induction of bile acid synthesis could regularly be detected in patients with normal levels of serum bile acids by increases in 7-alpha-C4, and by a consequential decrease of FGF-19 and FGF-21. However, in patients with cholestatic disease, this has not always been observed, or has not been investigated in all studies conducted.

Although the potential for drug-drug interaction appears to be low, and systemic interactions seem to be very unlikely or have partly been investigated (and excluded), the applicant has not fully addressed the potential for local interactions in the gastrointestinal tract with substrates of OATP1B2 and CYP3A4, and UDCA, or with fat-soluble vitamins or other food components with bile-acid dependent absorption.

However, the interaction potential with vitamins/food components has been evaluated in the safety assessment. The issues has been addressed with including respective warnings in the PI (see above).

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology package consists of a large number of studies. Due to the low absorption of maralixibat, PK parameters were not calculable with the doses employed in paediatric patients. The basic PK and PD properties of the compound have been adequately characterised. The dossier is considered approvable from a clinical pharmacology perspective.

2.6.5. Clinical efficacy

To support the target indication 6 study reports in patients with ALGS of 1-23 years of age (5 from completed clinical studies and one from historical comparison) have been submitted. Key evidence on efficacy has been provided from the pivotal phase 2 Study LUM001-304. Additionally, with the responses to the Day 180 LoOI, interim data from study MRX-801 in infants of 2-12 months of age was submitted to support the extension of the indication to this age group.

In addition, an EAP for patients with ALGS was opened in September 2020 in selected European countries, the United States, Canada, and Australia and as of 18 February 2022, has enrolled over 50 additional participants treated with maralixibat. No data relevant for efficacy have been made available.

Efficacy assessments across the studies was mainly focused on treatment effects on the key PD parameter of maralixibat – sBA and the key symptom in ALGS – pruritus. Further, liver enzymes and bilirubin, xanthomas, growth, and quality of life were evaluated.

In total efficacy database is limited to 86 patients of 1-23 years of age and 6 patients of 2-10 months of age. Summary table with the studies relevant for ALGS indication is presented below

Table 9 Summary Table of the Completed and Ongoing Clinical Studies and Programs in ALGS

Study ID	Locations (# Cent)	Study start Total enrollm / Enrollment goal Status	Design Control Type	Study and Control Drug Route & Regimen	Study Objective	Treatment dose # Participants by arm entered	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion criteria	Primary Efficacy Endpoint
LUM001-304	Australia Belgium France Spain Poland UK (10)	Start: 28 Oct 2014 Planned N=30 Enrolled N=31 Completed; and rolled into MRX-800 N=14	Double-blind, placebo-controlled, Randomised drug-withdrawal, long term optional follow-up	Oral MRX during OL run-in and after Week 22 MRX vs. PBO during RWD QD or BID	Evaluate safety and efficacy	QD: 400 µg/kg (n=31) During RWD: MRX: 13 / PBO: 16 After Amendment 4 (post Week 100) increase to 400 µg/kg BID (n=14)	OL run-in: 18 weeks RWD: 4 weeks (Weeks 19-22) Core period: 48 weeks LTE: Up to Week 288	19 M 12 F 5.0 (1-15) years	ALGS - Evidence of cholestasis - Average daily ItchRO(Obs) score >2	Mean change from Week 18 to 22 of fasting sBA in responder (reduction in sBA ≥50% from baseline to Weeks 12 or 18)
LUM001-301	USA Canada (13)	Start: 24 Nov 2014 Planned N=36 Enrolled N=37 Completed: and rolled into	Randomised placebo-controlled	MRX vs. PBO Oral once daily	Evaluate safety and efficacy	QD daily: 70 µg/kg (n=8) 140 µg/kg (n=11) 280 µg/kg (n=6)	13 weeks	21 M 16 F Median Age (Range):	ALGS - Evidence of cholestasis - Average daily ItchRO(Obs) score >2	Mean change from baseline to Week 13/ET in

Study ID	Locations (# Cent)	Study start Total enrollm / Enrollment goal Status	Design Control Type	Study and Control Drug Route & Regimen	Study Objective	Treatment dose # Participants by arm entered	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion criteria	Primary Efficacy Endpoint
		LUM001-305 N=35				PBO (n=12)		6.0 (1-17)		pruritus as per ItchRO(Obs) weekly average
LUM001-305	USA Canada (11)	Start: 16 Mar 2015 Planned N=36 Enrolled N=34 Completed and rolled into MRX-800 N=20	Single arm, extension study to LUM001-301	MRX Oral once daily	Evaluate long term safety and tolerability	Once daily: 280 µg/kg (n=34)	Up to Week 218	20 M 14 F Med Age (Range): 6.0 (1-17)	ALGS Completion of Study LUM001-301	Mean change from MRX baseline to Week 48 in fasting sBA level
LUM001-302	UK (3)	Start: 13 Sep 2013 Planned N=18 Enrolled N=20 Completed and rolled into LUM001-303 N=19	Randomised placebo-controlled	MRX vs. PBO Oral once daily	Evaluate safety and efficacy	Once daily: 140 µg/kg (n=6) 280 µg/kg (n=8) PBO (n=6)	13 weeks	10 M 10 F Median Age (Range): 4.0 (1-16)	ALGS - Serum bile acids >3 x ULN - Average daily ItchRO(Obs) >2	Mean change from baseline to Week 13/ET in fasting sBA

Study ID	Locations (# Cent)	Study start Total enrollm / Enrollment goal Status	Design Control Type	Study and Control Drug Route & Regimen	Study Objective	Treatment dose # Participants by arm entered	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion criteria	Primary Efficacy Endpoint
LUM001-303	UK (3)	Start:17 Oct 2013 Enrolled N=19 Completed and rolled into MRX-800 N=6	Single arm, extension study to LUM001-302	MRX Oral QD After Week 72 oral QD or BID	Evaluate long-term safety and tolerability	QD: 280 µg/kg (n=19) Increase to 280 µg/kg BID (n=5)	Up to Week 336	10 M 9 F Med Age (Range): 5.0 (1-16)	ALGS Completion of Study LUM001-302	Mean change from MRX baseline to Week 48 in fasting sBA
MRX-800	UK, USA, Canada, Spain, France, Australia, Poland, Belg (17)	Start: 16 Jan 2020 Enrolled N=52 Ongoing	Open label	MRX Oral QD or BID	Evaluation of long-term safety, tolerability	ALGS: up to a max of 450 µg/kg QD or BID if previously at that dose	Until commercially available	26 M 26 F	Completion of previous MRX study ≥1 year	Mean change from baseline in pruritus, sBA, bilirubin
MRX-801	USA, UK, Poland, Belgium, France (n=15)	Start: no FPFV yet ALGS: N≥6 Ongoing	Open label	MRX	Evaluation of safety and tolerability	Once daily: 400 µg/kg (ALGS) BID	13 weeks followed by extension period till 1 year of age	Not Applicable	ALGS: ALGS with cholestasis <12 months	Change from baseline in sBA and CSS
EAP	USA, Canada, Australia,	Start: Sep 2020 Enrolled N=24 as of 10May2021 Ongoing	Open label	MRX QD	Access to MRX	400 µg/kg QD	Until commercially available	NA	ALGS with significant cholestatic pruritus	None

Study ID	Locations (# Cent)	Study start Total enrollm / Enrollment goal Status	Design Control Type	Study and Control Drug Route & Regimen	Study Objective	Treatment dose # Participants by arm entered	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion criteria	Primary Efficacy Endpoint
	France, UK, NL								>12 months	

ALGS=Alagille syndrome; EAP=expanded access programme; ET=end of treatment; ID=identification; ItchRO(Obs)=Itch Reported Outcome (Observer); LTE=long-term extension; MRX=maralixibat; N=number of participants; NA=not available; OL=open label; PBO=placebo; RWD=randomised withdrawal; sBA=serum bile acid; UK=United Kingdom; USA=United States of America. FPFV=first patient, first visit.

2.6.5.1. Dose response study(ies)

The proposed dosing regimen is a starting dose of 200 µg/kg maralixibat (190 µg/kg free base) once daily, followed by an increase to 400 µg/kg (380 µg/kg free base) once daily after 1 week. The maximum dose to be applied is 28.5 mg maralixibat (base) QD per day, calculated as 380 µg/kg/day maralixibat (base) or the equivalent 400 µg/kg/day maralixibat chloride (referred to as "maralixibat" throughout this report) for a 70 kg person. Weight-based dose adjustment is proposed. The drug is to be taken before (up to 30 minutes) or with a meal in the morning.

Features of the studies testing various doses of maralixibat in ALGS population are summarised in the figure below.

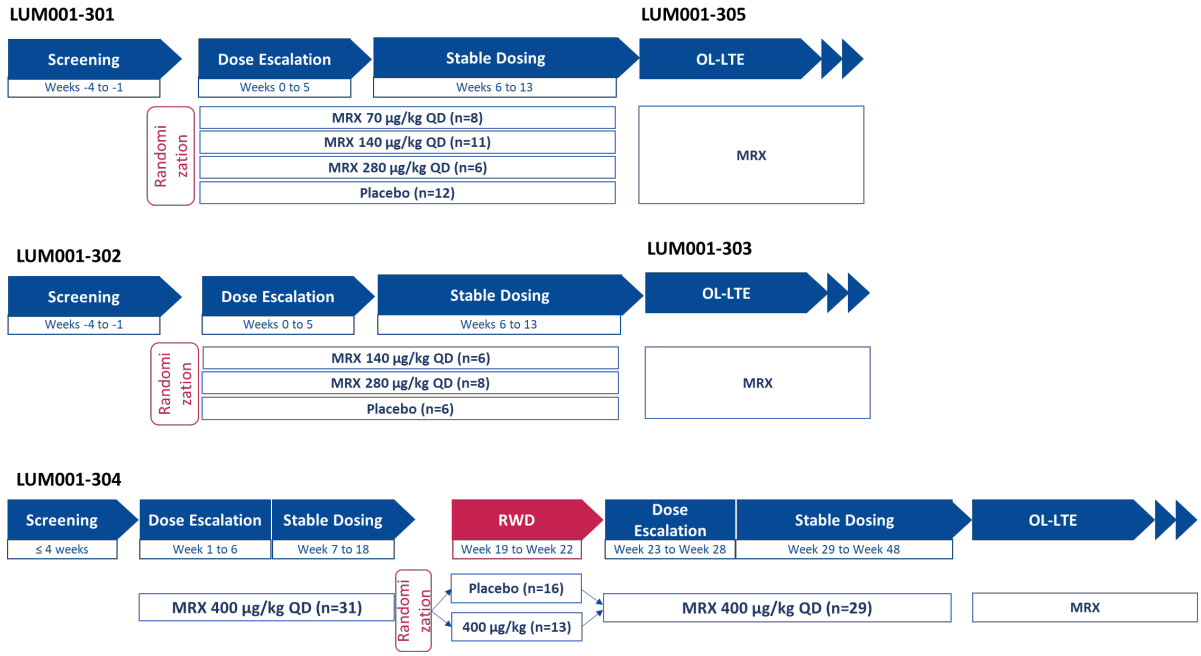


Figure 5 Study Designs for the Maralixibat Alagille Programme

The proposed therapeutic dose has been tested in the LUM001-304 study (short and long-term treatment, 1-23 year olds) and in the MRX-801 study (short-term effects; interim data in infants). The LUM001-304 study showed significant difference on maralixibat compared to placebo Efficacy and safety of this dose is discussed further in the document.

The supporting Studies LUM001-301 and LUM001-302 used lower doses of maralixibat (70 to 280 µg/kg once daily). These studies did not show significant difference to placebo in respect to reductions in pruritus and sBA. Numerical differences to placebo were observed on lower doses (70 µg/kg/day and 140 µg/kg/day). Within Studies LUM001-301 and LUM001-302, a dose response relationship was not shown; this was attributed to the relatively small sample size, placebo-effect, staggered treatment groups recruitment, suboptimal dosing, and the impact of outliers.

The long-term extension (LTE) Studies LUM001-303 and LUM001-305 used doses of 280 µg/kg once daily with an increase to 280 µg/kg twice daily after Week 124 permitted for participants in Study LUM001-303. These long-term open-label studies demonstrated statistically significant improvements in pruritus and sBA at most time points in the overall maralixibat population with associated improvements in quality of life and height z-score over time.

Starting dose of 200 µg/kg maralixibat once daily and quick dose escalation to 400 µg/kg once daily after 1 week is proposed. The simplified dose escalation is based on the safety data from the

maralixibat early access programme (EAP) in 37 participants (age range 1-27 years) with ALGS (34 being treatment-naïve) and on MRX-801 study (8 infants with ALGS). In EAP average treatment duration (SD) was 231.5 (101.02) days. No deaths, or drug-related SAEs have been reported as of 18 February 2022 in the EAP. Of the 37 participants who received maralixibat, 16 participants (43.2%) experienced TEAEs and 6 (16.2%) drug-related TEAEs (transaminitis [Grade 3], 2 cases of elevated LFTs [Grade 1 and 2], emesis [Grade 1], 2 cases of diarrhoea [Grade 1]). The drug-related events led to dose modification (in 3 cases), treatment interruption (1 case – elevated LFT), and treatment discontinuation (in 1 case – transaminitis). Interim data from MRX-801 are summarised in the section if clinical safety of this report and show that no discontinuations due to the tolerability issues took place. The data are still preliminary and very limited.

The proposed weight-based dosing for paediatric patients is suggested to account for the increase in average length of the small intestine with age from birth through 20 years (Weaver et al. 1991) that follows a similar curve to that of weight growth.

Weaver et al., 1991 analysed reported measurements of small intestinal length from eight published reports describing necropsy specimens of female and male subjects (pre-natal phase and after birth various ages). Subjects with congenital gastrointestinal and cardiac disease have been excluded. The lengths of 1010 specimens were plotted against the lengths or heights of the subjects. To establish the relation between intestinal length and body length or height, the data were fitted by cubic spline regression. The spline curve was fitted to both the original data and to the log transformed data. In the latter case, the slope of the regression curve indicated the power relation between small intestinal length and body length.

Analysis showed that after birth, growth in intestinal length continued during early postnatal life, but from about 1 year (75 cm body length) onwards it slowed and remained linear with increasing age to adulthood. From birth there was a wide range in intestinal lengths reported, with 100% variation from early childhood onwards.

For fully grown patients, a weight-based dosing should no longer be followed. The proposed dosing for patients with a body weight of ≥70 kg is 28 mg once daily (400 µg/kg * 70 kg).

All ALGS patients included into the clinical studies were children and majority had body weight below 50 kg at study entry. There have been 9 participants who reached ≥18 years of age during the studies and continued on maralixibat treatment, with the oldest participant currently 23 years of age as of 22 February 2022. Some patients reached body weight above 50 kg during long-term treatment (3 patients in LUM001-304, 1 in LUM001-303 and 4 in LUM001-305).

2.6.5.2. Main study

Title of Study: Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome (ICONIC)

Methods

This was a randomised, placebo-controlled, drug-withdrawal study with a long term open-label (OL) extension in children with Alagille syndrome (ALGS) designed to evaluate the safety and efficacy of maralixibat (MRX). The study comprised an 18-week OL run-in period (OL phase), a 4-week randomised, double-blind, placebo-controlled drug-withdrawal period (randomised withdrawal phase; RWD), a 26-week stable-dosing period at doses up to 400 µg/kg/day (after randomised withdrawal phase; ARW), and an optional long-term treatment period (long-term extension phase; LTE).

Study Participants

Male and female participants between the ages of 12 months and 18 years, inclusive, meeting the following key criteria were eligible to participate in the study:

- A diagnosis of ALGS based on the diagnostic criteria.
- Evidence of cholestasis (one or more of the following):
    - Total sBA >3× upper limit of normal (ULN) for age.
    - Conjugated bilirubin >1 mg/dL.
    - Fat-soluble vitamin deficiency otherwise unexplainable.
    - Gamma-glutamyltransferase (GGT) >3× ULN for age.
    - Intractable pruritus explainable only by liver disease.
- Average daily score >2 on the Itch Reported Outcome (ItchROTM) questionnaire (0=none; 4=very severe pruritus) for 2 consecutive weeks in the screening period, prior to dosing.
- Absence of the following (incomplete list): chronic diarrhoea requiring specific intravenous fluid or nutritional intervention; surgical disruption of the enterohepatic circulation; liver transplant, decompensated cirrhosis (alanine transaminase [ALT] >15× ULN, INR >1.5, albumin <3.0 g/dL; history or presence of clinically significant ascites; variceal haemorrhage, and/or encephalopathy); history or presence of other concomitant liver disease, or history or presence of any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, including bile salt metabolism in the intestine, history or presence of gallstones or kidney stones; administration of bile acid or lipid-binding resins within 28 days prior to screening and throughout the trial; participants weighing over 50 kg at screening or any other conditions or abnormalities which, in the opinion of the investigator or medical monitor, may compromise the safety of the participant, or interfere with the participant participating in or completing the study.

Treatments

The proposed therapeutic dose of 400 µg/kg/day (QD) was applied after careful titration of maralixibat from 35 µg/kg/day via the dose steps of 70 µg/kg/day, 140 µg/kg/day and 280 µg/kg/day (for 1 week each). Placebo arm was included in the RWD phase. During the long-term treatment period, participants may have had their dose of maralixibat increased to a maximum of 800 µg/kg/day (400 µg/kg twice daily [BID]), based on efficacy (serum bile acid (sBA) levels and Itch Reported Outcome (Observer) (ItchRO[Obs]) score) and safety assessments. In all cases, maralixibat, or placebo were administered orally, 30 min prior to the main meal of the day.

Objectives

The objectives of this study (up to and including Week 48) were:

- To evaluate the long-term safety and tolerability of maralixibat
- To evaluate the effect of maralixibat on sBA levels
- To evaluate the effect of maralixibat on biochemical markers of cholestasis and liver disease
- To evaluate the effect of maralixibat on pruritus
- To evaluate the long-term effect of maralixibat during 48 weeks of treatment

The objectives of the optional long-term follow-up treatment period (after Week 48) were:

• To offer eligible participants treated in the LUM001-304 study continued study treatment at Week 48 until the first of the following occurred: 1) the participants were eligible to enter another maralixibat study, 2) maralixibat was available commercially, or 3) the sponsor stopped the programme or development in this indication

Outcomes/endpoints

Primary endpoint of the study was Mean change from Week 18 to Week 22 of fasting sBA levels in participants who previously responded to maralixibat treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 (mITT Population).

Secondary Efficacy Endpoints were

• The change from Week 18 to Week 22 in: fasting sBA, Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]), liver function tests (ALP, ALT, total and direct bilirubin) (ITT).

• The change from baseline to Week 18 in: fasting sBA, Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]), liver function tests (ALP, ALT, total and direct bilirubin) (ITT)

Additional Efficacy Endpoints

• Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 in: Pruritus response rates as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]) and CSS.

• Change from baseline to Weeks 18, 22, and 48 and then every 12 weeks in: fasting sBA, Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]), liver function tests (ALP, ALT, total and direct bilirubin), other biochemical markers of cholestasis (total cholesterol, LDL-C), Bile acid synthesis (7αC4)

Change from baseline for PedsQL, PIC, CIC, CGTB, Xanthoma scale score, height, weight, over the whole treatment period (run-in, randomised withdrawal and follow-up phases).

Sample size

The planned sample size of 30 evaluable ALGS subjects was based on practical considerations, rather than a desired power for a pre-specified difference

Randomisation and Blinding (masking)

The study included open-label and double-blind phases. 1:1 randomisation in the RWD phase was applied. Patients were stratified as per their response in the run-in phase.

Statistical methods

In the LUM001-304 the following analysis populations were planned:

- Safety Population (SAF): The Safety Population is defined as all subjects who were enrolled and received at least one dose of the study drug.
- Intent-To-Treat Population (ITT): The ITT Population includes all subjects who were enrolled and received at least one dose of the study drug.
- Modified Intent-To-Treat Population (MITT): The MITT Population includes all subjects who were enrolled, received study drug through Week 18, and had a reduction from baseline in sBA of ≥50% at the Week 12 or Week 18 measurement (sBA responder). Notably, definition of responder was adapted after completion of the RWD phase.

For each treatment phase, the following subjects were included in each respective analysis population:

- OL Phase: Subjects dosed during the OL phase.
- RW Phase: Subjects randomised and dosed during the RW phase.
- ARW Phase: Subjects dosed after the RW phase.

The primary analysis population for efficacy was the MITT Population. Analyses for the primary and secondary efficacy outcome variables were also performed on the ITT Population.

The difference between treatment groups in change from Week 18 to Week 22 in serum bile acid were evaluated using an ANCOVA model with treatment group as a factor, and Week 18 serum bile acid as a covariate. An ANCOVA model that includes the stratification variable sBA responder indicator as an additional covariate was also performed on the ITT Population. This model also included the sBA responder covariate by treatment sequence interaction term. The LS mean difference between treatment groups (MRX minus PBO) with standard error, 95% CI for the LS mean difference, and p-value for testing if the treatment group LS means are equal were calculated to determine if the change in sBA levels between the treatment groups are statistically significant.

Secondary, exploratory, and other efficacy variables that are continuous measures were analysed similarly to the primary efficacy analyses, using summary statistics and, with the exception of PIC, CIC, and CGTB, by ANCOVA.

Efficacy measures that are categorical binary responder outcomes were analysed using the chi-square or Fisher's Exact test, as appropriate based on sample sizes.

No adjustments were made for multiple comparisons.

For subjects who early terminated from the study prior to Week 100 or are otherwise missing Week 18, Week 22, Week 48, and/or Week 100 data were imputed in a LOCF approach.

Results

Participant flow

Thirty-six children with ALGS were screened between October 2014 and August 2015, at which time the predefined sample size was filled. Five participants were excluded during the screening period. In total, 31 participants were enrolled into the open label period of the study.

A total of 28 participants completed the core study to Week 48, and 14 participants were receiving maralixibat in the LTE at the time of transition to the rollover LTE Study MRX 800 in May 2020.

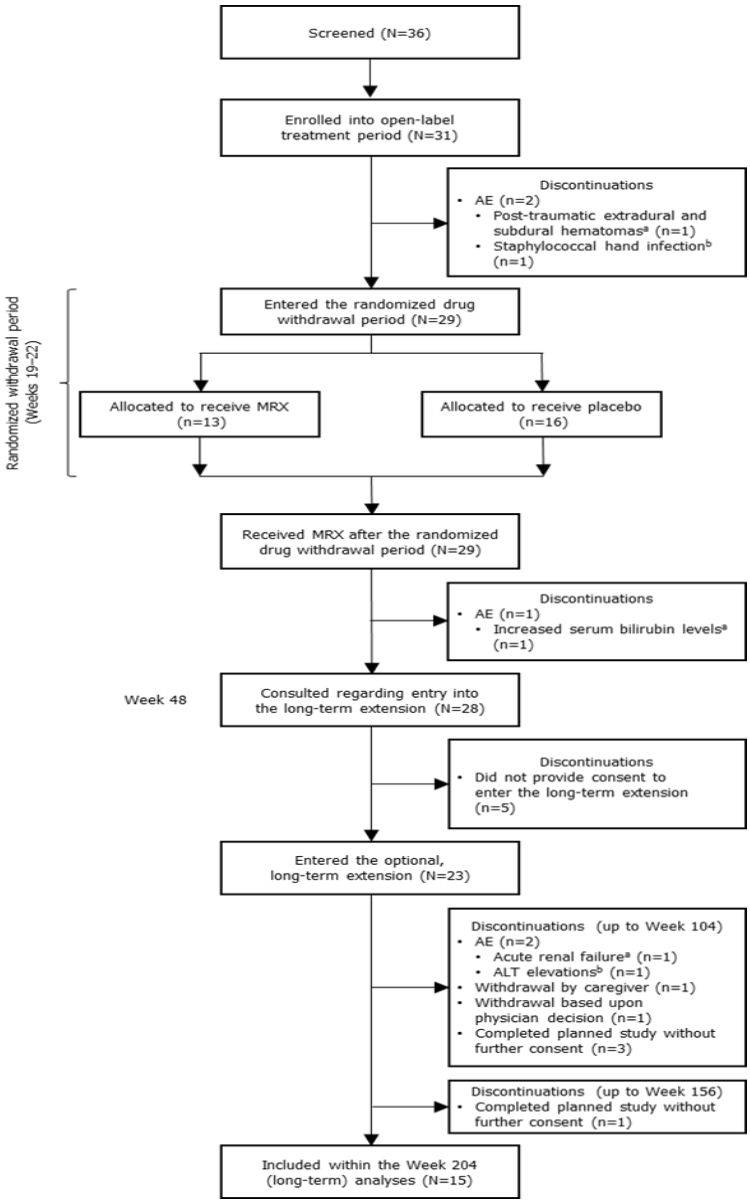


Figure 6 CONSORT diagram

AE=adverse event; CONSORT=Consolidated Standards of Reporting Trials; LTE=long-term extension; MRX=maralixibat.

Note: There were 2 protocol extensions to the core study: participants were consulted at Week 48 regarding entry into the LTE (5 did not provide consent), and 4 completed the planned study but did not provide consent to enter the further extension.

[a] Deemed unrelated to maralixibat by the investigator; [b] Deemed possibly related to maralixibat by the investigator.

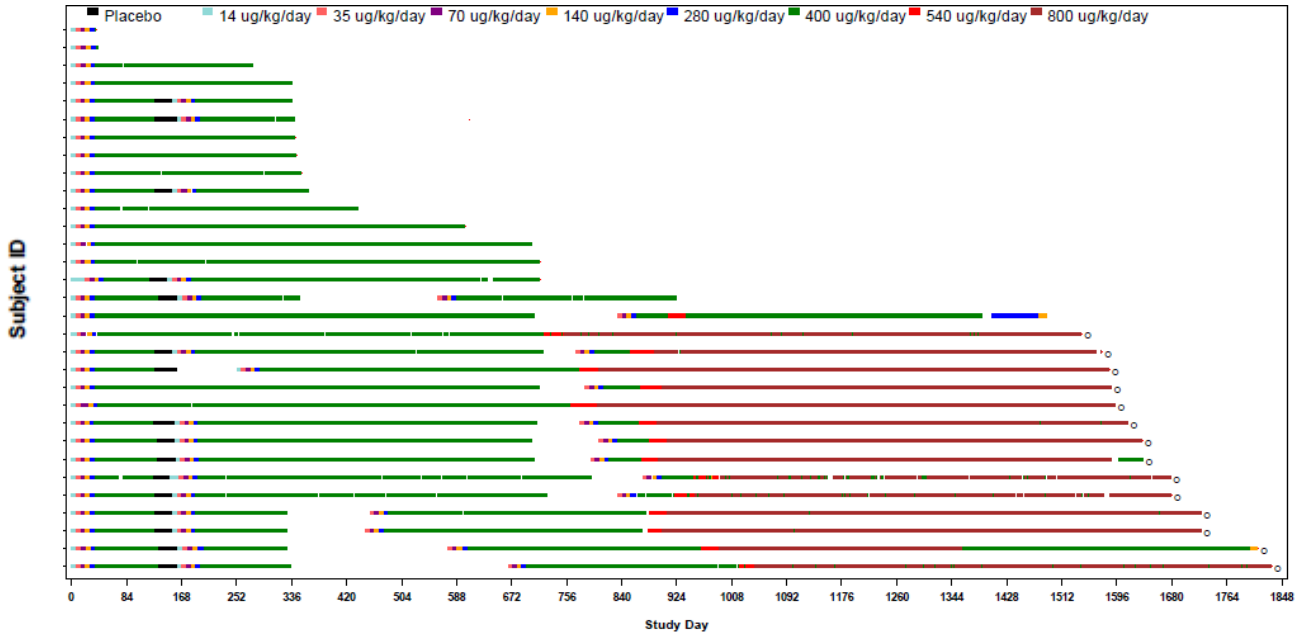


Figure 7 Study Drug Exposure Over Time by Participant (Safety Population) – Study LUM001-304

As indicated in the figure above, the majority of participants increased the dose to 400 µg/kg twice daily under Protocol Amendment 5, and after Week 100 of the study.

Recruitment

The study was conducted in 7 countries (Australia, France, Spain, Poland, United Kingdom) and 10 clinical sites. Majority of the patients were recruited in the EU. The study centres were mainly hospital-based paediatric centres specialised in liver diseases. Two-thirds of the study participants were enrolled in Australia or France (about 30% in each).

First participant was screened on 28 October 2014 and last subject last visit took place on 28 May 2020.

Conduct of the study

The study was conducted in conformity with the GCP rules, Declaration of Helsinki, CIOMS and other applicable rules, regulations and guideline. In total 6 protocol amendments were introduced. Key changes being changes in inclusion-exclusion criteria (limitation of allowed body weight, exclusion of patients with renal and hepatic stones, etc.), change in the responder definition for randomised withdrawal phase for definition of mITT, and addition of extension phases. EC and regulatory approvals for the sites have been submitted.

Baseline data

Baseline characteristics of the participating patients are displayed in the table below. The study included 1 to 15 years old children with ALGS distributed over all age categories. All had confirmed JAGGED1 mutation and suffered from chronic cholestasis. Delay in height and weight growth was also apparent (z-scores of -1.7 (1.34) and -1.7 (1.18) respectively). Mean values of the sBA and liver function parameters were high at the baseline. However, 9 patients had normal or only slightly elevated levels of sBA at the baseline.

Table 10 Baseline Disease Characteristics by Treatment Group; Study LUM001-304

Parameter Category	Baseline All Participants (N=31)	Baseline MRX-MRX-MRX Group (N=13)	Baseline MRX-PBO-MRX Group (N=16)
Age, in years[a]			
Mean (SD)	5.4 (4.25)	5.5 (5.03)	5.8 (3.75)
Median	5.0	4.0	5.0
Min, max	1, 15	1, 15	1, 14
Sex			
Male	19 (61.3%)	9 (69.2%)	10 (62.5%)
Family history of ALGS			
Yes	8 (25.8%)	1 (7.7%)	7 (43.8%)
Presence of bile duct paucity			
Yes	18 (58.1%)	4 (30.8%)	12 (75.0%)
Additional clinical criteria/features of ALGS[b]			
Chronic cholestasis	31 (100.0%)	13 (100.0%)	16 (100.0%)
Cardiac disease	29 (93.5%)	12 (92.3%)	15 (93.8%)
Renal abnormalities	12 (38.7%)	4 (30.8%)	8 (50.0%)
Vascular abnormalities	5 (16.1%)	1 (7.7%)	3 (18.8%)
Skeletal abnormalities	17 (54.8%)	7 (53.8%)	9 (56.3%)
Ocular abnormalities	17 (54.8%)	7 (53.8%)	8 (50.0%)
Characteristic facial features	29 (93.5%)	12 (92.3%)	15 (93.8%)
Used anything to treat itch in the past			
Yes	29 (93.5%)	12 (92.3%)	15 (93.8%)
Clinician Scratch Scale Score[c]			
Mean (SD)	3.3 (0.90)	3.0 (1.08)	3.5 (0.73)
ItchRO(Obs) Weekly Morning Average Severity (Item 1) Score[d]			
Mean (SD)	2.909 (0.5480)	2.879 (0.5378)	2.93 (0.5592)
ItchRO(Pt) Weekly Morning Avg Severity (Item 1) Score[d]			
Mean (SD)	2.903 (0.6616)	2.848 (0.6231)	2.934 (0.7170)
PedsQL Total Scale Score (Parent)			
Mean (SD)	61.10 (16.988)	64.79 (13.773)	55.90 (17.800)
Serum Bile Acid (µmol/L)			
Mean (SD)	283.43 (210.569)	317.97 (233.671)	249.56 (196.804)
Aspartate Aminotransferase (U/L)			
Mean (SD)	167.7 (75.87)	172.4 (76.12)	146.8 (61.34)
Alanine Aminotransferase (U/L)			
Mean (SD)	181.0 (108.56)	217.8 (149.93)	147.0 (54.60)
Gamma Glutamyl Transferase (U/L)			

Parameter Category	Baseline All Participants (N=31)	Baseline MRX-MRX-MRX Group (N=13)	Baseline MRX-PBO-MRX Group (N=16)
Mean (SD)	508.4 (389.35)	613.9 (482.48)	404.0 (300.19)
Total Bilirubin (mg/dL)			
Mean (SD)	6.09 (5.781)	6.52 (6.571)	4.83 (4.265)

ALGS=Alagille syndrome; ItchRO(Obs)=Itch Reported Outcome (Observer); ItchRO(Pt)=Itch Reported Outcome (Patient); MRX=maralixibat; PBO=placebo; SD=standard deviation.

[a] Age at time of the baseline visit.

[b] Participants reporting more than 1 clinical criteria/feature for ALGS are counted in each category reported.

[c] The Clinician Scratch Scale uses a 5-point scale, where 0=None, 1=Rubbing or mild scratching when undistracted, 2=Active scratching without evident skin abrasions, 3=Abrasion evident, 4=Cutaneous mutilation, haemorrhage, and scarring evident.

[d] ItchRO average scores are based on the 7 days prior to the baseline visit date. Caregivers for all participants complete the ItchRO(Obs); children at least 9 years of age complete the ItchRO(Pt); children aged 5-8 years complete the ItchRO(Pt) with the assistance of their caregiver; there is no ItchRO(Pt) report for participants under the age of 5 years.

[e] The Clinician Xanthoma Scale uses a 5-point scale, where 0=None, 1=Minimal, 2=Moderate, 3=Disfiguring, 4=Disabling.

Numbers analysed

The safety set included 31 patients. Efficacy analysis was conducted in 29 patients (ITT; 13 on MRX and 16 on PLA). The primary analysis included 15 patients (mITT; 5 on MRX and 10 on PLA).

Outcomes and estimation

Change in Serum Bile Acid (Primary Efficacy Endpoint – mITT Population)

There was a statistically significant LS mean (SE) difference in change from Week 18 to 22 in sBA between the maralixibat and placebo groups (-117.28 [52.828] µmol/L, p=0.0464). Participants administered placebo during the RWD phase had a statistically significant LS mean (SE) increase in sBA from Week 18 to Week 22 of 95.55 (30.488) µmol/L (p=0.0086), whereas those who received maralixibat had no notable change (-21.73 [43.125] µmol/L, p=0.6234).

Change in Serum Bile Acids Over Time (Prespecified Endpoint - Overall Study Population)

In the overall ITT Population (N=31 participants), with all participants randomised to either placebo or maralixibat during the RWD phase, there was a significant mean (SE) decrease in sBA during the OL phases up to Week 18 (-87.73 [22.280] µmol/L, p=0.0005, N=29) and Week 48 (-96.44 [32.068] µmol/L, p=0.0058, N=27).

At the end of the RWD phase (Week 22), participants who had continued to receive maralixibat maintained their mean (SE) sBA treatment effect (-16.73 [30.412] µmol/L, p=0.5923, N=13), whereas those on placebo had experienced a significant increase (93.58 [33.219] µmol/L, p=0.0130, N=16). The LS mean difference between the 2 treatment groups was statistically significant (-113.95 µmol/L, 95% CI -212.68 to -15.21, p=0.0254).

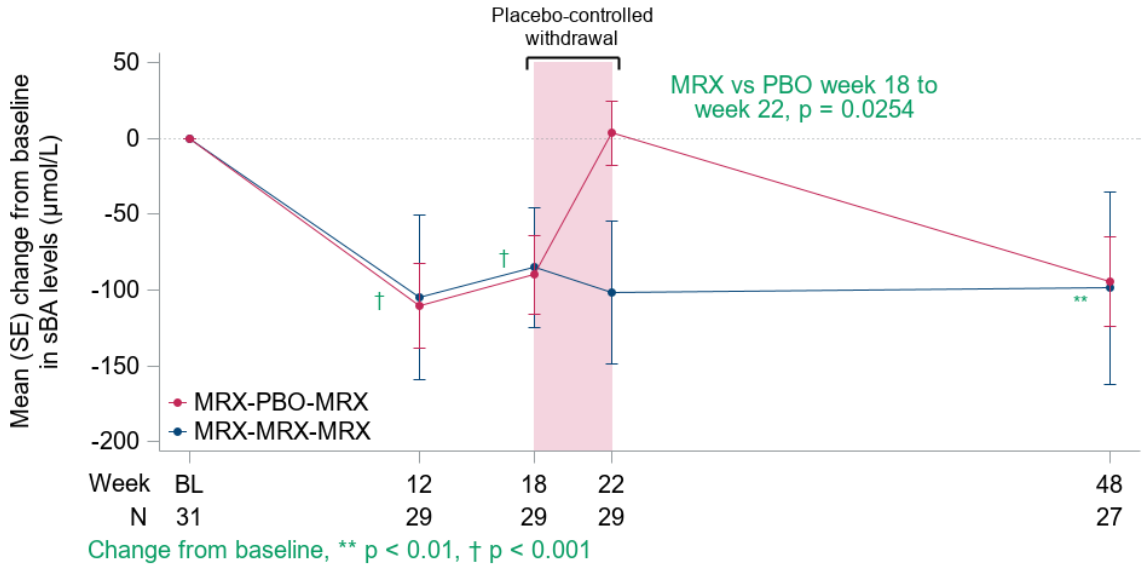


Figure 8 Mean (±SE) Change from Baseline in sBA (µmol/L) by Randomised Treatment Group Through Week 48 in the Overall Study Population (ITT Population); Study LUM001-304

ITT=intent-to-treat; MRX=maralixibat; PBO=placebo; sBA=serum bile acid; SE=standard error of the mean.

Notes: Vertical reference lines indicate the period during which study participants received either placebo or maralixibat; during all other treatment periods all study participants were treated with maralixibat.

Throughout the entire treatment period statistically significant decreases from baseline in sBA were observed at each time point, with the exception of Week 108 and Weeks ≥240. After Week 22, at the visits with statistically significant results, mean (SE) decreases from baseline in sBA after Week 22 ranged from -83.71 (32.915) µmol/L at Week 100/LOCF (p=0.0170) to -180.84 (47.672) µmol/L at Week 204 (p=0.0020). The results at Week 108 and ≥240 may be explained by a smaller number of participants on study medication at those visits (N=13 and <5, respectively).

After Week 100, 14 of 16 participants remaining in the study, who had sBA levels above the ULN (8 µmol/L) or pruritus (ItchRO(Obs) ≥1.5) increased maralixibat doses of 800 µg/kg/day (400µg/kg BID). Five of these patients had additional reduction in sBA on the BID dose.

ItchRO(Obs) Weekly Average Morning Severity Score

At Week 22, a statistically significant increase (worsening) in mean (SE) change from Week 18 in ItchRO(Obs) scores was identified in the placebo group (1.712 [0.2513], p<0.0001, n=16), whereas no relevant change was observed in the maralixibat group (0.201 [0.2180], p=0.3754, n=12). Participants who received placebo experienced a return of their pruritus severity similar to their baseline scores, whereas those who continued to receive maralixibat generally maintained the treatment effect observed during the OL phase.

At comparison of the ItchRO(Obs) scores at the end of the RWD phase (Week 22) mean (SE) values were 1.380 (0.2685) vs. 2.839 (0.2126) in the maralixibat and placebo groups, respectively. The LS mean (SE) difference between the maralixibat and placebo groups at Week 22 was statistically significant (-1.483 [0.3103]; p<0.0001).

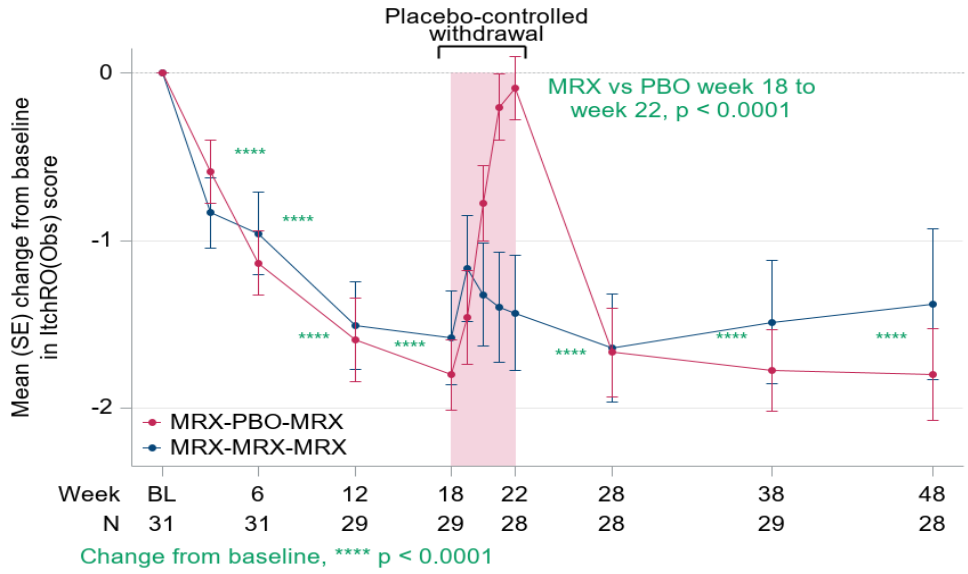


Figure 9 Mean (±SE) Change from Baseline in ItchRO(Obs) Weekly Average Morning Severity Score by Randomised Treatment Group Over Time (Through Week 48); Study LUM001-304

ANCOVA=analysis of covariance; ItchRO(Obs)=Itch Reported Outcome (Observer); ITT=intent-to-treat; MRX=maralixibat; PBO=placebo; SE=standard error of the mean.

Notes: Area shaded in red indicates the period during which study participants received either placebo or maralixibat; during all other treatment periods all study participants were treated with maralixibat. An ANCOVA was used to test for a statistically significant difference between the treatment groups and statistically significant difference from baseline in both treatment groups combined. Analysis was performed on the ITT Population.

Improvements in pruritus were maintained as per ItchRO(Obs) over the extension period as well. A responder analysis performed using different responder definitions that were based on changes in ItchRO(Obs) weekly average morning severity score responder rate of >70% at Week 48, as defined by change from baseline of ≥1.0 point. Clinically relevant responder rates were observed using increasingly conservative response thresholds. At the end of the placebo-controlled RWD phase at Week 22, there was a consistently higher proportion of responders in the maralixibat group compared with those in the placebo group, using various responder criteria.

A post hoc analysis of pruritus response evaluating days of pruritus control as determined by proportion of days with an ItchRO(Obs) score of 1.0 or lower in any given week showed an increasing proportion of days with pruritus control on maralixibat. At Week 18, participants had pruritus control 44.8% of days. At the end of the RWD phase, the proportion of days with pruritus control dropped to 6.2% in the placebo group while it was maintained at 41.7% in the maralixibat group, suggesting the maralixibat-driven pruritus control. Pruritus control was observed 42.9% to 51.7% of days during Weeks 28 to 48 with only 1 participant discontinuing during this study period.

Table 11 Changes in Clinical Manifestations of Cholestasis – Study LUM001-304 (original analyses without accounting for confounders)

Parameter	Total Cholesterol (mg/dL)	LDL-Cholesterol (mg/dL)	Xanthoma (Score)	Fatigue (Score)	Growth (z-Score)
Population	**Overall ITT**		**Participants with xanthoma at baseline**	**Overall ITT**	
Change from baseline to Week 18 on MRX (open-label)					
No. of participants	29	29	14	22	29
Mean (95% CI)	-87.1 (-139.6, -34.6)	-27.9 (-42.5, -13.3)	-0.4 (-0.9, 0.1)	20.39 (8.91, 31.87)	0.124 (-0.040, 0.288)
p-value	0.0020	0.0005	0.0823	0.0013	0.1332
Change from baseline to Week 48 on MRX (open-label)					
Number of participants	27	27	12	21	28
Mean (95% CI)	-62.9 (-105.3, -20.6)	-27.8 (136.5, 199.5)	-0.9 (-1.3, -0.5)	20.30 (8.98, 31.63)	0.178 (-0.016, 0.373)
p-value	0.0052	0.0126	0.0006	0.0013	0.0704
Observed Change from Week 18 to Week 22 – Randomised Withdrawal Period – MRX vs. PLA (DB phase)					
Number of participants	29	29	N/A	21	N/A
NLS Mean (95% CI)	-76.4 (-135.5, -17.2)	-29.2 (-60.5, 2.2)		14.03 (-2.78, 30.84)	
p-value	0.0135	0.0668		0.0966	

iCSR=interim clinical study report; ItchRO(Obs)=Itch-Reported Outcome (Observer); ITT=intent to treat; LDL=low density lipoprotein; sBA=serum bile acid.

Other parameters

Changes in CSS score were in line with the changes in the ItchRO(Obs). No relevant changes were observed in bilirubin and other liver parameters. Quality of life, cholesterol, xanthoma and Z-scores for height and weight improved over the whole study period. However, no changes after switch to placebo were reported in the quality of life.

Ancillary analyses

To account for the drop-outs in the follow-up phase of the study, sensitivity analyses applying 3 different imputation methods (BOCF, MMRM and multiple imputation) were conducted for sBA and ItchRO(Obs) parameters to assess the maintenance of effects. Even with the most conservative BOCF method, changes from baseline to weeks 48 and 204 were found statistically significant.

To account for natural fluctuations in sBA post hoc analyses of changes in sBA were conducted against adapted baselines applying two values prior to treatment (screening and baseline visit) and prior to randomised withdrawal in LUM001-304. Treatment effects on sBA were smaller than in the main analysis, but statistically significant for run-in and randomised withdrawal phase.

Study in infants – MRX-801 study

Design and methodology: This is an ongoing open-label, multicentre, Phase 2 study to evaluate the safety and tolerability of maralixibat in the treatment of infants (≥ 2 months to <12 months old) with cholestatic liver disease (Alagille syndrome [ALGS] or progressive familial intrahepatic cholestasis [PFIC]).

The study comprises screening (up to 4 weeks), core study period to Week 13 and long-term extension (LTE).

Evidence of efficacy was provided in 8 patients of 2 to 10 months of age with ALGS change in pruritus as assessed with Clinician Scratch Scale (where 0=none and 4=cutaneous mutilation, haemorrhage and scarring evident) at week 13 was mean (SD; median; range) -0.2 (1.91; -1.0; -3.0 to 3.0) and in sBA mean (SD; median; range) -88.91 µmol/L (113.348; -53.65; -306.1 to 14.4). Two patients experienced improvement in both pruritus and sBA.

Summary of main efficacy results

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

Table 12 Summary of Efficacy for Trial LUM001-304

Title: Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome (ICONIC)			
Study identifier	LUM001-304 EudraCT number: 2013-005373-43 ClinicalTrials.gov ID: NCT02160782		
Design	This was a randomised, placebo-controlled, drug-withdrawal study with a long term open-label (OL) extension in children with Alagille syndrome (ALGS) designed to evaluate the safety and efficacy of maralixibat (MRX). The study comprised an 18-week OL run-in period (OL phase), a 4-week randomised, double-blind, placebo-controlled drug-withdrawal period (randomised withdrawal phase; RWD), a 26-week stable-dosing period at doses up to 400 µg/kg/day (after RWD - ARW), and an optional long-term treatment period (long-term extension phase; LTE). During the long-term treatment period, participants may have had their dose of maralixibat increased to a maximum of 800 µg/kg/day (400 µg/kg twice daily [BID]), based on efficacy (serum bile acid (sBA) levels and Itch Reported Outcome (Observer) (ItchRO[Obs]) score) and safety assessments.		
	Duration of OL run-in phase: Duration of RWD phase: Duration of ARW phase:		18 weeks 4 weeks From Week 22 Up to Week 288
Hypothesis	Superiority		
Treatment groups	MRX(OL)-MRX(RWD)-MRX(ARW)		Treated with MRX during OL run-in, RWD and ARW phase. 13 participants.
	MRX(OL)-PBO(RWD)-MRX(ARW)		Treated with MRX during OL run-in phase, with PBO during RWD phase and with MRX during ARW phase. 16 participants.
	MRX(OL)		All 31 participants treated with MRX in OL.
Endpoints and definitions	Primary endpoint	Mean change from Week 18 to Week 22 in fasting sBA (mITT)	The difference between treatment groups in change from Week 18 to Week 22 in fasting sBA levels was evaluated using an analysis of covariance (ANCOVA) model with treatment group as a factor, and Week 18 sBA as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the mITT population, including all enrolled, who received study drug through Week 18, and had a reduction from baseline in sBA of ≥50% at the Weeks 12 or 18. The P-value for testing if the treatment group least squares (LS) means were equal was calculated.
	Secondary endpoint	Change from Week 18 to Week 22 in sBA (ITT)	The difference between treatments in change from Week 18 to Week 22 in fasting sBA levels was evaluated using ANCOVA model with treatment group as a factor, and Week 18 sBA as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the ITT population. The P-value for testing if the treatment group least squares (LS) means were equal was calculated.

	Secondary endpoint	Change from Week 18 to Week 22 in ItchRO(Obs) and ItchRO (Pt)	Similar as the sBA for secondary endpoint.
	Secondary endpoint	Change from Week 18 to Week 22 in ALP, ALT, Total and Direct bilirubin	Similar as the previous secondary analyses.
	Secondary endpoint	Change from baseline to Week 18 in sBA levels	sBA levels (mean values) at week 18 was compared to baseline in ITT. The null hypothesis that the mean change was equal to zero was tested using the Student's t-test.
	Secondary endpoint	Change from baseline to Week 18 in pruritus as measured by ItchRO(Obs) and ItchRO (Pt)	ItchRO score at week 18 was compared to baseline (ITT). The null hypothesis that the mean change was equal to zero was tested using the Student's t-test.
	Secondary endpoint	Change from baseline to Week 18 in ALP, ALT, Total bilirubin, Direct bilirubin	This analysis investigated whether a statistically significant change in ALP, ALT, Total bilirubin and Direct bilirubin levels was observed when comparing baseline to Week 18 (ITT). The null hypothesis that the mean change was equal to zero was tested using the Student's t-test.

Database lock	21-Aug-2020 (Last Participant Visit on 19-Jun-2020)		
Results and Analysis			
Analysis description	**Primary - Mean change from Week 18 to 22 in fasting sBA (mITT)**		
Analysis population and time point description	Modified Intention-to-Treat (participants who had a reduction in sBA ≥50% from baseline to Week 12 or Week 18) Timepoint: Week 18 to Week 22		
Descriptive statistics and estimate variability	Treatment group	MRX (RWD)	PBO (RWD)
	Number of subjects	5	10
	Change from Week 18 to Week 22 in sBA Level (Least Squares Mean, µmol/L)	-21.73	95.55
	95% Confidence Interval	-115.69 to 72.23	29.12 to 161.97
	Standard Error	43.125	30.488
Effect estimate per comparison	LS Mean Difference	-117.28	
	95% Confidence Interval	-232.38 to -2.18	
	Standard Error of the Mean	52.828	
	p-value	0.0464	
Analysis description	**Secondary - Change from Week 18 to 22 in sBA levels (ITT)**		
Analysis population and time point description	Intention-to-Treat Timepoint: Week 18 to Week 22		
	Treatment group	MRX (RWD)	PBO (RWD)

Descriptive statistics and estimate variability	Number of subjects	13	16
	Change from Week 18 to Week 22 in sBA Level (Least Squares Mean Mean, µmol/L)	-18.74	95.21
	95% Confidence Interval	-91.20 to 53.72	30.08 to 160.34
	Standard Error	35.251	31.686
Effect estimate per comparison	LS Mean Difference	-113.95	
	95% Confidence Interval	-212.68 to -15.21	
	Standard Error of the Mean	48.032	
	p-value	0.0254	
Analysis description	**Secondary - Change from Week 18 to 22 in ItchRO(Obs)**		
Analysis population and time point description	Intention-to-Treat Timepoint: Week 18 to Week 22		
Descriptive statistics and estimate variability	Treatment group	MRX (RWD)	PBO (RWD)
	Number of subjects	12	16
	Change from Week 18 to Week 22 in pruritus as measured by ItchRO(Obs) (Least Squares Mean)	0.217	1.700
	95% Confidence Interval	-0.266 to 0.700	1.282 to 2.119
	Standard Error	0.2345	0.2031
Effect estimate per comparison	LS Mean Difference	-1.483	
	95% Confidence Interval	-2.122 to -0.844	
	Standard Error of the Mean	0.3103	
	p-value	<0.0001	
Analysis description	**Secondary analysis - Change from Week 18 to 22 in ItchRO (Pt)**		
Analysis population and time point description	Intention-to-Treat Timepoint: Week 18 to Week 22		
Descriptive statistics and estimate variability	Treatment group	MRX (RWD)	PBO (RWD)
	Number of subjects	5	9
	Change from Week 18 to Week 22 in pruritus as measured by ItchRO(Pt) (Least Squares Mean)	-0.149	1.839
	95% Confidence Interval	-0.968 to 0.669	1.229 to 2.448
	Standard Error	0.3719	0.2771

Effect estimate per comparison	LS Mean Difference	-1.988	
	95% Confidence Interval	-3.009 to -0.967	
	Standard Error of the Mean	0.4641	
	p-value	0.0013	
Note	ItchRO(Pt) was completed independently in participants 9 years old or older. For children between the ages of 5 and 8 years old the completion of the patient instrument with the assistance of their caregiver was optional.		
Analysis description	**Secondary - Change from Week 18 to 22 in ALP**		
Analysis population and time point description	Intention-to-Treat Timepoint: Week 18 to Week 22		
Descriptive statistics and estimate variability	Treatment group	MRX (RWD)	PBO (RWD)
	Number of subjects	13	16
	Change from Week 18 to Week 22 in ALP (Least Squares Mean, U/L)	2.8	-7.2
	95% Confidence Interval	-43.6 to 49.1	-49.0 to 34.6
	Standard Error	22.55	20.31
Effect estimate per comparison	LS Mean Difference	10	
	95% Confidence Interval	-52.6 to 72.6	
	Standard Error of the Mean	30.44	
	p-value	0.7455	
Analysis description	**Secondary analysis- Change from Week 18 to 22 in ALT**		
Analysis population and time point description	Intention-to-Treat Timepoint: Week 18 to Week 22		
Descriptive statistics and estimate variability	Treatment group	MRX (RWD)	PBO (RWD)
	Number of subjects	13	16
	Change from Week 18 to Week 22 in ALT (Least Squares Mean, U/L)	34.5	19.4
	95% Confidence Interval	5.6 to 63.4	-6.4 to 45.2
	Standard Error	14.04	12.56
Effect estimate per comparison	LS Mean Difference	15.1	
	95% Confidence Interval	-25.1 to 55.2	
	Standard Error of the Mean	19.53	
	p-value	0.4472	

Analysis description	**Secondary - Change from Week 18 to Week 22 in Total bilirubin**		
Analysis population and time point description	Intention-to-Treat Timepoint: Week 18 to Week 22		
Descriptive statistics and estimate variability	Treatment group	MRX (RWD)	PBO (RWD)
	Number of subjects	13	16
	Change from Week 18 to Week 22 in Total Bilirubin (Least Squares Mean, mg/dL)	0.32	0.46
	95% Confidence Interval	-0.23 to 0.86	-0.03 to 0.95
	Standard Error	0.265	0.238
Effect estimate per comparison	LS Mean Difference	-0.14	
	95% Confidence Interval	-0.88 to 0.60	
	Standard Error of the Mean	0.361	
	p-value	0.7000	
Analysis description	**Secondary - Change from Week 18 to Week 22 in Direct bilirubin**		
Analysis population and time point description	Intention-to-Treat Timepoint: Week 18 to Week 22		
Descriptive statistics and estimate variability	Treatment group	MRX (RWD)	PBO (RWD)
	Number of subjects	12	15
	Change from Week 18 to Week 22 in Direct Bilirubin (Least Squares Mean, mg/dL)	0.13	0.14
	95% Confidence Interval	-0.28 to 0.53	-0.22 to 0.50
	Standard Error	0.195	0.174
Effect estimate per comparison	LS Mean Difference	-0.02	
	95% Confidence Interval	-0.56 to 0.53	
	Standard Error of the Mean	0.265	
	p-value	0.9517	
Analysis description	**Secondary – Change in sBA from baseline to Week 18**		
Analysis population and time point description	Intention-to-Treat Timepoint: Baseline to Week 18		
Descriptive statistics and estimate variability	Treatment group	MRX Baseline	MRX Week 18
	Number of subjects	31	29
	Mean sBA (µmol/L)	283.43	192.50
	95% Confidence Interval	206.19 to 360.67	131.15 to 253.84

	Standard Deviation	210.569	161.278
Effect estimate per comparison	Mean Difference	-87.73	
	95% Confidence Interval	-133.37 to -42.09	
	Standard Deviation	119.979	
	p-value	0.0005	
Analysis description	**Secondary - Change in ItchRO(Obs) from baseline to Week 18**		
Analysis population and time point description	Intention-to-Treat Timepoint: Baseline to Week 18		
Descriptive statistics and estimate variability	Treatment group	MRX Baseline	MRX Week 18
	Number of subjects	31	29
	Mean ItchRO(Obs)	2.909	1.203
	95% Confidence Interval	2.708 to 3.110	0.882 to 1.525
	Standard Deviation	0.5480	0.8446
Effect estimate per comparison	Mean Difference	-1.704	
	95% Confidence Interval	-2.051 to -1.357	
	Standard Deviation	0.9114	
	p-value	<0.0001	
Analysis description	**Secondary - Change in ItchRO(Pt) from baseline to Week 18**		
Analysis population and time point description	Intention-to-Treat Timepoint: Baseline to Week 18		
Descriptive statistics and estimate variability	Treatment group	MRX Baseline	MRX Week 18
	Number of subjects	14	14
	Mean ItchRo(Pt)	2.903	0.831
	95% Confidence Interval	2.521 to 3.285	0.362 to 1.300
	Standard Deviation	0.6616	0.8122
Effect estimate per comparison	Mean Difference	-2.072	
	95% Confidence Interval	-2.645 to -1.498	
	Standard Error of the Mean	0.9931	
	p-value	<0.0001	
Analysis description	**Secondary – Change in ALP from baseline to Week 18**		
Analysis population and time point description	Intention-to-Treat Timepoint: Baseline to Week 18		
Descriptive statistics and estimate variability	Treatment group	MRX Baseline	MRX Week 18
	Number of subjects	31	29
	Mean ALP (U/L)	601.3	580.8

	95% Confidence Interval	500.5 to 702.1	498.8 to 662.7
	Standard Deviation	274.77	215.50
Effect estimate per comparison	Mean Difference	-27.8	
	95% Confidence Interval	-72.8 to 17.2	
	Standard Deviation	118.33	
	p-value	0.2163	
Analysis description	**Secondary – Change in ALT from baseline to Week 18**		
Analysis population and time point description	Intention-to-Treat Timepoint: Baseline to Week 18		
Descriptive statistics and estimate variability	Treatment group	MRX Baseline	MRX Week 18
	Number of subjects	31	29
	Mean ALT (U/L)	181.0	177.4
	95% Confidence Interval	141.1 to 220.8	142.4 to 212.5
	Standard Deviation	108.56	92.08
Effect estimate per comparison	Mean Difference	-1.3	
	95% Confidence Interval	-33.4 to 30.9	
	Standard Deviation	84.54	
	p-value	0.9358	
Analysis description	**Secondary – Change in Total Bilirubin from Baseline to Week 18**		
Analysis population and time point description	Intention-to-Treat Timepoint: Baseline to Week 18		
Descriptive statistics and estimate variability	Treatment group	MRX Baseline	MRX Week 18
	Number of subjects	31	29
	Mean Total Bilirubin (mg/dL)	6.09	5.12
	95% Confidence Interval	3.97 to 8.21	3.09 to 7.15
	Standard Deviation	5.781	5.337
Effect estimate per comparison	Mean Difference	-0.47	
	95% Confidence Interval	-1.01 to 0.08	
	Standard Deviation	1.424	
	p-value	0.0893	
Analysis description	**Secondary - Change in Direct Bilirubin from Baseline to Week 18**		
Analysis population and time point description	Intention-to-Treat Timepoint: Baseline to Week 18		
Descriptive statistics and estimate variability	Treatment group	MRX Baseline	MRX Week 18
	Number of subjects	31	28

	Mean Direct Bilirubin (mg/dL)	4.57	3.98
	95% Confidence Interval	3.23 to 5.92	2.67 to 5.28
	Standard Deviation	3.666	3.369
Effect estimate per comparison	Mean Difference	-0.50	
	95% Confidence Interval	-0.90 to -0.11	
	Standard Deviation	1.012	
	p-value	0.0139	

2.6.5.3. Clinical studies in special populations

The key target population is children and the studies were conducted in the patients from 2 months to 17 years of age.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

See below

2.6.5.5. Supportive study(ies)

Detailed description of the study designs and key study characteristics of all studies relevant for efficacy is provided above.

Placebo-controlled studies – LUM001-301 and -302

Changes in sBA were selected as either primary efficacy endpoint (Studies LUM001-302) or secondary efficacy endpoint (Study LUM001-301) in all placebo-controlled studies, given the importance of sBA as an objective PD biomarker and its critical role in the pathogenesis of cholestasis and cholestatic clinical manifestations. Pruritus was also selected as clinical parameter as either the primary (LUM001-301) or key secondary endpoint (LUM001-302 and LUM001-304) in all placebo-controlled clinical studies in the programme. Assessment of pruritus was done by means of a specifically developed Clinical Outcome Assessment tool to assess pruritus in ALGS (ItchRO, versions for observer and for patients over 9 years of age) and a clinician scratch severity score (CSS).

Additional efficacy endpoints related to cholestatic liver disease in ALGS and representing the overall disease burden were also evaluated: xanthomas, growth impairment, and fatigue, serum markers of liver disease (bile acids, ALT, bilirubin, ALP). Impact on quality of life and fatigue were assessed by means of specific paediatric quality of life questionnaire (PedsQL, including fatigue dimension).

Because ALGS is a rare disease, the sample sizes for the clinical studies were determined for practical reasons, and no specific sample size calculation was performed. Main statistical analyses were prespecified in their respective study SAPs. A number of sensitivity analyses (pre-specified and post hoc were also conducted). The main population for efficacy was the mITT Population in all studies.

In the dose finding studies LUM301 and -302 it was defined as all subjects from the ITT Population receiving at least one dose of treatment and having at least one post-baseline efficacy assessment (Itch Reported Outcome (observer instrument) average daily score, or sBA, depending on the study).

In these studies the primary analyses of the primary efficacy endpoints - change from baseline to Endpoint (Week 13/ET) in pruritus as measured by ItchRO(Obs) or in mean sBA (in LUM301 and -302

respectively) - were based on an ANCOVA model with treatment and baseline average scores of the respective efficacy parameter as covariates.

Secondary and exploratory efficacy variables were analysed similarly to the primary efficacy analyses.

The following doses of maralixibat - 70 mg/kg, 140 µg/kg, 280 µg/kg once daily (QID) – were tested against placebo. In all cases, the drug was titrated very slowly, starting with 14 µg/kg/day and escalating up-to the respective targeted dose via the dose steps of 35 µg/kg/day, 70 µg/day and 140 µg/day (1 week per dose step). After titration of study medications treatment was kept stable.

No change in baseline therapies was allowed.

The entry criteria for the patients were similar to those in the main study.

Long-term extension studies – LUM001-305 and -303

Primary objective of these studies was to provide evidence of maintenance of effects and of safety of maralixibat on long-term treatment. Patients from the preceding -301 and 302 studies were enrolled. Statistical analysis and efficacy parameters remained the same as in the preceding studies. Doses of 280 µg/kg QD and BID was tested in these studies. Changes in concomitant medication were allowed.

Cross-study comparisons – Results

Populations included into the placebo-controlled studies were roughly similar at baseline.

Key efficacy outcomes across the studies is presented in the tables and figure below.

Table 13 Short-Term Efficacy in ALGS Studies – Change from Baseline on MRX

	LUM001-304[a] **(N=31)**	**LUM001-301[a]** **(N=25)**	**LUM001-302[a]** **(N=14)**
	Week 12	**Week 13/ET**	**Week 13/ET**
Parameter	Mean (SD)	LS Mean (SE)	LS Mean (SE)
Statistic[b]	p-value	p-value	p-value
sBA (µmol/L)	-107.91 (152.613)	-61.732 (23.9476)	-66.126 (33.1208)
	0.0007	0.0149	0.0644
ItchRO(Obs)	-1.555 (0.9615)[c]	-1.192 (0.1766)[d]	-0.610 (0.1776)[d]
	<0.0001	<0.0001	0.0037
ItchRO(Pt)	-2.085 (0.8909)[c]	-1.282 (0.2831)[d]	-0.883 (0.3484)[d]
	<0.0001	0.0003	0.0522
PedsQL Total Score	10.73 (16.237)[e]	8.432 (3.4646)	11.95 (3.103)
	0.0016	0.0216	0.0020
CSS	-1.6 (1.38)	-1.29 (0.026)	-0.48 (0.26)
	<0.0001	<0.0001	0.0858

ALGS=Alagille syndrome; CI=confidence interval; ET=end of treatment; ItchRO(Obs)=Itch Reported Outcome (Observer) (5-point questionnaire, where 0=none; 4=very severe pruritus; ItchRO(Pt)=Itch Reported Outcome (Patient); ITT=intent-to-treat; LS=least squares; PedsQL=Pediatric Quality of Life Inventory; sBA=serum bile acid; SD=standard deviation; SE=standard error of the mean.

Note: Change from baseline to Week 18 (Study LUM001-304) and to Week 13/ET (Studies LUM001-301 and LUM001-302).

[a] ITT Population for Study LUM001-304; Modified ITT Population for Studies LUM001-301 and -302; 70-280 µg/kg maralixibat doses.

[b] Mean (SD) is presented for LUM001-304 and LS Mean (SE) is presented for LUM001-301 and LUM001-302 based on available statistics for each study.

[c] Weekly average morning severity score.

[d] Weekly average (daily maximum) score.

[e] Results are from Week 18, the nearest time point to Week 12 where data was collected.

Largest effects in the short-term treatment were observed on 400 µg/kg/day dose of maralixibat. No statistically significant differences to placebo were observed on maralixibat in LUM001-301 and -302 for any of the parameters. Data from the LUM001-304 originate from run-in phase.

Table 14 Long-Term Efficacy - Change from Baseline to Week 48 – Overall Maralixibat

	LUM001-304[a] (N=31)	**LUM001-305[a] (N=34)**	**LUM001-303[a] (N=19)**
Parameter, Statistic	**Week 48/LOCF**	**Week 48/LOCF**	**Week 48**
sBA (µmol/L), mean (SD)	-96.44 (166.631)	-61.40 (144.799)	-94.40 (98.915)
	p=0.0058	p=0.0187	p=0.0012
ItchRO(Obs)[b], mean (SD)	-1.579 (1.3023)	-1.578 (0.9801)[c]	-1.095 (0.7173)
	p <0.0001	p <0.0001	p <0.0001
CSS, mean (SD)	-1.7 (1.31)	-1.6 (1.50)	-0.7 (0.99)
	p <0.0001	p <0.0001	p=0.0093
PedsQL Total, mean (SD)	8.40 (18.268)	9.20 (18.050)	11.48 (12.113)
	p=0.0196	p=0.0119	p=0.0018
Clinician Xanthoma Scale Score, mean (SD)	-0.4 (0.69)	-0.3 (0.53)	NA[d]
	p=0.0095	p=0.0046	
Total cholesterol (mg/dL), mean (SD)	-62.9 (107.08)	-35.3 (213.12)	-27.1 (34.19)
	p=0.0052	p=0.3412	p=0.0082
Height z-score, mean (SD)	0.192 (0.4976)	0.121 (0.3021)	0.248 (0.3887)
	p=0.0470	p=0.0254	p=0.0181
Weight z-score, mean (SD)	0.019 (0.4146)	0.075 (0.5343)	0.091 (0.5382)
	p=0.8020	p=0.4161	p=0.4979

CI=confidence interval; CSS=Clinician Scratch Scale; ET=end of treatment; ItchRO(Obs)=Itch Reported Outcome (Observer); ITT=intent-to-treat; LOCF=last observation carried forward; NA=not applicable; PedsQL=Pediatric Quality of Life Inventory; sBA=serum bile acids; SD=standard deviation.

Note: Comparisons are change from overall maralixibat Baseline to Week 48.

[b] ITT Population for Study LUM001-304; Safety Population for Studies LUM001-305 and -303.

Weekly average morning severity score.

Week 46/LOCF.

Only summary statistics are available (i.e., no change from baseline)

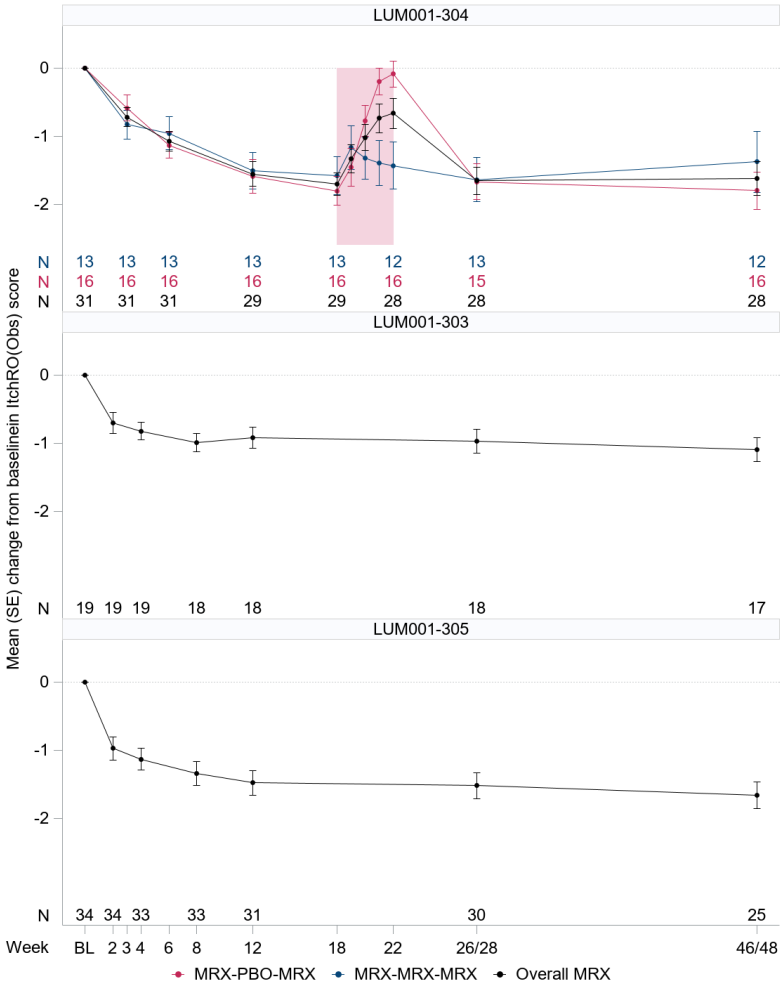


Figure 10 Comparisons of Mean (±SE) Change from Baseline in ItchRO(Obs) Weekly Average Morning Severity Score Over Time (Overall Population – Studies LUM001304, LUM001-303 and LUM001-305)

ItchRO(Obs)=Itch Reported Outcome (Observer); MRX=maralixibat; PBO=placebo; SE=standard error of the mean.

Week refers to the week within the listed study. The baseline refers to the last value prior to receiving MRX. For Study LUM001-304, the shaded area indicates the period during which study participants received either PBO or MRX; during all other treatment periods all study participants were treated with MRX. For Studies LUM001-303 and LUM001-305, participants who received MRX within studies LUM001-302 and LUM001-301 (respectively) have 13 additional weeks of exposure (the duration of 301/302 not shown) to MRX than the week listed.

Long-term observations showed maintenance of effects in majority of the parameters. Post hoc sensitivity analyses accounting for use of concomitant medications, drop-outs, confirmed that the effects on sBA and ItchRO(Obs) were maintained over long-treatment period of at least 2 years duration on 400 µg/kg/day dose in LUM001-304.

No relevant changes were observed in bilirubin or other liver parameters in overall population. Post hoc analysis in the small group of patients (N=15) from LUM001-304 with considerable sBA reduction showed improvement in the levels of bilirubin.

Comparison with external control (GALA)

A natural history comparison study was conducted to compare disease outcomes between 2 groups of patients with ALGS: 1) maralixibat treated study participants and 2) patients who are ASBTi naïve

from a natural history global clinical research database (GALA). The GALA clinical research database is recognised internationally by academic and tertiary referral liver transplant centres, with a high level of participation. The GALA clinical research database includes clinical and laboratory data as well as disease outcomes.

Long-term outcomes associated with maralixibat treatment were assessed by comparing event-free-survival (EFS) (composite endpoint of first event of liver decompensation [ascites, variceal bleeding], SBD, liver transplantation, and death) in maralixibat-treated participants with ALGS to a selected external control cohort of patients from the GALA clinical research database. The maralixibat clinical study data included in this natural-history comparison comprised the aggregated data from all maralixibat-treated participants from the long term maralixibat ALGS programme (N=84), with follow up data up to 6 years. GALA clinical research database controls were selected based on prespecified criteria similar to those from MRX studies. In addition, patient selection was limited to regions in which the maralixibat studies were conducted: North America, Europe, and Australia.

A patient may have been eligible with multiple visit time points. The best visit to represent baseline equal to the start of follow-up was aligned with maralixibat ALGS studies was selected by maximum likelihood methods. The balance between the maralixibat cohort and the GALA control group had to be established before selection was considered completed and before effects of treatment on the outcome events were described.

This natural-history comparison followed a prespecified SAP, and its primary analysis was the comparison of the time to first clinical event between the maralixibat-treated participants (maralixibat cohort) and the GALA control group.

Depiction of the time to first occurrence of events was performed with Kaplan-Meier survival curves. In addition, the HR estimate of the treatment comparison with 95% CI was calculated with Cox proportional hazards regression analysis that included age, sex, baseline bilirubin, baseline ALT, and treatment as factors. The appropriateness of the proportional hazards model was assessed.

Pre-specified and additional post-hoc sensitivity analyses of the primary analysis and subgroup analyses were conducted.

A total of 490 patients, with 3906 visits, were included in the analyses in the GALA control group. Baseline characteristics generally demonstrate balance between the maralixibat cohort and GALA control group, with no statistically significant imbalance in the baseline covariates. Importantly, bilirubin, GGT, and ALT were well balanced. Median sBA was higher in the maralixibat cohort; however, sBA data were limited in the GALA clinical research database (approximately 85% do not have sBA measures) since sBA are not sampled regularly on a clinical basis, often only at a single time point in some patients (at entry into the database), and not longitudinally.

Table 15 Distribution of First Event in the Maralixibat Cohort and GALA Control Group

	Maralixibat Cohort (N=84)	**GALA Control Group (N=469)**
Number of Events	21	163
Liver transplantation	10	110
Surgical biliary diversion	4	33[a]
Liver decompensation	3	5
Death	4[b]	15

GALA=**G**lobal **Al**agille **A**lliance.

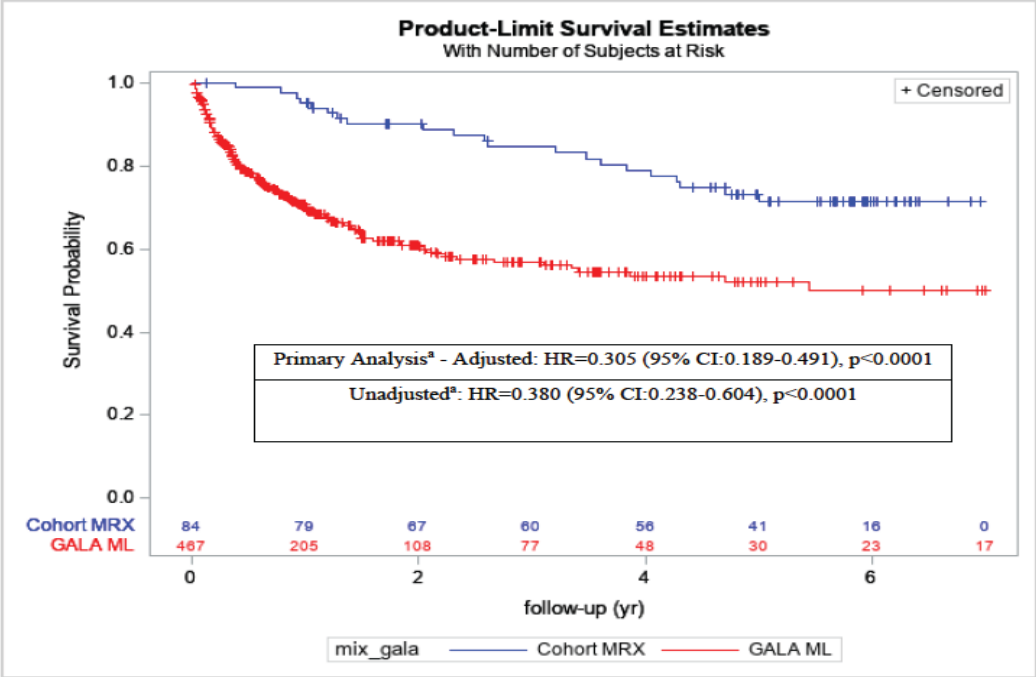
[a] Includes 1 patients with an event of Kasai procedure.

[b] Death information was collected from public records (deaths occurred at 2, 7, 9 months and 3.5 years after study discontinuation), no further information was available.

Reasons for liver transplantation and death were provided. There were 5 deaths reported in the maralixibat cohort; 1 related to liver disease (decompensation events of ascites and hepatic encephalopathy preceded death); the other 4 remain unknown as these participants had discontinued the study and the investigators were not able to obtain/provide the reason for death. Also, among the reasons for transplantation, a number of cases might not had been triggered by cholestasis/liver disease.

The time to clinical event (SBD, liver transplantation, liver decompensation, or death) in the maralixibat cohort was delayed compared with the GALA control group (Figure).

In the primary analysis (with adjustments for age, sex, bilirubin, and ALT), EFS was statistically significantly higher in the maralixibat cohort compared with the GALA control group (HR=0.305; 95% CI:0.189-0.491; p<0.0001), indicating a 70% improvement in EFS with maralixibat treatment.



GALA=Global ALagille Alliance; HR=hazard ratio; ML=maximum likelihood; MRX=maralixibat; SAP=statistical analysis plan; yr=year.
[a] Cox regression models:
Primary: Cox regression - effect of MRX vs. GALA log likelihood test adjusted for age, sex, bilirubin, and ALT (according to the SAP).
Unadjusted: crude model.
Source: Figure 14.2.1.

Figure 11 Kaplan-Meier Plot for Event-Free Survival –Maralixibat Cohort versus GALA Control Group: Primary Analysis

To consider the impact of different clinically meaningful parameters such as age, sex, serum levels of total bilirubin, ALT, GGT, region, and year of birth, Cox regression analyses were performed with adjustment for different combinations of these parameters.

The time to clinical events depends on the baseline definition. This can be defined as the first, last, or a random visit or date of birth. Sensitivity analyses using different baseline definitions (prespecified as well as post hoc) all confirmed that EFS in the maralixibat cohort was prolonged compared with the GALA control group.

Given potential differences in standard of care between regions and centres, subgroup analyses were conducted for specific regions, including North America, Europe, and Australia, to address any such differences. In addition, a subgroup analysis was conducted between overlapping centres. Results showed consistency with the primary result, suggesting that differences in standard of care did not have an impact on the result of improved EFS with maralixibat.

The immediate events in the GALA control group shown in the Kaplan-Meier curve may be suggestive of an immortal time bias. Pruning analyses for comparison of EFS that excluded patients who had events in the first 3, 6, or 12 months confirmed significant improvement in EFS with maralixibat treatment.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Initially, the target indication proposed for Livmarli was treatment of cholestatic liver disease in patients with Alagille syndrome (ALGS) 1 year of age and older. To support this indication 6 study reports (5 from completed clinical studies and one from historical comparison) were submitted, including the data from 86 patients with ALGS of 1-17 years of age and body weight of under 50 kg. The efficacy database is, thus, very limited. Additionally, few data in children who reached adult status and weight over 50 kg were submitted. Given the rarity of the disease limited size of the population is however acceptable.

Key evidence on efficacy has been provided from the pivotal phase 2 long-term Study LUM001-304. Supportive evidence is derived from two phase 2 clinical dose-finding studies (LUM001-301 and LUM001-302) and their open-label (OL) long-term follow-up studies (LUM001-303 and LUM001-305). Additionally comparative analysis of long-term observations from the above clinical studies in ALGS and the natural history data from an external GALA clinical research database (GALA-MRX-ALGS) has been submitted, as well as few safety data from the EAP and children below age of 1 year as a support of the proposed starting dose of 200 µg/kg QD.

Studies LUM001-301 and -302 were similar studies testing the 70 µg/kg/day (only in LUM001-301), 140µg/kg/day and 280 µg/kg/day QD doses of maralixibat in the ALGS patients. In the LUM001-304 (core study) currently proposed therapeutic dose of 400 µg/kg/day QD maralixibat was applied.

The positive feature of the LUM001-304, -301 and -302 studies is that these were double-blind, randomised, multicentre, placebo-controlled studies in the population that can be considered representative of the target indication. LUM001-301 and -302 had a parallel-arm design with the duration of 13 weeks, whereas key efficacy evidence (on the therapeutic dose of 400 µg/kg/day) was collected in the LUM001-304 during an 18 weeks-long active run-in followed by a 4-week long randomised withdrawal phase. Generally, parallel-group design is preferable to a randomised withdrawal design, as the latter does not allow for usual comparison of efficacy between treatments, extrapolation of the treatment effects to the general population is difficult, as analyses is usually limited to the "enriched" population, and as unblinding and carry over effects may confound the study outcomes. In the case of LUM001-304, the risk of carry-over is regarded negligible, given the quick removal of maralixibat from the body and its local mode of action. All patients completing the run-in phase were subjected to randomised withdrawal and only 2 patients were excluded from the efficacy analysis (ITT), which suggests that the tested population remained not enriched.

Duration of all 3 studies was short (max 13 weeks), so that the data allow to evaluate only short-term effects of maralixibat. Notably, double-blind phase of the LUM001-304 study was 4 weeks long only, that is too short to draw conclusions on the maintenance of "withdrawal" effects over prolonged time

period. This is considered a limiting factor in the assessment of the drug efficacy, as the RWD phase is the only phase in the presented clinical development programme providing placebo comparison for the proposed therapeutic dose of maralixibat.

All 3 placebo-controlled studies were small in size and planned without sample size calculation. This is not surprising, given the rarity of the disease. Overall, all 3 studies are regarded as exploratory and adequate studies for testing proof of concept and short-term maralixibat effects, but not to provide confirmatory evidence on efficacy for the initially targeted indication treatment of cholestatic liver disease in patients with Alagille syndrome.

Efficacy assessment was focused on evaluating maralixibat effects on sBA, pruritus, liver enzymes and bilirubin, xanthomas, growth, and quality of life. All efficacy parameters are regarded relevant and are accepted. However, key parameters are sBA and pruritus, given the finally targeted indication of cholestatic pruritus. sBA is the key PD parameter for maralixibat and is assumed to play a key role in the pathogenesis of the disease, in the development of pruritus, as well as progressive liver impairment. Pruritus is one of the main, most burdensome and difficult to manage symptoms of ALGS, that commonly requires surgical treatment (including liver transplantation). These 2 parameters were chosen as a primary or secondary endpoints in all studies to test short and long-term efficacy of the drug. There is a link between the effects on sBA and effects on cholestatic pruritus. Consequently, reductions in sBA, if these are accompanied with improvement in pruritus, can be regarded supportive.

Maintenance of effects and the long-term treatment effects were evaluated in the long-term open label single arm settings of the extension phase of LUM001-304 and extension studies to LUM001-301 and -302 - LUM001-303 and LUM001-305 - over a time period of up-to 6 years. In these studies also dose escalation up-to 400 µg/kg/day (follow-up phase of LUM-001-304) was also allowed. Overall, duration of the long-term studies is considered adequate to characterise maintenance of effects. However, interpretation especially of subjective parameters as pruritis is difficult in the absence of a placebo control and presence of multiple confounders.

For the initially targeted indication, “treatment of cholestatic liver disease”, ultimate long-term objective of prevention or delay of development of liver impairment, and of surgical interventions, such as biliary diversion procedure or liver transplantation due to intractable pruritus or progressed liver impairment, on treatment with maralixibat would be expected. It was hypothesised, that these effects are possible if stable and clinically relevant suppression of sBA levels and improvement in pruritus can be achieved. Due to the absence of an internal long-term control arm, the applicant conducted a comparison with an external historical control, that contains the patients from an ALGS registry (GALA). The efficacy of maralixibat on the clinically relevant hard endpoints was assessed by comparing event free survival (EFS) (composite endpoint of first event of liver decompensation [ascites, variceal bleeding], SBD, liver transplantation, and death) in maralixibat-treated patients against the external control patients from the GALA clinical research database. A prospective, pre-specified SAP was generated before patient selection or analysis was initiated.

Generally, comparisons against historical control are considered problematic. There is an inherent risk to natural history comparisons that certain unknown factors may have contributed to the results and could not be taken into consideration in the analysis. In addition, comparisons with external controls are susceptible to selection bias, which can unlikely be fully accounted for. Most importantly, presence of data on sBA was apparently not the major inclusion criterion. In the absence of the baseline information on sBA (i.e., the key PD parameter and the pathophysiological factor in ALGS progression), assessment of comparability of the patient cohorts is not possible and differences in the treatment effects cannot be assigned to changes in this parameter.

Overall, to summarise, there was a number of relevant uncertainties detected in the methodology, which limited the value of the external comparison as supportive evidence for the claimed indication (see below).

With the response to the Day180 AR the applicant proposed to adapt the indication to "treatment of cholestasis in patients with Alagille syndrome (ALGS) 2 months of age and older". However, no pivotal new data have been submitted to substantiate the indication of "cholestasis". Basically, some of the data, which were presented previously in >1 years old, had been picked and summarised as new (sBA, cholesterol, LDL-cholesterol, xanthomas, pruritus, fatigue, z-score for growth), whereas others, not less relevant tests (e.g., direct bilirubin, liver function tests), had been disregarded. Also, sensitivity analyses were presented accounting for confounders (e.g., concomitant treatments, concomitant conditions, drop-outs, etc.).

In agreement with the applicant the indication was further adapted to "treatment of cholestatic pruritus in patients with ALGS".

To support the extension of the indication to infants, interim short-term treatment data (up-to week 13) on CSS and sBA in 8 patients (age 2 months and older) from an ongoing open-label study MRX-801 have been presented. These data have exploratory character and are considered limited. However, based on similar effects on sBA and pruritus in the older population extrapolation to the youngest population was accepted.

Efficacy data and additional analyses

Dose-finding and the proposed dosing regimen

The proposed dosing regimen is a starting dose of 200 µg/kg maralixibat (190 µg/kg free base) once daily, followed by 400 µg/kg (380 µg/kg free base) once daily after 1 week. The maximum dose to be applied is 28.5 mg maralixibat (base) QD per day, calculated as 380 µg/kg/day maralixibat (base) or the equivalent 400 µg/kg/day maralixibat chloride for a 70 kg person. Intake of the medication is recommended up-to 30 min prior to and during a meal, orally.

The doses of 70 µg/kg/day (only in LUM001-301), 140µg/kg/day and 280 µg/kg/day were tested in the parallel-group studies LUM001-301 and -302 and showed inconsistent and partly inverse dose-response relationship.

The applicant conducted an exploratory dose-response analysis, that did show difference to placebo in terms of treatment effects on sBA, but no clear dose-response relationship was observed. Although the conducted analysis was considered somewhat flawed, as known confounders such as the changes in the relevant concomitant treatment, were not considered, the proposed dose regimen was accepted based on its use in the study LUM001-304.

Weight-based dosing is based on the assumption, that increased length of intestines translates into higher number of the target receptors for maralixibat in the gut. As the length of the intestines increases with age (up-to the adulthood) and height, and, since height and weight in children correlate, the applicant considers weight-based dosing plausible and appropriate. This rationale cannot be fully supported, as due to the lack of information (e.g., on correlation of the number of targeted receptors with the length of bowels in ALGS, correlation of height and weight with the length of intestines in ALGS) no proper assessment can be made. Moreover, high variability of up-to 100% has been reported in the length of the intestines in the same-aged/same-height population. Considering the above, individual dose-selection, based on efficacy and tolerability in individual patients, may be more reasonable approach in this patient population. However, given that the key data on efficacy are collected with 400 µg/kg/day and limited evidence has been collected on lower doses, 400 µg/kg/day appears acceptable as a therapeutic dose.

There is uncertainty around the adequacy of the proposed dosing in the infants, given the non-linear character of the growth of intestines in children below the age of 1 year. However, low systemic exposure reported in study MRX-801 is reassuring in terms of potential systemic off-target effects.

For the cases of poor tolerability, temporary reduction of dose, or treatment interruption has been recommended in the SmPC, which is agreed

In contrast to the slow titration regimen with low starting dose of 35 µg/kg/day in the studies, a two-step titration scheme starting with 200 µg/kg/day dose is being proposed, based on the experience in 37 patients (including 34 maralixibat naïve subjects) from the ongoing EAP, which showed good tolerability of this starting dose and fast titration regimen. The same dosing regimen has also been tested in infants with acceptable tolerability. It can be agreed that the data suggest overall good tolerability of the 200 µg/kg/day maralixibat as a starting dose.

It is agreed that 800µg/kg/day dose should not be recommended as a therapeutic dose, as there is very limited evidence supporting this dose and that an increased number of abdominal pain, vomiting and diarrhoea were reported on the 800 µg/kg/day regimen compared to 400 µg/kg/day. Also, pronounced and gradual elevation of mean ALT was observed with 800 µg/kg/day. In conclusion, dose-finding has not been comprehensively done, but the presented data allow to conclude, that the proposed dosing regimen is overall acceptable.

Evidence of efficacy – short-term effects (LUM001-301, -302 and run-in and RWD phases of the LUM001 -304)

Based on the presented evidence the following conclusions can be made:

The double-blind study LUM001-301 was formally a failed study that failed to demonstrate statistically significant effects in the primary evaluation, change from baseline in pruritus (scores of ItchRO(Obs)). However, the results indicate activity of the compound based on the numerical differences observed, especially with regard to the changes in itch scores and quality of life. These results are somewhat questioned with a paradoxical inverse dose-response relationship favoring the lowest doses used. Contrary to the itch and QoL scales, no relevant changes were detected for the changes in bile acids (as well as other liver markers), and the inverse dose-response is also seen for this parameter.

The explorative study LUM001-302 did also not meet its primary endpoint, the change in sBA and the high dose did not show a clinically relevant effect, while reduction of sBA compared to placebo was seen in the lower dose group. The changes induced for the secondary endpoint "itch" did not show overall statistically significant effects, and also an inverse dose-response relationship. A combined analysis of itch- and sBA-based responses, however, showed higher responder rates for the active treatment groups, especially when the most stringent response criterion was chosen. The evaluation of Quality of Life demonstrated effects of the active treatment over placebo, which was again, more pronounced in the low-dose treatment group.

The main study LUM001-304 studied the proposed 400 µg/kg/day maralixibat dose in the target population against placebo, although in a randomised withdrawal (RWD) setting with only a short (4-week) placebo-controlled phase. The primary endpoint was analysed in the mITT population (defined as patients with at least 50% reduction in sBA at weeks 12 or 18 in the run-in phase as compared to the baseline at enrollment). The study was – in conjunction with the supportive studies – finally found to provide sufficient evidence for the ability of the compound to reduce sBAs and symptoms of cholestasis.

Overall, the study population was heterogeneous, but relatively balanced across the treatment arms in respect to the baseline at the study entry. In regards to the baseline prior to the RWD phase, the treatment groups differed. However, post hoc sensitivity analyses with adapted baseline prior to the

RWD showed statistically significant changes on each treatment indicating clear differentiation between treatment effects. Further, normal or only slightly elevated levels of sBA (below the level of 100 µmol/L, e.g. 20.2 µmol/L) and bilirubin were reported in about 30% of the study population at enrollment. Potential impact of these mild cases on study outcomes remains unclear.

Overall, it can be agreed, that the study population is representative of the general population with ALGS. Overall, the study was a "positive" study as, after randomised withdrawal, patients on maralixibat maintained their reduction in sBA and pruritus (ItchRO(Obs and Pt) and CSS), whereas worsening was observed on placebo with parameters almost returning to the baseline levels. Restart of maralixibat treatment in the placebo population again lead to improvement in these parameters. Similar changes on MRX vs placebo were observed for other parameters, such as cholesterol, LDL-cholesterol, and fatigue. Positive effects were maintained up-to the week 48. Sensitivity analyses provided by the applicant to account for the high variability in sBA values, use of concomitant treatments, presence of concomitant conditions, drop-outs up-to week 48, yielded results for sBA, pruritus (ItchRO(Obs)), cholesterol, and xanthomas that were consistent with the main analyses and can be considered reassuring. These data are convincing.

In the study MRX-801, limited efficacy data in 8 infants with ALGS of age of 2 to 10 months have been collected. The data suggest that 2 of 8 patients showed positive effects of MRX such as decrease in sBA and pruritus (as assessed with CSS). In one patient these were accompanied by improvements in liver function tests (e.g., ALT, total bilirubin). Limitation of this study is lack of a comparator and very small sample. However, in the vulnerable population included no study with placebo control would be deemed ethical. Also, the small size of the population is justified, given the rarity of the disease. Since reduction in sBA was accompanied with improvement in pruritus in the "responder" patients, and effects of MRX on sBA are considered established in older ALGS population, extrapolation of placebo-controlled data on pruritus to infants with ALGS is considered acceptable.

Long-term treatment and maintenance of effects

Maintenance of effects and long-term treatment effects were characterised in the OLE of the LUM001-304 study, in the study LUM001-305, that was the extension of LUM001-301 and in LUM001-303, that was the extension of LUM001-302 study.

Key parameters sBA and ItchRO(Obs) showed maintained effects over prolonged (over 5 years) duration of time, but the data are burdened with multiple confounders (high fluctuations in sBA, use of concomitant treatment, dose escalation to non-therapeutic dose of 800 µg/kg/day). Furthermore, only a minor proportion of the patients completed the single arm, open label long term follow-up, which further introduces uncertainties to the long-term effect. The applicant has presented sensitivity analyses utilizing various imputation methods to account for the drop-outs, use of concomitant treatments, fluctuations in the sBA. These analyses, all point towards maintenance of effects on sBA and ItchRO(Obs) during the first 1 and 2 years of treatment (that excludes the data on escalated dose) in one part of the treated population. These data are sufficiently convincing to support the claim of long-term treatment effects on these two parameters. Seen in the light of the above-mentioned methodological issues, uncertainties still remain with regards to the maintenance of effect. Further effectiveness data will be gathered post-authorisation by means of a long-term safety and clinical outcomes study that is made specific obligation of this marketing authorisation. Furthermore, the applicant has agreed to collect full 1-year treatment data in infants with ALGS (MRX-801 study). The patients will be advised to continue treatment in the study for at least 1 year instead of switching to compassionate use programs, or to commercial product once the commercial product becomes available on the market. Further, the company will submit the final report of the MRX-800 study by end of 2023 as stated in the RMP which will provide additional evidence of efficacy.

There was no change in liver function tests overall in the studies, all of which were pathologically elevated at baseline. This sheds doubt on the benefits of the treatment with regard to the preservation of liver function in the long-term. Thus, the data do not support the claim of "treatment of cholestasis", but they are considered sufficient to substantiate the indication "treatment of cholestatic pruritus". No long-term data exist on pruritus in the infant ALGS population. However, there is no reason to believe, that maintenance of effect would differ from that in older children.

Long-term treatment effects – clinically relevant hard endpoints (comparison vs. external control)

When regarding the survival analysis against an external control (GALA cohort), at first sight, the selected external cohort appears to be roughly similar to the maralixibat cohort. However, only 73 patients from GALA database had sBA available in the external control chosen and baseline values of sBA in this small control group differed significantly from the maralixibat cohort (p=0.003). As the positive effects of maralixibat on sBA (and ALGS) are hypothesised to result in long-term clinically relevant benefits on hard clinical endpoints giving proof of a disease modifying effect, presence of baseline information on sBA to gain some assurance on the adequacy and comparability of the selected external patient cohort, would be considered necessary. Value of the survival analysis (including multiple sensitivity analyses) in the total population of 469 patients from GALA is therefore questioned.

Further, from the methodological perspective comparison with the GALA population is considered problematic. The selection mechanisms for including patients in a clinical trial and a patient registry are fundamentally different, and there are serious doubts that this can be compensated by accounting for confounders by adjustment or matching based on the information available in the registry as the assumption of no unmeasured confounding is unlikely to be fulfilled.

Although it is reassuring that 65% of GALA patients were initially diagnosed at participating centres, there is still potential that the remaining patients were referred to the centres due to worsening of disease. The exact reasons for transfer are not available.

Follow-up of patients from GALA was considerably shorter than for MRX-treated patients although the applicant claims that GALA patients had similar year for index time. The reasons are not entirely clear. Thus, there is a concern of bias due to differential drop-out and potential informative censoring. Balance regarding confounding factors at index date would be of questionable relevance when balance was lost soon after index date because of differential drop-out.

Regarding the management of patients, no detailed information is available on concurrent therapies in GALA. It is agreed with the applicant that comparison restricted to centres contributing to GALA and MRX studies is of particular importance because these can be assumed to use the same standards. However, this comparison was not adjusted for centre because of small sample sizes per centre. Furthermore, as the applicant claims that patients selected as controls from the GALA registry and patients treated with MRX were at the same age, diagnosed during the same years and were aimed to be balanced regarding baseline characteristics, the question arises why some patients in these centres were included in the MRX studies while others were not, i.e. there is potential for residual confounding.

The applicant acknowledges that individuals in the GALA control group for whom providers might anticipate that transplant/surgical biliary diversion/death is inevitable and imminent would not be included in clinical studies; despite having comparable baseline disease characteristics, these individuals theoretically could be sicker or have other factors than the treated cohort at baseline and would present an opportunity for residual confounding of disease severity. However, that means, in other words, that patients in GALA may not have comparable baseline characteristics but there may be factors influencing the risk of an EFS event that are not captured. The applicant argues that pruning analysis, which exclude events and person-time up to 12 months from the index time, substantially mitigate this concern. This is not agreed. The likely existence of strong confounding factors that are

not captured is of concern and such factors may still influence the event risk after one year; the size of their influence can hardly be quantified. In addition, selection due to the occurrence of events and differential drop-out during the first 12 months may take place such that the baseline balance regarding confounding factors between the overall groups may not be given for the subgroups of patients that are event-free for at least one year.

To summarise, due to the above listed limitations, the comparison to external controls cannot be accepted as pivotal evidence of efficacy to support the indication of "cholestatic liver disease". However, this is not regarded critical, since the indication is no longer pursued and is restricted to "cholestatic pruritus" for which sufficient evidence has been provided by the clinical studies conducted.

Additional efficacy data needed in the context of a MA under exceptional circumstances

The evidence of efficacy is mainly based on a small, single, mostly uncontrolled, open-label trial with a 4-week randomised placebo-controlled withdrawal phase in patients 1 year and older and on short-term and open-label data on sBA and pruritus as well as on a limited set of data in infants ≥ 2 months of age. In consequence, the treatment effect was demonstrated in a relatively small sample size and its precision is therefore naturally low. The absence of a placebo-control for most of the observation period further adds uncertainties to the true effect size. The maintenance of effect has been shown up-to week 48, which can be considered sufficient to estimate long-term efficacy. However, absence of placebo control specifically for the subjective and variable symptom of pruritus is acknowledged as limitation. Whilst the mechanism of action of the product is clearly described, it remains unclear whether the proposed dosing regimen is optimal. Nevertheless, the effect on sBA and pruritus are sufficiently large to conclude on a relevant benefit, and endpoints are considered to be clinically meaningful, as these capture various aspects of the burden of cholestatic pruritus on the affected patients.

Whilst the benefit risk of the product can be considered acceptable within a marketing authorisation under exceptional circumstances (see Benefit risk discussion at the end of the report) above, uncertainties need to be balanced by means of the provision of further data post authorisation. Accordingly, the applicant will provide further data on long term effectiveness (and safety) of the product from a prospective long-term safety and clinical outcomes study (LEAP study). The study will, from the efficacy side, monitor maintenance of effect. Furthermore, the applicant will provide yearly updates on any new emerging efficacy and safety information becoming available under the scope of the annual reassessment.

2.6.7. Conclusions on the clinical efficacy

The currently submitted data package is sufficient to substantiate the targeted indication "treatment of cholestatic pruritus" since effects on sBA and pruritus are sufficiently convincing based on the pivotal study 304, supported by several open-label studies.

Extrapolation of efficacy from children >1 years to infants > 2 and to 12 months is accepted, mainly based on the PD marker sBA. However, the available data in infants is currently very limited and additional data on safety, but also efficacy in the post-authorisation phase, is required. This can be provided in post-approval phase via a specific obligation (SOB), which is the mandatory condition for the applications under exceptional circumstances. The applicant will conduct and submit the results of a safety and clinical outcomes registry-based study in patients with ALGS according to an agreed protocol. Furthermore, the applicant will submit yearly updates on any new information concerning the

safety and efficacy of maralixibat, both requirements are made specific obligations to this MA under exceptional circumstances.

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

Description	Due date
In order to further characterise the long-term safety and efficacy of maralixibat in the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS), the MAH shall conduct and submit the results of study LEAP (MRX-310) according to an agreed protocol.	Annual (within annual reassessment)
In order to ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with Alagille syndrome (ALGS), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of maralixibat.	Annual (within annual re-assessment)

2.6.8. Clinical safety

Clinical safety for maralixibat in the applied target population with Alagille syndrome (ALGS) is primarily based on an analysis of safety data from the five studies in paediatric participants with ALGS (LUM001-301, -302, -303, -304, -305). Additional preliminary data are provided from the ongoing study in children less than 1 year of age (MRX-801; N=6) and from an Early Access Programme EAP (N=37) in ALGS. The latter are briefly described in the efficacy section of this report.

However, data from Study LUM001-304 is proposed as the main source for pivotal safety data.

The other safety data can be seen as more or less supportive in the applied indication considering the underlying relatively similar underlying diseases and the claimed mode of action.

A short overview about the trial relevant for safety assessment is here provided:

- Studies LUM001-301 and LUM001-302 were short term RCTs (13-week, randomised, placebo-controlled, phase 2 studies) in ALGS subjects
- Studies LUM001-305 and LUM001-303 are optional long-term treatment extension studies to the LUM001-301 and LUM001-302 studies, respectively, also in ALGS subjects.

However, the latter 4 studies used lower doses of maralixibat than the proposed therapeutic dose of 400 µg/kg once daily, since in these Phase 2 studies, participants underwent a dose-escalation period to reach their target dose.

The applied posology was investigated in the pivotal Study LUM001-304, a randomised, placebo-controlled, 4-week drug-withdrawal study with an open-label, long-term extension, which assessed the efficacy and safety of maralixibat at higher doses. In addition, preliminary safety information from the ongoing study MRX-801 in children less than 1 year of age treated with the proposed dosing regimen (including titration scheme and the therapeutic dose) have been made available with day 180 response.

The following table provides an overview about the trials and their design:

Table 16 Overview of Safety is on 5 completed studies in the ALGS programme

Study Identifier/ Type of Study	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Population /Number of Subjects	Duration of Treatment
LUM001-304 **Pivotal for Efficacy**	Efficacy, safety and tolerability, PK	Randomised, placebo-controlled, drug-withdrawal study with an open label extension	Maralixibat: 400 µg/kg once daily AM During RWD phase:400 µg/kg once daily or Placebo 400 µg/kg once or twice daily after Week 100 Oral	31 Paediatric patients with ALGS During RWD: Maralixibat n=13 Placebo n=16	Up to 5 years Complete Interim (data cut-off 01 Dec 2019)
LUM001-301 **Supportiv for Efficacy**	Efficacy, safety and tolerability	Randomised, double-blind, placebo controlled, parallel	Maralixibat 70, 140, 280 µg/kg once daily or placebo Oral	37 Paediatric patients with ALGS Maralixibat n=25	13 weeks Complete; Full
LUM001-305 **(Extension trial to 301)**	Safety and tolerability, efficacy	Extension to Study LUM001-301	Maralixibat: Up to 280 µg/kg once daily Oral	34 Paediatric patients with ALGS	Over 4 years Complete; Interim(data cut-off 01 Dec 2019)
LUM001-302	Safety and tolerability, efficacy	Randomised, double-blind, placebo controlled	Maralixibat 140, 280 µg/kg once daily or placebo Oral	20 Paediatric patients with ALGS Maralixibat n=14	13 weeks Complete; Full
LUM001-303	Safety and tolerability, efficacy	Extension to Study LUM001-302	Maralixibat: 280 µg/kg once daily	19 Paediatric patients with ALGS	Approx. 5 years Complete;

Study Identifier/ Type of Study	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Population /Number of Subjects	Duration of Treatment
(Extension trial to 301)			Up to 280 µg/kg twice daily in long-term extension		Interim (data cut-off 01 Dec 2019)
MRX – 801 ***(RISE)***	Safety and tolerability	Open-label	Maralixibat: 200 µg/kg/day (QD) one week followed with 400 µg/kg/day (QD)	8 Patients with ALGS All <1 y.o.	Ongoing (Interim data cut-off April 2022)

Non-clinical trials have identified the following safety issues:

Nonclinical as well as clinical PK data demonstrate that maralixibat is only minimally absorbed after oral administration, is metabolically stable *in vivo*, excreted almost exclusively in the faeces as intact parent drug, and shows low potential for drug-drug interactions.

Prolongation of coagulation times (rat) and emesis (dog) at doses significantly higher than doses required for therapeutic effect in humans, probably due to vitamin K deficiency is noted.

The applicant concludes from the animal data that emesis and vitamin K deficiency are not significant hazards in humans at therapeutic dose levels.

Moreover, it is correctly argued that dogs are known to be particularly susceptible to emesis, potentially contributing to apparent disconnect between those findings in dogs and the clinical experience with maralixibat.

Relatively higher bioavailability (approximately 17%) was seen in the rat juvenile toxicity study testing the youngest pups as further detailed in the non-clinical part of this AR and as likely due to the known extreme immaturity of the rodent GI tract in neonatal pups.

The applicant considers the possibility that absorption could be higher in the youngest human patients based on juvenile animal toxicity studies.

2.6.8.1. Patient exposure

The following table presents an overview of the general characteristics of TEAEs and safety relevant events in the applied ALGS Safety Population during the pivotal study:

Table 17 Adverse Events – Pivotal Study LUM001-304

Open-Label Treatment Week ≤18						
	MRX 400 µg/kg/day (N=31)					
Category	**n (%)**		**EAIR**			
Participants with at least 1 adverse event	30 (96.8)		0.8			
Adverse event potentially related to study drug a	12 (38.7)		0.3			
Serious adverse event	4 (12.9)		0.1			
Serious adverse event potentially related to study drug a	**0**					
Randomised Withdrawal (Weeks >18 to 22)						
	n (%)	**EAIR**	**n (%)**	**EAIR**		
Participants with at least 1 adverse event	7 (53.8)	0.2	12 (75.0)	0.5		
Adverse event potentially related to study drug a	1 (7.7)	0.0	3 (18.8)	0.1		
Serious adverse event	1 (7.7)	0.0	1 (6.3)	0.0		
Serious adverse event potentially related to study drug a	0		0			
Open-Label Treatment Week >22						
	MRX 400 µg/kg/day (N=14)		**MRX >400 µg/kg/day (N=15)**		**Overall MRX (N=29)**	
	n (%)	**EAIR**	**n (%)**	**EAIR**	**n (%)**	**EAIR**
Participants with at least 1 adverse event	**14 (100.0)**	**0.4**	**15 (100.0)**	**0.7**	**29 (100.0)**	**1.2**
Adverse event potentially related to study drug a	**2 (14.3)**	**0.1**	**7 (46.7)**	**0.3**	**9 (31.0)**	**0.4**
Serious adverse event	**5 (35.7)**	**0.1**	**5 (33.3)**	**0.2**	**10 (34.5)**	**0.4**
Serious adverse event potentially related to study drug a	0		0		0	
Source: ISS Table 2.1.1.2 and Table 2.1.1.5						

AE=adverse event; EAIR=exposure-adjusted incidence rate; MRX=maralixibat; n=number in a given category; N=number of participants.

Note: Percentages are 100*n/N. Treatment groups are based on the highest dose (µg/kg/day) received during the analysis period. EAIR is estimated by the number of participants experiencing the AE divided by the population-level time at risk in patient-years.

Any AE determined as possibly related or related, or is missing, is considered as potentially related to study drug.

The applicant has provided additional more comprehensible information regarding exposure of study participants from the ALGS population exposed with the proposed posology (400 µg/kg/day) with the response to the D120 list of questions. According to the results it can be confirmed that during the clinical trial (most importantly LUM001-304) the study participants were sufficiently exposed to the proposed posology (400 µg/kg/day) with an average duration of 536.6 days to allow adequate conclusion on safety outcome.

In addition, it is acknowledged that all participants were additionally exposed to lower doses during dose escalations and dose reductions due to AEs for between 35 and 463 days, with an average of 156.9 days. Also, the proposed dosing regimen (200 µg/kg/day QD 1 week followed with 400 µg/kg/day QD) is currently being tested in the MRX-801 study in the patients older than 1-12 months of age.

In summary, exposure safety data presented seems to reflect reliably the tolerability of maralixibat in the limited number of patients in the target population.

2.6.8.2. Adverse events

It is reported that across the studies in the ALGS integrated population, including participants exposed to maralixibat and placebo, events of diarrhoea, vomiting and abdominal pain were the most commonly reported AEs. This is in accordance with that noted in animals and can be explained by maralixibat's mechanism of action.

In pivotal Study LUM001-304 events of diarrhoea and abdominal pain were reported in up to 41.9% and 41.4% (based on the period of the study) of participants exposed to maralixibat, respectively. During the RWD period of Study LUM001-304, those events occurred in 1 participant each in the maralixibat (7.7%) and placebo (6.3%) groups.

In the 13-week, placebo-controlled studies (LUM001-301 and LUM001-302), events of diarrhoea were reported in 43.6% vs. 44.4% of participants from the overall maralixibat group and placebo group, respectively, whereas events of abdominal pain were reported in 25.6% vs. 16.7%, respectively. The majority of these events were mild to moderate in severity, transient in nature, and resolved with no action taken with maralixibat.

In Study MRX-801 in infants, the most frequent TEAEs were nasopharyngitis (50.0%) and abdominal pain, diarrhoea, teething, and pyrexia (37.5% each). Overall, 7 participants with ALGS (87.5%) had at least 1 treatment-emergent adverse event (TEAE), 2 participants (25.0%) had a TEAE related to study drug, and 4 participants (50.0%) had a Grade ≥3 TEAE. Grade ≥3 TEAEs were diarrhoea, Infantile colic, pyrexia, crying, Corona virus infection, Varicella, virus infection. One patient had 2 TEAEs related to laboratory abnormalities (ALT increased, and AST increased); both were Grade 1 in severity and not related to the study drug. Causal relationship of these events to treatment with MRX is difficult to establish.

No AE led to MRX discontinuation as of the data cutoff.

Most common TEAES

The most common TEAEs (using a threshold of > 10%) observed across the entire maralixibat programme (PFIC and ALGS) were from the SOCs of GI disorders, general disorders and administration site conditions, and infections and infestations.

The following preferred terms were reported as most common TEAEs (> 10% overall) in every study (derived from ISS Tables 2.1.1.4-2.1.1.6):

- Abdominal pain
- Cough
- Diarrhoea
- Headache
- Nasopharyngitis
- Pyrexia
- Upper respiratory tract infection
- Vomiting

Details of the TEAEs are shown in the following table:

Table 18 Incidence of Common (> 10%) Treatment-Emergent Adverse Events with Maralixibat – Study LUM001-304 – ALGS-Population

Open-Label Treatment ≤ Week 18		
System Organ Class[a] **Preferred Term**	**MRX 400 µg/kg/day** **(N=31)**	
	n (%)	
Participants with at Least 1 Common TEAE	25 (80.6%)	
Gastrointestinal disorders Diarrhoea Abdominal pain	21 (67.7%) 13 (41.9%) 12 (38.7%)	
General disorders and administration site conditions	6 (19.4%)	
Infections and infestations Upper respiratory tract infection	11 (35.5%) 6 (19.4%)	
Injury, poisoning and procedural complications	5 (16.1%)	
Nervous system disorders	5 (16.1%)	
Randomised Withdrawal (Weeks > 18 to 22)		
	MRX 400 µg/kg/day **(N=13)**	**Placebo** **(N=16)**
	n (%)	**n (%)**
Participants with at Least 1 Common TEAE	5 (38.5%)	10 (62.5%)

General disorders and administration site conditions	0	2 (12.5%)
Infections and infestations	4 (30.8%)	2 (12.5%)

System Organ Class **Preferred Term**	**Open-Label Treatment > Week 22**		
	MRX **400 µg/kg/day**	**MRX** **> 400 µg/kg/day**	**Overall MRX (N=29)**
	n (%)	**n (%)**	**n (%)**
Participants with at Least 1 Common TEAE	13 (92.9%)	15 (100.0%)	28 (96.6%)
Gastrointestinal disorders	8 (57.1%)	12 (80.0%)	20 (69.0%)
Abdominal pain	2 (14.3%)	10 (66.7%)	12 (41.4%)
General disorders and administration site conditions	5 (35.7%)	9 (60.0%)	14 (48.3%)
Infections and infestations	8 (57.1%)	13 (86.7%)	21 (72.4%)
Nasopharyngitis	2 (14.3%)	8 (53.3%)	10 (34.5%)
Ear infection	1 (7.1%)	7 (46.7%)	8 (27.6%)
[illegible]	[illegible]	[illegible]	[illegible]
Injury, poisoning and procedural complications	2 (14.3%)	1 (6.7%)	3 (10.3%)
Nervous system disorders	1 (7.1%)	5 (33.3%)	6 (20.7%)
Respiratory, thoracic and mediastinal disorders	2 (14.3%)	10 (66.7%)	12 (41.4%)

Source: ISS Table 2.1.3.2.

MedDRA = Medical Dictionary for Regulatory Activities; MRX = maralixibat; n = number in a given category;

N = number of participants; TEAE = treatment-emergent adverse event.

Note: Percentages are 100*n/N. Treatment groups are based on the highest dose (µg/kg/day) received during the

analysis period. Participants were counted only once for each System Organ Class and Preferred Term. A common adverse event is any event that occurs at a rate of ≥ 1%.

a Adverse events were coded using MedDRA version 22.1.

2.6.8.3. Serious adverse event/deaths/other significant events

The incidence of SAEs in the open-label, long-term extension ALGS studies was 25/84 participants (29.8%) for overall maralixibat. The system organ class with the most SAEs was Infections and infestations with 8 (9.5%) participants in the overall maralixibat group experiencing at least 1 SAE. This is followed by GI disorders, with 7 (8.3%) participants in the overall maralixibat group experiencing at least 1 SAE; and Injury, poisoning and procedural complications, with 6 (7.1%)

participants in the overall maralixibat group experiencing at least 1 SAE. SAEs occurred in less than 5% of participants in all other SOCs.

Table 19 Incidence of Serious Adverse Events – Pooled Open-Label, Long-Term Extensions

Overall	**Studies LUM001-303/305/304 Pooled**			
System Organ Classa Preferred Term	**MRX ≤ 140 µg/kg/day (N=10)**	**MRX 280 µg/kg/day (N=38)**	**MRX > 280 µg/kg/day (N=36)**	**Overall MRX (N=84)**
Participants with at Least 1 SAE	3 (30.0%)	6 (15.8%)	16 (44.4%)	25 (29.8%)
Blood and lymphatic system disorders	1 (10.0%)	0	1 (2.8%)	2 (2.4%)
Anaemia	1 (10.0%)	0	0	1 (1.2%)
Aplasia pure red cell	0	0	1 (2.8%)	1 (1.2%)
Cardiac disorders	0	0	2 (5.6%)	2 (2.4%)
Bradycardia	0	0	1 (2.8%)	1 (1.2%)
Cardiac dysfunction	0	0	1 (2.8%)	1 (1.2%)
Pericardial effusion	0	0	1 (2.8%)	1 (1.2%)
Ear and labyrinth disorders	0	0	1 (2.8%)	1 (1.2%)
Ear haemorrhage	0	0	1 (2.8%)	1 (1.2%)
Gastrointestinal disorders	2 (20.0%)	1 (2.6%)	4 (11.1%)	7 (8.3%)
Vomiting	0	1 (2.6%)	1 (2.8%)	2 (2.4%)
Abdominal pain	0	0	1 (2.8%)	1 (1.2%)
Diarrhoea	0	0	1 (2.8%)	1 (1.2%)
Gastrointestinal haemorrhage	0	0	1 (2.8%)	1 (1.2%)
Haematemesis	1 (10.0%)	0	0	1 (1.2%)
Haematochezia	1 (10.0%)	0	0	1 (1.2%)
General disorders and administration site conditions	0	0	3 (8.3%)	3 (3.6%)
Pyrexia	0	0	2 (5.6%)	2 (2.4%)
Influenza like illness	0	0	1 (2.8%)	1 (1.2%)
Hepatobiliary disorders	0	2 (5.3%)	0	2 (2.4%)
Autoimmune hepatitis	0	1 (2.6%)	0	1 (1.2%)
Chronic hepatic failure	0	1 (2.6%)	0	1 (1.2%)
Infections and infestations	1 (10.0%)	0	7 (19.4%)	8 (9.5%)
Campylobacter gastroenteritis	0	0	1 (2.8%)	1 (1.2%)
Epstein-Barr virus infection	0	0	1 (2.8%)	1 (1.2%)
Fungal infection	1 (10.0%)	0	0	1 (1.2%)
Gastroenteritis	0	0	1 (2.8%)	1 (1.2%)
Gastrointestinal infection	0	0	1 (2.8%)	1 (1.2%)
Rotavirus infection	0	0	1 (2.8%)	1 (1.2%)
Tonsillitis	0	0	1 (2.8%)	1 (1.2%)
Viral pharyngitis	0	0	1 (2.8%)	1 (1.2%)
Injury, poisoning and procedural complications	0	1 (2.6%)	5 (13.9%)	6 (7.1%)
Forearm fracture	0	1 (2.6%)	1 (2.8%)	2 (2.4%)
Extradural haematoma	0	0	1 (2.8%)	1 (1.2%)
Humerus fracture	0	0	1 (2.8%)	1 (1.2%)
Post procedural haemorrhage	0	0	1 (2.8%)	1 (1.2%)
Procedural haemorrhage	0	0	1 (2.8%)	1 (1.2%)
Subdural haemorrhage	0	0	1 (2.8%)	1 (1.2%)
Toxicity to various agents	0	0	1 (2.8%)	1 (1.2%)
Investigations	0	2 (5.3%)	2 (5.6%)	4 (4.8%)
Alanine aminotransferase increased	0	1 (2.6%)	0	1 (1.2%)
Blood bilirubin increased	0	0	1 (2.8%)	1 (1.2%)
Gastrointestinal stoma output decreased	0	1 (2.6%)	0	1 (1.2%)
International normalised ratio increased	0	0	1 (2.8%)	1 (1.2%)
Metabolism and nutrition disorders	1 (10.0%)	1 (2.6%)	0	2 (2.4%)
Dehydration	0	1 (2.6%)	0	1 (1.2%)
Malnutrition	1 (10.0%)	0	0	1 (1.2%)

Musculoskeletal and connective tissue disorders	0	0	1 (2.8%)	1 (1.2%)
Pathological fracture	0	0	1 (2.8%)	1 (1.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (2.8%)	1 (1.2%)
Marrow hyperplasia	0	0	1 (2.8%)	1 (1.2%)
Nervous system disorders	0	0	1 (2.8%)	1 (1.2%)
Seizure	0	0	1 (2.8%)	1 (1.2%)
Renal and urinary disorders	0	0	1 (2.8%)	1 (1.2%)
Acute kidney injury	0	0	1 (2.8%)	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	0	1 (2.6%)	1 (2.8%)	2 (2.4%)
Epistaxis	0	1 (2.6%)	0	1 (1.2%)
Hypoxia	0	0	1 (2.8%)	1 (1.2%)
Productive cough	0	0	1 (2.8%)	1 (1.2%)
Surgical and medical procedures	0	1 (2.6%)	0	1 (1.2%)
Medical device change	0	1 (2.6%)	0	1 (1.2%)
Vascular disorders	0	0	2 (5.6%)	2 (2.4%)
Hypertension	0	0	1 (2.8%)	1 (1.2%)
Hypotension	0	0	1 (2.8%)	1 (1.2%)

Source: ISS Table 2.2.1.3.

MRX = maralixibat; MedDRA = Medical Dictionary for Regulatory Activities; n = number in a given category; N = number of participants; SAE = serious adverse event.

Note: Percentages are 100*n/N. Treatment groups are based on the highest dose (µg/kg/day) received during the analysis period. Participants were counted only once for each System Organ Class and Preferred Term.

Adverse events were coded using MedDRA version 22.1.

For the overall open-label, long-term extension studies (excluding those recruited in MRX-801), only 3 (3.6%) participants in the overall maralixibat group experienced treatment-related SAEs; 2 were in the maralixibat 280 µg/kg once daily group: 1 (2.6%) participant with an SAE of autoimmune hepatitis, and 1 (2.6%) participant with an SAE of ALT increased; and 1 (10.0%) participant was in the maralixibat ≤ 140 µg/kg once daily group and experienced an SAE of haematochezia (ISS Table 2.4.1.3).

In MRX-801 there were 4 participants (50.0%) who had serious adverse events (SAEs), none of which were considered to be related to the study drug. No TEAE led to study drug discontinuation or death. The reported SAEs (n=7) included infantile colic and crying in 1 participant, coronavirus infection and varicella in 1 participant, 2 events of pyrexia in 1 patient, and viral infection in 1 participant. The SAE of crying occurred in the same participant who had an SAE of infant colic 3 months prior. No diagnosis for the crying has been provided to date. All SAEs resolved and the maralixibat dose was not changed in response to the events.

No AEs of special interest were reported.

In the supportive PFIC target population included in study LUM001-501 about half of the participants (45.5%) had an SAE. SAEs of diarrhoea, abdominal pain, and gastroenteritis were the only events (based on PT) that were reported in more than 1 participant (each SAE was reported in 2 participants; 6.1%). 5 of these SAEs (15.2%, all in 280µg/kg QD) were classified as potentially drug-related. However, without sufficient information it seems difficult to evaluate this classification, since drug-related TEAEs/SAEs are in general difficult to differentiate from disease-associated events due to the mainly gastrointestinal adverse events/toxicity of maralixibat.

No death event occurred during the clinical development in the paediatric population.

2.6.8.4. Laboratory findings

Across the ALGS integrated population, mean changes from baseline in most laboratory parameters are described as minimal and proposed to show no apparent patterns over time. Moreover, data from the long-term extension studies in ALGS did reveal an increase in mean ALT which should be further evaluated.

Haematology: With respect to clinical laboratory evaluations of haematological parameters in both populations (PFIC and ALGS) the mean changes from baseline in haematology parameters were minimal, short lasting and probably resolved at the next study visit. TEAEs with respect to this class were reported in about 3%. During response it was clarified that most of these events are likely to be caused by hypersplenism or other adverse events caused by the underlying disease. Serum Transaminases and Hepatic Safety: With respect to the hepatic safety, elevations in transaminases have been seen in the ALGS development programme for maralixibat that may be a sign of hepatotoxicity. Hepatotoxicity is an important potential risk outlined in the RMP.

Fat-Soluble Vitamins, Coagulation, and Lipid Panel: The mean changes from baseline in FSV, coagulation, and lipid parameters were also only minimal during the 18-week open-label period of Study LUM001-304 in ALGS. After Week 22 in the overall maralixibat group, there was no pattern of increasing proportions of participants with abnormalities among these parameters over time.

Vitamin deficiency, particularly FSV deficiency, is common in children with chronic liver diseases; this may be explained by the reduced food intake, impaired nutrient uptake, and reduced synthesis of carrier proteins caused by these patients' damaged liver function. According to literature data the incidence of vitamin deficiency could be 20% to 30% in patients with cholestatic liver disease as in the target population. However, FSV substitution is normally provided in these population. In order to avoid complications this issue has been mentioned in the product information (SmPC 4.4 and PL).

In infants (MRX_801) episodes of mild increase in INR in one patient (801-802) were observed.

Vital Signs and Other Safety Evaluations: Changes from baseline in vital signs were minimal in Study LUM001-501 and across the ALGS integrated studies and no pattern was identified which could be interpreted as a potential signal from the analyses. Moreover, since the drug is not absorbed it seems plausible that no concerns for QT prolongation risk following maralixibat administration were raised in the clinical programme.

2.6.8.5. Safety in special populations

The applicant has provided subpopulation analysis for participants from the ALGS-integrated population (excluding the patients from MRX-801 - infants) for the age ranges < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to 18 years) and gender subgroups. The analyses of the data did not reveal a specific subpopulation to be notable for a preponderance of specific events/increase in severity of a particular event. However, the number of patients in these subgroups were notably low, limiting the informative value of these analyses.

2.6.8.6. Immunological events

In the investigated population there was no specific signals regarding adverse events as anaphylactic reactions or other suspect events like urticaria indicating an significantly increased allergenic potential of maralixibat.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Since maralixibat chemical structure is designed to be minimally absorbed following oral administration because the site of action is within the lumen of the GI tract, is metabolically stable *in vivo*, excreted almost exclusively in the faeces as intact parent drug, it seems plausible that the drug has only a low potential for drug-drug interactions in general. Moreover, the applicant stated that no safety concerns regarding drug interactions with maralixibat were identified during the trials. Thus, it is agreed that, considering the very low plasma drug levels for maralixibat at therapeutic doses (often below the LLOQ), and also based on in silico modeling and clinical DDI studies, drug interactions with maralixibat are unlikely.

It is agreed that currently there is no evidence that maralixibat has any risk for drug abuse or with respect to the ability to drive or operate machinery or leads to an impairment of mental abilities. Several cases of drug overdose occurred but were not associated with any TEAEs during the clinical development programme. Moreover, there were no apparent treatment-related withdrawal effects except for a return of pruritus among participants who stopped treatment with maralixibat.

2.6.8.8. Discontinuation due to adverse events

Review of the safety data for the ALGS integrated population demonstrated that AEs leading to discontinuation of maralixibat occurred mainly during the long-term extension period of the studies.

Of the 39 participants in the 13-week, placebo-controlled studies, 2 participants had an event that led to discontinuation; 1 participant (4.0%) in the maralixibat ≤ 140 µg/kg group had an event of ALT increased and 1 participant (5.6%) in the placebo group had an event of abnormal behaviour.

Of the 84 participants in the open-label, long-term extension studies, a total of 13 participants (15.5%) had an AE that led to discontinuation.

ALT increased was the most commonly reported event that led to discontinuation of maralixibat, which included 6 participants (7.1%) from the long-term extension studies. Whereas a causal attribution with maralixibat was considered for some of these events, the events seem to be rather explained by the natural history of the ALGS and progression of the underlying disease from the assessment of the details in the response. In particular, since data from the adult population with liver diseases and hypercholesterolaemia does also not indicate a potential intrinsic hepatotoxicity.

No patients discontinued in the MRX-801 study due to an AE.

2.6.8.9. Post marketing experience

The product was approved by the FDA in 2021. No data on post marketing experience were submitted within this application.

2.6.9. Discussion on clinical safety

Maralixibat is a minimally absorbed oral agent that is designed to maximise local exposure of the molecule to its target and minimise systemic exposure.

Safety data in the target population is available from 6 trials (pivotal trial LUM001-304, as well as supportive trials 301/302, long term extension trials 303 and 305 and one trial in infants – MRX-801).

In addition, upon request, the applicant has provided information on maralixibat's safety from placebo-controlled RCTs in ~ 1200 adults in a different indication (mainly hypercholesterinaemia). This

confirmed the risks identified in the paediatric ALGs population and do not indicate additional safety signals.

Exposure

Maralixibat has been studied in > 1600 participants, but only data from 127 children with cholestatic liver disease (n = 33 with PFIC; n = 94 with ALGS) was analysed regarding the safety outcome for this submission. Subjects were treated for up to 5 years. During the clinical trials (most importantly LUM001-304; excluding MRX-801) the limited number of study participants were sufficiently exposed to the proposed posology (400 µg/kg/day) with an average duration of 536.6 days to allow adequate conclusion on safety outcome.

In conclusion, overall exposure and particularly in the applied rare orphan paediatric disease population seems in principle acceptable; however limitations due to the small number need to be considered.

In infants (MRX-801) the overall mean (SD, Median) duration of treatment by the data cut-off point of May 2022 was 149.0 (50.02; 136.5) days and ranged from 101 to 250 days. This is considered very limited. applicant has agreed to collect full 1-year treatment data post-approval in this study.

Adverse events

In accordance with the known safety profile of the pharmacological class of ASBT inhibitors GI events including diarrhoea, vomiting and abdominal pain were the most frequently reported adverse drug reactions for maralixibat for the applied target-population across the clinical trials.

In trial LUM001-304 the most frequently reported TEAEs (>40% overall) were abdominal pain (58.1%), diarrhoea (54.8%), vomiting and pyrexia (51.6% each), and cough and nasopharyngitis (41.9% each).

Safety data in the paediatric population of ALGS subjects from the 13-week, placebo-controlled studies (LUM001-301 and LUM001-302) revealed a similar incidence of events of diarrhoea in the overall maralixibat and placebo groups (43.6% vs. 44.4% of participants, respectively), while events of abdominal pain were slightly rarer reported in M: 25.6% versus P: 16.7%, respectively. This demonstrates that GI symptoms are also likely to be present among the underlying patient population of paediatric cholestasis as disease complication.

Most common TEAEs (> 10% overall) in every study (including long term exposure) were abdominal pain (45,5%), cough (34.5), diarrhoea (39.4%), headache (20.7%), nasopharyngitis (34.5%), pyrexia (48.3), upper respiratory tract infections (20.7%) and vomiting (37.9%). (e.g. from LUM001-304; ISS Table 2.1.3.2.). It has been noted, that "loose stool" was reported as an ADR in various studies (including adults), on MRX.

The majority of these events were described to be mild to moderate in severity, transient in nature, and resolved with no action taken with maralixibat and no special approaches for monitoring were required. Median time to first onset for events of diarrhoea and abdominal pain was 30 days and 61 days, respectively. The duration of the gastrointestinal events was short as reflected by a median duration for events of diarrhoea and abdominal pain were 2 days and 1 day, respectively. Specific mitigation activities for these events included provision of dosing modification guidelines for GI symptoms, including diarrhoea and abdominal pain, within the clinical study protocols.

Regarding symptoms of upper respiratory tract infection as nasopharyngitis, cough and pyrexia it needs to be considered that these TEAEs are in general frequent in a paediatric population (simple infections during the first 3 years of life, with 71% being respiratory infections, followed by gastrointestinal infections according to Vissing et al. 2018).

Preliminary data in infants are difficult to interpret due to low number of patients. Considerable portion of patients (50%) had increase in transaminases.

A more permeable intestinal barrier may occur in situations where the gastrointestinal system is acute or chronically disturbed and could lead to higher exposure of maralixibat and potentially induce other systemic adverse events particularly in infants. However, in this case, the higher systemic exposure has been tolerated in previous human (adults) and non-clinical studies without critical safety findings. These data suggest that even if higher exposure levels are reached in infants, these are likely not to represent a hazard. It is planned that the patients, especially those under the age of 1 year, are closely monitored for safety in the post-authorisation phase (LEAP study).

SAEs and deaths

In the pivotal Study LUM001-304, up to 34.5% of participants had an SAE, with the rates varying depending on the period of the study. No SAE (based on preferred term) was reported in more than 1 participant.

The majority of these SAEs were from the SOCs of Infections and infestations and GI disorders; vomiting was the only SAE (based on Preferred Term among the GI disorders SOC) that was reported in more than 1 participant (reported in 2 [2.4%] participants).

The available limited placebo comparison from LUM001-301/302) seems not to indicate a significant difference regarding SAEs considering the small numbers of patients involved (LUM001-301 and LUM001-302). No specific patterns or safety signals were identified based on review of SAEs.

From the submitted documents, it was not possible to fully assess the drug-relationship of the SAEs in the paediatric populations (PFIC/ALGS); However, it was clarified that drug-relation assessment was based on the investigator's opinion only, based on some acceptable criteria which were provided for orientation in the trial protocols.

Half of the patients in MRX-801 study had 7 SAEs. Notably, proportion of the patients with SAEs and the number of SAEs is appears larger in MRX-801 study than in LUM-301/302 and LUm001-304 studies. No specific patterns or apparent safety signals could, however, be identified based on review of SAEs. This phenomenon was contributing to the obvious need for generating more safety data post-licensing.

No death event occurred during the clinical development in the paediatric population.

Laboratory findings:

With respect to clinical laboratory evaluations of haematological parameters the mean changes from baseline described in haematology parameters were small, short lasting and probably resolved at the next study visit. TEAEs with respect to this class were reported in about 3%, but details from the additionally provided analyses and narratives at day 120 revealed that almost all of these events are likely to be not drug related and sufficiently explained due to concomitant hypersplenism caused by the underlying disease.

With respect to the hepatic safety, laboratory data showed probably isolated, asymptomatic elevations in ALT in some of the ALGS participants. Whether these events have to be seen as part of the natural history of ALGS and were not associated with concomitant rises in bilirubin -as the applicant concludes- remains somewhat uncertain at the end. Since the product was also investigated in other indications, particularly in hypercholesterolemia, in ~ 1600 adult patients, additional placebo-controlled safety data is available and relevant information was provided with the response.

According to these data it seems unlikely that maralixibat treatment is associated with a high risk for drug induced liver injury. However, degree of generalizability of these effects to children (including

infants) with ALGS is unclear. Since evidence in ALGS population is very limited more data is needed to conclude if there is a hepatotoxicity risk with maralixibat or not. If the risk will be confirmed this will have an impact on the benefit/risk of the product, accordingly this risk is considered important and is as such included in the RMP as an important potential risk. Further characterisation of the potential risk of hepatotoxicity via the proposed study LEAP (MRX-310; Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome) which is made specific obligation of this marketing authorisation. Furthermore, the applicant will provide annual updates on new emerging safety and efficacy data as part of the specific obligations outlined in this marketing authorisation under exceptional circumstances. Also, the applicant will provide data from the ongoing studies MRX-800 and MRX-801. This data may help in the clarification of the nature of the hepatic findings in patients with ALGS being treated with maralixibat. Also, an open-end post authorisation specific obligation has been implemented in which the marketing authorisation holder will give yearly updates on safety and efficacy information. Furthermore, a precautionary statement was included in section 4.4 of the SmPC, to monitor liver function in all patients prior to and during treatment with Livmarli.

Subgroup analyses:

The applicant has provided some attempts for subgroup analyses regarding gender and age subgroups (< 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to 18 years) and additional data in < 1 year olds. In general, they are less informative due to the small number of subjects in the cohorts. Thus, differences and potential trends across age groups, including the < 1 year old vs. 1 year and older patients remain not interpretable at the end.

Immunological events:

No information regarding immunological events was submitted nor was this issue discussed in the documents. Animal data indicate the absence of an increased risk for allergic reaction and related adverse events as anaphylactic reactions or other suspect events like urticaria are not reported.

DDI and other potential interactions

The applicant indicates that, since maralixibat chemical structure is designed to be minimally absorbed following oral administration because the site of action is within the lumen of the GI tract, is metabolically stable *in vivo*, excreted almost exclusively in the faeces as intact parent drug, it is plausible that the drug has only a low potential for drug-drug interactions in general. Based on the safety data to date (01 Dec 2019), no safety concerns regarding drug interactions with maralixibat were identified.

It is agreed that, given the very low plasma drug levels for maralixibat at therapeutic doses (often below the LLOQ), and also based on *in silico* modelling and clinical DDI studies, drug interactions with maralixibat are unlikely.

The impact of maralixibat on absorption of FSV seems not pronounced however -since prophylactic substitution was performed during the trial and is generally recommended in the target population- the potential need for FSV substitution was included in the product information (SmPC section 4.4).

It is agreed that currently there is no evidence that maralixibat has any risk for drug abuse or with respect to the ability to drive or operate machinery or leads to an impairment of mental abilities. Several cases of drug overdose occurred but were not associated with any TEAEs during the clinical development programme. Moreover, there were no apparent treatment-related withdrawal effects, except for a return of pruritus among participants who stopped treatment with maralixibat.

Discontinuation due to AEs

In the target population 6 subjects discontinued due to ALT increases assessed as potentially drug-

related during the long-term extension trial. Overall, this PT was the most frequent AE that led to discontinuation in the whole safety population. Even considering the underlying liver disease, hepatotoxicity of maralixibat is possible and more data on this important potential risk will be generated post-approval as part of the specific obligations as indicated above.

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

With a safety database of 86 treated patients, the number of patients is limited. In particular, it is not considered possible to draw robust conclusions on safety in relation to potential hepatotoxicity. Whilst the mechanism of action of the product is clearly described, it remains unclear whether the proposed dosing regimen is optimal.

It seems unlikely that maralixibat treatment is associated with a high risk for drug induced liver injury, but as the evidence provided on clinical safety in the ALGS population is very limited, more data is needed to conclude if there is a hepatotoxicity risk with maralixibat or not. As this risk, if confirmed, will have an impact on the benefit/risk of the product it is included in the RMP as an important potential risk.

Further characterisation of this potential risk of hepatotoxicity especially but not exclusively in infants via the proposed study LEAP (MRX-310; Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome), is made a specific obligation of this marketing authorisation. Furthermore, the applicant will provide annual updates on any new emerging safety and efficacy data as part of the specific obligations outlined in this marketing authorisation under exceptional circumstances.

2.6.10. Conclusions on clinical safety

Assessment of safety in this application is hampered due to the rare disease nature of ALGS. Gastrointestinal adverse events/toxicity as diarrhoea, abdominal pain and vomiting are reported to be the most common adverse drug reactions, however, may be also caused by the underlying disease. Almost all of the TEAEs observed were mild to moderate and resolved with no action taken.

Maralixibat was in general well tolerated and, considering the low degree of absorption, appears to have an acceptable safety profile in paediatric patients with cholestasis due to ALGS. However, a significant degree of uncertainty remains, particularly with respect to a potential intrinsic hepatotoxicity and, esp. in the patients younger than 1 year of age, due to the limited exposure and very limited size of the data base available. The applicant will provide further data on long term safety and in particular on potential hepatotoxicity by means of the planned long-term safety and clinical outcomes study and give yearly updates on all newly emerging safety and efficacy information on maralixibat under the scope of the annual reassessments.

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

Description	**Due date**
In order to further characterise the long-term safety and efficacy of maralixibat in the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS), the MAH shall conduct and submit the results of study LEAP (MRX-310) according to an agreed protocol.	Annual (within the annual reassessment)
In order to ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with Alagille syndrome (ALGS), the MAH shall provide	Annual (within the annual re-

Description	Due date
yearly updates on any new information concerning the safety and efficacy of maralixibat.	assessment)

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 20 Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

Table 21 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 authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
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				

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

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

2.7.3. Risk minimisation measures Part V.3 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation 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 minimisation measures:** No risk minimisation 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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.9 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 29.09.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Livmarli (maralixibat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Target indication for maralixibat is treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older.

ALGS is a rare and life-threatening disease with no approved pharmacological treatment for the associated cholestatic manifestations which often present in infancy with cholestatic pruritus, abnormal liver parameters, failure to thrive, and fat malabsorption. Elevated levels of sBA, bilirubin (especially direct) and cholesterol are key components of cholestasis, which are accompanied with clinical manifestations, like pruritus, xanthomas, fatigue and disturbance in growth. The accumulation of toxic bile acids in the hepatobiliary system damages bile duct epithelial cells and hepatocytes, causing liver injury and inflammation, which are manifested in elevated liver function parameters (e.g., ALT). Pruritus is reported to be the most bothersome symptom of ALGS across all ages by patients and caregivers (Kamath et al. 2018b), which is difficult to treat, leads to cutaneous mutilation, mood disturbances, disruption of sleep and school performance, and has negative impact on physical and psychosocial health (Elisofon et al. 2010; Kamath et al. 2015, Kamath et al. 2018b), as well as overall QoL (Abetz-Webb et al. 2014).

Progression of hepatic disease occurs in later childhood in many patients. The majority of patients with ALGS will either receive a liver transplantation or die, with only 24% to 41% of patients reaching adulthood with their native liver (Kamath et al. 2020; Vandriel et al. 2020). Typical indications for liver transplant in ALGS include severe pruritus, disfiguring xanthomas, synthetic dysfunction, portal hypertension, bone fractures, and growth failure (Lykavieris et al. 2001; Kamath et al. 2020).

Increased levels of sBA are assumed to mediate pruritus and contribute to liver damage in the ALGS population. Maralixibat is able to block reabsorption of sBA in the intestines and reduces sBA in blood. It is assumed that decreased levels of sBA lead to improvements in the pruritus, with subsequent improvement in the quality of life, and potentially, prolongation of survival with native liver/overall survival.

3.1.2. Available therapies and unmet medical need

Currently, there are no pharmacological therapies approved to treat cholestasis in ALGS and no therapy shown to be effective to improve clinical manifestations of liver disease with subsequent prevention or delay in liver transplantation. Certain drugs are prescribed off-label for the treatment of cholestatic pruritus or xanthomas, including UDCA, bile acid resins (e.g., cholestyramine), rifampicin, and naltrexone, but all have limited or transient efficacy and may have undesirable adverse effects (Düll and Kremer 2020). Surgical alternatives are often required.

Surgical interruption of the enterohepatic circulation has been used to treat cholestasis, hypercholesterolemia, and pruritus (Emerick and Whitington 2002; Modi et al. 2007). The most common procedure is partial external biliary diversion (PEBD), resulting in a permanent stoma that is not effective in approximately half of patients (Yang et al. 2009) and has surgical (e.g., bleeding, infections, and surgical complications), medical (e.g., electrolyte disturbances and dehydration) and psychosocial complications (Emerick et al. 1999; Kamath et al. 2018b).

Ultimately, the clinical manifestations of cholestasis, including intractable pruritus can be so severe that they are often an indication for liver transplantation (Lykavieris et al. 2001; Mattei et al. 2006; Kamath et al. 2018b).

The management of cholestasis in patients with ALGS remains largely supportive or surgical. Given the lack of approved pharmacotherapy, the invasive nature of surgical treatment options, and patients' short- and long-term morbidity and mortality, there remains a high unmet medical need for a pharmacological treatment alternative in patients with ALGS that is safe and efficacious to address the cholestatic disease burden and improve QoL.

3.1.3. Main clinical studies

The main trials that evaluated the proposed therapeutic dose of 400 µg/kg/day maralixibat in the targeted population are LUM001-304 (patients with ALGS 1-15 years of age at study entry) and MRX-801 (patients with ALGS 2-10 months of age at study entry). LUM001-304 was a randomised, placebo-controlled, drug withdrawal study with an open-label LTE in participants with ALGS designed to evaluate the safety and efficacy of maralixibat. The study consisted of 18 weeks-long open-label run-in phase, 4 week-long randomised withdrawal phase and follow-up/OLE phase that lasted more than additional 5 years. Placebo control was utilised in the RWD phase only. Overall, 31 patients children within the age range of 1 and 15 years (including) were treated and efficacy was analysed in 29 patients (ITT).

The recruited patient population was considered representative of the general ALGS population, all having confirmed genetic mutation (JAGGED1 in 100%), chronic cholestasis, moderate to severe pruritus, increased levels of sBA and liver functional parameters, bilirubin, delayed growth (height and weight) and typical non-liver related anomalies (cardiovascular, vascular, facial, etc.). Only about half of the patients had xanthoma at baseline and majority had a mild form of it. Absolute majority of the patients used medications against pruritus and cholestasis prior to study entry.

During the study (core part) change in concomitant treatments was not allowed.

All patients were randomised to maralixibat or placebo in the RWD phase.

Primary endpoint of the study was the difference in the change in the mean fasting sBA at the end of RWD phase compared to the baseline (week 18 before RWD phase) as analysed in the mITT (n=15).

Key secondary endpoints were the same endpoint on sBA, but analysed in the ITT set and the difference in the change in the pruritus (measured by means of ItchRO(Obs)) during RWD (ITT set).

Maintenance of the treatment effects over 6 years of treatment was also evaluated in this study base on the following parameters: sBA, pruritus (assessed by means of ItchRO and CSS), bilirubin and liver function parameters, growth parameters (height and weight), xanthoma, cholesterol, quality of life. However, no control arm was included.

MRX-801 is an open-label ongoing study in infants with ALGS with the primary endpoint to assess safety and tolerability of MRX in infants. Secondary and exploratory endpoints of the study are assessment of MRX effects on sBA, bilirubin, AST/ALT, FSV, ItchRo(Obs), CSS, growth. The study utilises the dosing regimen recommended in the SmPC with simplified titration. Only preliminary data on sBA and pruritus (CSS) over 13 week treatment period, on PK (sparce sampling) and safety in 8 patients are available.

3.2. Favourable effects

LUM001-304 (age ≥ 1 year and ≤ 18 years)

Primary endpoint: there was a statistically significant LS mean (SE) difference in change from Week 18 to 22 in sBA between the maralixibat and placebo groups (-117.28 [52.828] µmol/L, p=0.0464) during the randomised withdrawal phase in the mITT set (n=15). Participants administered placebo during the RWD phase had a statistically significant LS mean (SE) increase in sBA from Week 18 to Week 22 of 95.55 (30.488) µmol/L (p=0.0086), whereas those who received maralixibat had no notable change (-21.73 [43.125] µmol/L, p=0.6234).

Secondary endpoints:

Mean changes in sBA over treatment time:

In the overall ITT Population (N=31 participants), with all participants randomised to either placebo or maralixibat during the RWD phase, there was a significant mean (SE) decrease in sBA during the OL phases up to Week 18 (-87.73 [22.280] µmol/L, p=0.0005, N=29) and Week 48 (-96.44 [32.068] µmol/L, p=0.0058, N=27).

At the end of the RWD phase (Week 22), participants who had continued to receive maralixibat maintained their mean (SE) sBA treatment effect (-16.73 [30.412] µmol/L, p=0.5923, N=13), whereas those on placebo had experienced a significant increase (93.58 [33.219] µmol/L, p=0.0130, N=16). The LS mean difference between the 2 treatment groups was statistically significant (-113.95 µmol/L, 95% CI -212.68 to -15.21, p=0.0254).

Treatment effects on sBA in the run-in and RWD phases was confirmed in post hoc sensitivity analyses accounting for intraindividual variability in sBA levels.

Throughout the entire treatment period statistically significant decreases from baseline in sBA were observed at each time point, with the exception of Week 108 and Weeks ≥240. After Week 22, at the visits with statistically significant results, mean (SE) decreases from baseline in sBA after Week 22 ranged from -83.71 (32.915) µmol/L at Week 100/LOCF (p=0.0170) to 180.84 (47.672) µmol/L at Week 204 (p=0.0020). The results at Week 108 and ≥240 may be explained by a smaller number of participants on study medication at those visits (N=13 and <5, respectively).

Similar changes were observed in multiple sensitivity analyses accounting for various confounders, such as missing data and use of concomitant medication.

ItchRO(Obs) Weekly Average Morning Severity Score:

At Week 22, a statistically significant increase (worsening) in mean (SE) change from Week 18 in ItchRO(Obs) scores was identified in the placebo group (1.712 [0.2513], p<0.0001, n=16), whereas no relevant change was observed in the maralixibat group (0.201 [0.2180], p=0.3754, n=12). Participants who received placebo experienced a return of their pruritus severity similar to their baseline scores, whereas those who continued to receive maralixibat generally maintained the treatment effect observed during the OL phase.

At comparison of the ItchRO(Obs) scores at the end of the RWD phase (Week 22) mean (SE) values were 1.380 (0.2685) vs. 2.839 (0.2126) in the maralixibat and placebo groups, respectively. The LS mean (SE) difference between the maralixibat and placebo groups at Week 22 was statistically significant (1.483 [0.3103]; p<0.0001).

Long-term treatment effects on the pruritus were maintained in the patients remaining in the study.

Cholesterol, LDL cholesterol and xanthomas:

Improvements in the levels of cholesterol, LDL cholesterol and xanthomas were observed. The group receiving MRX during the RWD phase had a LS mean change (SE) from Week 18 to Week 22 of 2.2 (21.3) mg/dL (p=0.9167) in cholesterol, whereas those who received placebo had an increase of 78.6 (19.2) mg/dL (p=0.0004). similar effects were observed with LDL cholesterol. In 14 patients with xanthoma at the baseline reduction in xanthoma score mean (95% CI) of -0.4 (-0.9, 0.1) was reported at week 18 (p=0.0823) and of -0.9 (-1.3, -0.5) at week 48 (p=0.0006).

Total and direct bilirubin:

No clearly positive changes were observed.

Changes in liver pathology and liver biochemistry:

No clinically relevant changes were observed.

Growth:

Improvement in z-Scores of height was reported. Z-score (95% CI) for height changed by 0.178 (-0.016 to 0.373; p=0.0704) by week 48 from the mean (95%CI) baseline value of -1.7 (1.34).

Quality of life:

Scores of quality of life questionnaire (total and fatigue) improved during run-in and over prolonged treatment, but did not show difference to placebo in the RWD.

CSS:

Relevant changes in CSS also compared to placebo were observed.

MRX-801 (<12 months of age)

sBA:

The mean (SD) change in sBA from baseline at Week 13 was -88.91 (113.35) µmol/L. There were decreases in sBA from baseline to Week 3, 10, and 13. Two of the 6 patients with on-treatment sBA measurement had pronounced reduction in sBA. These patients also experienced decrease in bilirubin (total and, or direct) and improvement in pruritus. ALT and AST improved in one of these two patients, but ALT increased in another.

CSS:

The mean (SD) change from baseline to Week 13 for CSS score was -0.2 (1.91) and ranged from -3 to 3. During the study follow-up, 3 participants had a decrease in their CSS scores (2 of which had no pruritus recorded at Week 13 indicating full remission); 1 participant observed no change in their level of pruritus, and 3 participants had an increase in CSS score ranging from 1 to 3 points. No post-baseline value of CSS is available for one patient. Reduction in CSS in two patients was associated with reduction in sBA.

3.3. Uncertainties and limitations about favourable effects

The uncertainties related to the efficacy assessments in the LUM001-304 study originate from the following key factors:

Limited data-set on efficacy of the proposed therapeutic dose (n=29) derived from a single exploratory clinical study, that has placebo-controlled phase of only 4 weeks duration;

Apparent lack of standardisation of the study procedures across participating sites, which might have led to high variability in efficacy data, specifically in sBA values.

High rate of discontinuations/refusal to continue treatment in the follow-up extension phase with maralixibat after week 48, that limits robustness of long-term data; Also, data after Week 96 were collected on treatment with 800 µg/kg/day, i.e. the dose not proposed as a therapeutic dose. Thus, relevant data for 400 µg/kg/day are limited to 48 weeks treatment duration. Effectiveness will be further monitored by means of the planned long-term safety and clinical outcomes study that is made specific obligation to this marketing authorisation.

Major part of the study has been designed as an uncontrolled open-label study. This creates an uncertainty in interpretation of the data derived from subjective efficacy parameters (like assessment of pruritus, quality of life) and those parameters, where natural course of development in this particular population is not known (e.g., changes in growth), as it is difficult to isolate the true effects of maralixibat treatment, esp. since ALGS is a multiorgan disease and changes in nutrition may impact the patient's condition (e.g., growth);

Lack of the changes in bilirubin and liver function parameters in response to maralixibat treatment question efficacy of MRX in treatment of cholestasis, the indication initially claimed, and the applicant agreed in the course of the assessment to amend the indication to the treatment of cholestatic pruritus in patients with Alagille syndrome.

In the infant population data are very limited, although inclusion of 8 infants with ALGS in study 801 exceeds the minimum number of 6 stipulated in the PIP. Currently, post-baseline sBA values at week 13 are available for 6 of these patients and measurements at earlier treatment time points have even lower number of patients. Accuracy and sensitivity of the CSS scale is uncertain given the very young age of the infant population. Extrapolation of efficacy from older age population is intrinsically burdened with uncertainty. Pruritus severity will be monitored over time by means of the ongoing MRX-801 study and the planned long term safety and clinical outcomes study that is made specific obligation to this Marketing authorisation.

3.4. Unfavourable effects

Safety data in the applied paediatric target population is limited to 88 children with Alagille-Watson-Syndrome (ALGS) in one pivotal trial (LUM001-304) and 4 small other trials (LUM001-301, -302, -303, -305).

In accordance with the known safety profile of the pharmacological class of ASBT inhibitors, GI events including diarrhoea (57.6%) and abdominal pain (45.5%) were the most frequently reported adverse drug reactions for maralixibat in the pivotal study LUM001-304 as well as in the pooled ALGS safety population. The majority of these events were described to be mild to moderate in severity, transient in nature, and resolved with no action taken with maralixibat and no special approaches for monitoring were required. Safety data from the 13-week, placebo-controlled studies (LUM001-301 and LUM001-302) revealed a similar incidence of events of diarrhoea in the overall maralixibat and placebo groups (43.6% vs. 44.4% of participants, respectively), while events of abdominal pain were slightly rarer reported in placebo subjects (M: 25.6% versus P: 16.7%), respectively.

The most frequent TEAEs in the ALGS population are reported as abdominal pain (45,5%), cough (34.5), diarrhoea (39.4%), headache (20.7%), nasopharyngitis (34.5%), pyrexia (48.3), upper respiratory tract infections (20.7%) and vomiting (37.9%). (e.g. from LUM001-304). Median time to first onset for events of diarrhoea and abdominal pain was 30 days and 61 days, respectively. The

duration of the gastrointestinal events is described as short with a median duration for events of diarrhoea and abdominal pain of 2 days and 1 day, respectively.

The incidence of SAEs in the ALGS open-label, long-term extension studies is reported slightly lower with about 29.8% (25/84 participants) for participants exposed to maralixibat. The available limited placebo comparison from LUM001-301/302) seems not to indicate a significant difference regarding SAEs between maralixibat and placebo. No child died during the trials.

Laboratory data showed several mostly isolated and seemingly asymptomatic, but significant elevations in ALT in some ALGS subjects during treatment and a related warning statement was included in 4.4 of the SmPC. Assessing the totality of data it is concluded that these are too limited to draw firm conclusions regarding potential hepatotoxicity of maralixibat. Hepatotoxicity has been defined as significant potential risk in the RMP and will be monitored post-approval by means of the planned long term safety and clinical outcomes study that is made specific obligation to this Marketing authorisation.

Preliminary data in 8 infants (MRX-801) showed that 7 participants (87.5%) had at least 1 treatment-emergent adverse event (TEAE), 2 participants (25.0%) had a TEAE related to study drug, and 4 participants (50.0%) had a Grade ≥3 TEAE. There were 4 participants (50.0%) who had serious adverse events (SAEs), none of which were considered to be related to the study drug. No TEAE led to study drug discontinuation or death. Four patients had increased levels of transaminases.

3.5. Uncertainties and limitations about unfavourable effects

The safety population is too small to identify reliably signals for infrequent or rare toxicities and safety assessment is hampered by the fact that the observed safety event may reflect the underlying disease as well as drug-related TEAEs. Accordingly, the applicant will provide annual updates on any new emerging safety and efficacy data in annual updates to be provided in the annual reassessments of this marketing authorisation under exceptional circumstances. Furthermore, the safety database will be enlarged by means of the planned post authorisation long term safety and clinical outcomesstudy. Both requirements are defined specific obligations to this marketing authorisation.

Laboratory data showed several elevations in ALT in some ALGS subjects during treatment. Although the underlying liver disease might have contributed to this finding, the DSM was sufficiently concerned and triggered an assessment of these events by an independent panel of liver experts. The experts concluded that based on the literature, the accumulated pre-clinical and clinical trial data as well as the detailed independent external liver safety review, there is evidence that maralixibat may cause ALT elevations in a certain percentage (2-5% probably, 10-20% probably or possibly related events) of subjects with ALGS. No predictors of this treatment response have been identified so far. None of the observed events were assessed as serious and none led to liver-related morbidity or mortality. Since data in the paediatric population is very limited more data will we generated post-approval in a 5 year prospective, long term safety and clinical outcomes study on the long-term safety and clinical outcomes of Livmarli as outlined in the specific obligations of this marketing authorisation under exceptional circumstances. Furthermore, the applicant will provide yearly updates on all newly emerging data on safety and efficacy to be assessed within the annual reassessments for an unlimited time.

Due to the underlying disease, it is difficult to identify potential drug-related gastrointestinal adverse events.

Maralixibat was designed to be minimally absorbed following oral administration because the site of action is within the lumen of the GI tract. It is metabolically stable *in vivo* and excreted almost

exclusively in the faeces as intact parent drug. However, it needs to be considered from the non-clinical data that in the human paediatric population bioavailability may increase. A more permeable intestinal barrier may result from situations in which the gastrointestinal system is chronically disturbed and could lead to higher blood levels of maralixibat and induce other systemic adverse events particularly in children below the age of one year. Even though higher systemic exposure has been tolerated in previous human (adults) and non-clinical studies without critical safety findings it is planned that the patients, especially those under the age of 1 year, are closely monitored for safety in the post-authorisation phase (MRX-801 study, LEAP study, SOB to this marketing authorisation).

3.6. Effects Table

Table 22 Effects Table for Livmarli (treatment of cholestasis in ALGS) (data cut-off: 1 December 2019)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence*	References
Favourable Effects						
Change in sBA in RWD (mITT)	Change in LS mean (SE) weeks 22 vs. 18	µmol /L	-21.73 (43.125) p=0.6234	95.55 (30.488) p=0.0086	Small sample size, retrospective adaptation in response criterion. Very weak evidence.	LUM001 -304
Δ Change in sBA in RWD (mITT)	Diff between Treatment and Control in Change in LS mean (SE) Week 22 vs 18	µmol /L	-117.28 (52.828) p=0.0464		Small sample size, retrospective adaptation in response criterion. Very weak evidence.	LUM001 -304
Change in sBA in RWD (ITT)	Change in mean (SE) weeks 22 vs. 18	µmol /L	-16.73 (30.412) p=0.5923	93.58 (33.219) p=0.0130	Small sample size, short observation time. Placebo-control. Moderately strong evidence	LUM001 -304
Change in sBA in run-in (ITT)	Change in mean value weeks 18 vs. baseline	µmol /L	-87.73 (22.280) p=0.0005	N/A	Small sample size, lack of placebo control. Objective parameter. Moderately strong evidence	LUM001 -304
Change in sBA in OLE (ITT)	Change in mean value weeks 48 and 204 vs. baseline	µmol /L	-96.44 (32.068) p=0.0058 -180.84 (47.672) p=0.0020	N/A	Small sample size, absence of placebo, but objective parameter. Moderately strong evidence up-to week 48. Unknown effects from confounders (concomitant treatment, drops-outs, switch to different dose) after week 48. Very weak evidence	LUM001 -304
Change in ItchRO(Obs) RWD (ITT)	Change in mean value weeks 22 vs. 18	scores	0.201 (0.2180), p=0.3754	1.712 (0.2513) p<0.0001	Small sample size. Short duration, but placebo-control. moderately strong evidence	LUM001 -304

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence*	References
Change in ItchRO(Obs) OLE W48 (ITT)	Change in mean value (CI) week 48 vs. baseline	score	-1.620 (-2.124, -1.116), p<0.0001	N/A	Small sample, lack of control. Limited evidence	LUM001-304
Change in ItchRO(Obs) OLE W204 (ITT)	Change in mean value (CI) week 204 vs. baseline		-2.320 (-2.893, -1.748), p<0.0001	N/A	Small sample size, lack of control, unknown effects from confounders (concomitant treatment, drops-outs, switch to different dose). Very weak evidence	LUM001-304
Unfavourable Effects						
TEAE		n/N %	30/31 96.8 %	N/A	<18 weeks treatment duration, no placebo control	LUM001-304
Drug-related TEAE	TEAE Potentially Related to Study Drug	n/N %	12/31 38.7%	N/A	<18 weeks treatment duration, no placebo control	LUM001-304
Serious TEAE		n/N %	4/31 12.9%	N/A	<18 weeks treatment duration, no placebo control	LUM001-304
Drug related SAE	Serious TEAE Potentially Related to Study Drug	n/N %	0/31 0.0 %	N/A	<18 weeks treatment duration, no placebo control	LUM001-304
Death	Death	n/N %	0/84 0.0 %	N/A	Paediatric Population	SCS
Drug related Discontinuation	TEAE Leading to Study Drug Discontinuation	n/N %	13/84 15.5 %	N/A	Paediatric Population	SCS
Diarrhoea		n/N %	13/31 41.9%	N/A	<18 weeks treatment duration, no placebo control	LUM001-304
Abdominal pain	PT= Abdominal+ upper abdominal pain	n/N %	12 /31 38.7 %	N/A	<18 weeks treatment duration, no placebo control	LUM001-304
Vomiting		n/N %	11/31 35.5 %	N/A	<18 weeks treatment duration, no placebo control	LUM001-304

Abbreviations: MRX – maralixibat; PLA - placebo

*The assessments of the strength of evidence consider also a number of sensitivity analyses accounting for confounders provided post-hoc and not displayed in the table.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Reductions observed in sBA and esp. in sBA-related pruritus (based on ItchRO(Obs, Pt) and CSS) in the main study (DB phase) are considered highly clinically relevant favourable effects, as intractable pruritus is generally a burdensome and difficult to manage clinical symptom, that is also a key reason

for surgical intervention (biliary diversion or liver transplantation) in patients with ALGS. Improvement in the pruritus was accompanied with improvements in the quality of life, sleep and fatigue (mostly over the open-label long-term treatment period), which are also considered important favourable effects. Multiple sensitivity analyses indicate that these effects seem to be maintained in the "responder" patients over at least 2 years period of time.

In addition to sBA reductions, beneficial effects were also observed on cholesterol (obligatory precursor of sBA) and in xanthoma (small effects). However, these were not accompanied with clinically relevant improvements in bilirubin and liver function parameters (key indicators of liver damage due to toxic effects of bile acids).

Maralixibat appears to have an acceptable safety profile in patients with ALGS. Gastrointestinal adverse events as diarrhoea, abdominal pain and vomiting are reported to be the most common adverse drug reactions. Almost all of the TEAEs observed were mild to moderate and resolved with no action taken with maralixibat, which is suggestive of an overall favourable safety/tolerability profile.

However, a significant degree of uncertainty remains at present. In particular, this concerns the risk for potential intrinsic hepatotoxicity of maralixibat, which seems possible from the data available. Better characterisation of this potential risk will be done post approval by means of the planned long-term safety and clinical outcomes study and the annual updates on safety and efficacy within annual reassessments. Both requirements were made specific obligation to this marketing authorisation.

The ALGS trial population is a paediatric orphan disease population and thus very small. Therefore, the degree of remaining uncertainties is naturally high.

Data submitted in the infants to substantiate broadening of the indication are very limited. However, extrapolation of efficacy and safety data from older children appears justified, given that similar effects on sBA and on CSS as in the older population were observed, and since no new and unique AEs were reported in the infant population. Nonetheless, the degree of uncertainty remains high and post-approval monitoring of safety and efficacy will be conducted.

3.7.2. Balance of benefits and risks

Currently, efficacy of maralixibat in the claimed indication for treatment of cholestatic pruritus in ALGS is based on a placebo-controlled short-term withdrawal trial and long-term open-label data on pruritus and sBA (key PD marker of efficacy and acknowledged driver of pruritus in ALGS) in patients of 1 year of age and older and on short-term and uncontrolled open-label data on sBA and pruritus in a very limited set of infants 2-10 months of age. The data provided on efficacy are limited but sufficient considering the rarity of the disease and the continuous provision of new emerging data on an annual basis in this marketing authorisation under exceptional circumstance.

The safety profile in patients >2 months of age, even though based on limited data, is considered acceptable for marketing authorisation. The important potential risk of hepatotoxicity of maralixibat is considered balanced with a warning statement on liver monitoring in 4.4 of the SmPC. Both uncertainties will be followed up upon post approval within this marketing authorisation under exceptional circumstances.

The benefits gained from maralixibat treatment in relation to cholestatic pruritus and its sequelae together with the acceptable safety profile are considered to be sufficient to support an indication for "treatment of cholestatic pruritus in ALGS patients of 2 months of age or older".

3.7.3. Additional considerations on the benefit-risk balance

The comprehensiveness of the data package

The comprehensiveness assessment in the finally agreed indication is provided below referring to "treatment of cholestatic pruritus in patients with ALGS of age of 2 months and older":

1. Quality of evidence. The key evidence of efficacy is limited to a small, single, mostly uncontrolled, open-label trial in a 1 to 17 years old patient population with only a 4-week randomised placebo-controlled withdrawal phase. To allow for a more robust assessment of efficacy and safety the duration of the placebo-controlled phase should have been longer as suggested in a previous EMA scientific advice. It is however acknowledged by the CHMP that there should be a restricted use of placebo in this rare disease and consistency is seen across various parameters interlinked (e.g., sBA levels, ItchRO, CSS, fatigue scores), which suggest sufficient robustness of the effects observed. Evidence of efficacy in infants is limited to a small, single-arm, open-label trial, with efficacy parameters restricted to sBA and CSS assessments over the time period of around 13 weeks.
2. The precision of effect size: Treatment effect was demonstrated in a small sample size and its precision is therefore naturally low. The absence of a placebo-control for most of the observation period further adds uncertainties to the true effect size. However, the effects on sBA and pruritus are sufficiently large to conclude on a relevant benefit.
3. The endpoints are considered to be clinically meaningful, as these capture various aspects of the burden of cholestatic pruritus on the affected patients.
4. The maintenance of effect has been shown for up to week 48, which can be considered sufficient to establish long-term efficacy. However, absence of placebo control specifically for the subjective and variable symptom of pruritus is acknowledged as limitation.
5. Safety exposure. With a safety database of 86 treated patients, the number of patients is limited. It is not considered possible to draw robust conclusions on safety in relation to potential hepatotoxicity and post-marketing data will be necessary.
6. The safety follow up duration is considered acceptable in the patients above the age of 1 year, but not in younger population. Post-approval collection of safety information especially in younger patients is, therefore, planned.
7. The proposed target population can be substantiated with the data from the studies. Extrapolation of data to older patients with >50 kg of body weight is accepted.
8. Mechanism of action of the product is clearly described. However, it remains unclear whether the proposed dosing regimen is optimal.
9. The natural history of the disease is relatively well described.

In conclusion, the CHMP does not consider the data provided to be sufficiently comprehensive to support a full MA. Therefore, at Day 181 of the procedure, the applicant applied for a MA under exceptional circumstances.

The CHMP agrees with the applicant that, due to the very low prevalence of the disease, it cannot reasonably be expected that comprehensive efficacy and safety data can be generated within a reasonable timeframe. Availability of patients for placebo controlled trials due to widespread use of ileal bile acid transport inhibitors in ongoing and completed clinical studies and expanded access programmes can be expected to become even more difficult once the medicinal product is placed on the EU market. Therefore, the CHMP considers that the applicant has sufficiently demonstrated that it

is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use.

Within a marketing authorisation under exceptional circumstances the applicant will annually provide post-authorisation long term safety data and data on long-term clinical outcome events in patients with Alagille Syndrome to address the above-mentioned general uncertainties by means of a long term safety and clinical outcomes trial which is a specific obligation of the marketing authorisation. In particular the trial will also further evaluate hepatotoxicity and monitor pruritus severity and sBA over time. Furthermore, the applicant will provide yearly updates on all new emerging information concerning safety and efficacy of maralixibat within the annual reassessments.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant. At Day 181 of the procedure, the applicant applied for a MA under exceptional circumstances.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

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

4. Recommendations

Outcome

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

Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product

within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
In order to further characterise the long-term safety and efficacy of maralixibat in the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS), the MAH shall conduct and submit the results of study LEAP (MRX-310) according to an agreed protocol.	Annual (within annual reassessment)
In order to ensure adequate monitoring of safety and efficacy of maralixibat in the treatment of patients with Alagille syndrome (ALGS), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of maralixibat.	Annual (within annual re-assessment)

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that maralixibat is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0133/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.