30 May 2024
EMA/299965/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIVMARLI

International non-proprietary name: Maralixibat

Procedure No. EMEA/H/C/005857/II/0003/G

Note

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

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List of abbreviations

Abbreviation	Definition
7αC4	7α-hydroxy-4-cholesten-3-one
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse event of special interest
ALGS	Alagille syndrome
AUC_{last}	AUC from Time 0 to last measurable concentration
BID	Twice daily
BLQ	Below the limit of quantification
BSEP	Bile salt export pump
C_{max}	Maximum concentration observed
CIC	Caregiver Impression of Change
CIS	Caregiver Impression of Severity
CSR	Clinical study report
CSS	Clinician scratch scale
CYP	Cytrochrome P450
DDI	Drug-drug interaction
ECI	Event of clinical interest
EDQ(Obs)	Exploratory diary questionnaire (observer)
ET	Early termination
fBA	Fecal bile acid
FDA	US Food and Drug Administration
FDSC	Fixed drug substance concentrations
FDV	Fixed dosing volume
FMQ	Fda medical queries
FSV	Fat-soluble vitamin
FXR	Farnesoid X receptor
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HCC	Hepatocellular carcinoma
IBAT	Ileal bile acid transporter

Abbreviation	Definition
IND	Investigational new drug
INR	International normalized ratio
IR	Immediate release
ItchRO(Obs)	Itch reported outcome – observer
ItchRO(Pt)	Itch reported outcome – patient
ITT	Intent-to-treat
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLOQ	Lower limit of quantitation
LPA	Lysophosphatidic acid
LTE	Long-term extension
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
NAPPED	Natural Course of Progression of PFIC and Effect of Biliary Diversion
NLS	Native liver survival
nt-PFIC	Nontruncating PFIC
OATP	Organic anion transporting polypeptide
PBC	Primary biliary cholangitis
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamic
PEBD	Partial external biliary diversion
PedsQL	Pediatric Quality of Life Inventory
PFIC	Progressive familial intrahepatic cholestasis
PIBD	Partial internal biliary drainage
PIC	Patient Impression of Change
PIP	Pediatric investigational plan
PIS	Patient Impression of Severity of Pruritus
PK	Pharmacokinetic
PSC	Primary sclerosing cholangitis
PT	Preferred term
QD	Once daily
QoL	Quality of life
QTc	Corrected QT interval

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
sBA	Serum bile acid
SBD	Surgical biliary diversion
SD	Standard deviation
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFS	Transplant-free survival
TJP2	Tight junction protein 2
t-PFIC	Truncating PFIC
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Mirum Pharmaceuticals International B.V. submitted to the European Medicines Agency on 3 April 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	Type IA	None

Grouped variation consisting of:
1) Extension of indication to include treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in patients 2 months of age and older for LIVMARLI, based on results from studies MRX-502, LUM001-501, MRX-503, MRX-800 and MRX-801; MRX-502 is an international, multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 3 study that evaluated the efficacy and safety of maralixibat in PFIC participants aged >12 months to <18 years on a proposed dosage of up to 600 µg/kg BID over 6 months. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Annex II are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the product information.
2) B.I.b.1.b - type IA - To tighten the active substance maralixibat specification limits for genotoxic impurities. In addition, further editorial changes are made in module 3 which are consequential to the extension of indication and the higher maximum daily dose.

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

Information relating to orphan designation

LIVMARLI, was designated as an orphan medicinal product EU/3/13/1216 on 18.12.2013 in the following condition: Treatment of progressive familial intrahepatic cholestasis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Livmarli II-0003-G 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: ema.europa.eu/en/medicines/human/EPAR/livmarli.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0436/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0436/2022 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

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

Protocol assistance

The MAH received protocol assistance from the CHMP, please refer to 2.1.3.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: N/A

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	22 Apr 2023	22 Apr 2023	☐
☐	CHMP Rapporteur Assessment Report	16 Jun 2023	04 Jul 2023	☐
☐	PRAC Rapporteur Assessment Report	23 Jun 2023	26 Jun 2023	☐
☐	PRAC members comments	28 Jun 2023	28 Jun 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	29 Jun 2023	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	06 Jul 2023	06 Jul 2023	☐
☐	CHMP members comments	10 Jul 2023	10 Jul 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 Jul 2023	14 Jul 2023	☐
☐	RSI	20 Jul 2023	20 Jul 2023	☐
☐	Submission	13 Oct 2023	13 Oct 2023	☐

Status of this report and steps taken for the assessment				
☐	CHMP Rapporteur Assessment Report	14 Nov 2023	17 Nov 2023	☐
☐	PRAC Rapporteur Assessment Report	17 Nov 2023	20 Nov 2023	☐
☐	PRAC members comments	22 Nov 2023	22 Nov 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	23 Nov 2023	23 Nov 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	30 Nov 2023	30 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	04 Dec 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	07 Dec 2023	10 Dec 2023	☐
☐	2nd RSI	14 Dec 2023	14 Dec 2023	☐
☐	Submission	23 Feb 2023	23 Feb 2023	☐
☐	CHMP Rapporteur Assessment Report	25 Mar 2024	10 Apr 2024	☐
☐	PRAC Rapporteur Assessment Report	27 Mar 2024	28 Mar 2024	☐
☐	PRAC members comments	03 Apr 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Apr 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Apr 2024	11 Apr 2024	☐
☐	CHMP members comments	15 Apr 2024	15 Apr 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Apr 2024	19 Apr 2024	☐
☐	3rd RSI	25 Apr 2024	25 Apr 2024	☐
☐	Submission	02 May 2024	02 May 2024	☐
☐	CHMP Rapporteur Assessment Report	15 May 2024	22 May 2024	☐
☐	PRAC Rapporteur Assessment Report	15 May 2024	13 May 2024	☐
☐	PRAC members comments	21 May 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	21 May 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	23 May 2024	23 May 2024	☐
☐	CHMP members comments	23 May 2024	23 May 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	30 May 2024	26 May 2024 30 May 2024	☐
☒	Opinion	30 May 2024	30 May 2024	☐
☒	The CHMP adopted a report on similarity on	30 May 2024	30 May 2024	
☒	CHMP adopted a report on the significant	30 May 2024	30 May 2024	

	clinical benefit in comparison with existing therapies on			

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Maralaxibat is proposed to include the following additional indication: Treatment of Progressive Familial Intrahepatic Cholestasis (PFIC). Similar to the previously granted indication for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) the treatment with Livmarli was initially proposed for patients 2 months of age and older. During the procedure, the claimed age range was adapted to 3 months of age and older.

PFIC is a group of rare inherited diseases of hepatocellular origin resulting in disrupted bile formation, leading to accumulation of the components of bile within the liver, including bilirubin and bile acids (Davit-Spraul et al. 2009; Mehl et al. 2016).

State the claimed the therapeutic indication

The wording of the initially proposed indication was (additional indication is displayed in bold and underlined):

Livmarli is indicated in patients 2 months of age and older for the treatment of:

• Cholestatic pruritus in patients with Alagille syndrome (ALGS)

• Progressive familial intrahepatic cholestasis (PFIC)

The approved indication is (additional indication is displayed in bold and underlined):

Livmarli is indicated for the treatment of:

- Cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older,
- **Progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older**.

A different posology is proposed as compared to the existing indication in ALGS. While in ALGS, patients are treated with 190 µg/kg -380 µg/kg once daily, the proposed dosing for PFIC is 285 µg/kg (starting dose) to 570 µg/kg twice daily (maximum dose depending on tolerability).

(Of note: The given doses are based on maralixibat free base. In the following, mainly the maralixibat chloride equivalent will be used: the proposed BID dose of 570 µg/kg corresponds to 600 µg/kg maralixibat chloride (mainly referred as "600 µg/kg maralixibat" by the MAH.)

Epidemiology

The exact prevalence of PFIC is unknown, but the disease is estimated to affect 1 in every 50,000 to 100,000 births (Davit-Spraul et al. 2009). PFIC represents 10%–15% of causes of cholestasis in

children (Gunaydin and Bozkurter Cil 2018) and 10%–15% of indications for liver transplantations in children (Davit-Spraul et al. 2009).

Biologic features, Aetiology and pathogenesis

The main subtypes PFIC1, PFIC2, and PFIC3 are caused by mutations in ATP8B1, ABCB11, and ABCB4, respectively (Amer and Hajira 2014; see below). In addition, more rare subtypes of PFIC (PFIC subtypes 4-6, referring to loss of function in TJP2, FXR, and MY05B) have recently been identified. Additional disease-causing variants continue to be identified.

Figure 1 Subtypes of progressive familial intrahepatic cholestasis (PFIC)

Disease	Gene	Protein Deficiency	Proportion of PFIC Population	Additional Comments
PFIC1	*ATP8B1*	FIC1 (a phospholipid transporting floppase in canalicular membrane; involved in maintaining an asymmetric distribution of phospholipids across the canalicular membrane bilayer of hepatocytes, thereby protecting the canalicular membrane from hydrophobic bile acids and maintaining its integrity (Srivastava 2014)	10%–38%	• Also referred to as Byler disease • Impaired hepatocyte bile salt secretion resulting in cholestasis • Extrahepatic manifestations (e.g., diarrhea, pancreatic disease) • Onset of symptoms in early infancy
PFIC2	*ABCB11*	BSEP (bile salt export pump in canalicular membrane of hepatocytes, responsible for exporting bile acids from the hepatocyte into the bile canaliculus) (Strautnieks et al. 1998; Srivastava 2014)	38%–91%	• Also referred to as BSEP deficiency • Increased intracellular bile salt concentrations • Three subtypes based on BSEP activity (described in Section 2.5.1.1) • Onset of symptoms in early infancy
PFIC3	*ABCB4*	MDR3 (floppase in canalicular membrane that is involved in transporting phosphatidylcholine from the hepatocyte into the bile canaliculus to neutralize bile salts and prevent injury to biliary epithelia and bile canaliculi) (Deleuze et al. 1996; Srivastava 2014; Delaunay et al. 2016)	~30%	• Also referred to as MDR3 deficiency • Increased free bile salts in canaliculi causing damage of cholangiocytes • Increased cholesterol crystallization causing obstruction of small bile ducts • Associated with high levels of GGT • Age of onset of symptoms can vary widely
PFIC4	*TJP2*	TJP2 (involved in maintaining cell-to-cell adhesion required for integrity of the canalicular membrane) (Sambrotta et al. 2014)	not known	• Also referred to as TJP2 deficiency • Reduced integrity of the canalicular membrane and reflux of toxic bile acids through the paracellular spaces into hepatocytes, causing hepatocyte damage and cholestasis • Variable spectrum of presentation • Increased risk of hepatocellular carcinoma • Neurological and respiratory symptoms
PFIC5	*NR1H4*	FXR (in the liver FXR acts as a nuclear bile acid-sensing receptor involved in the expression of BSEP and sometimes MDR3) (Gomez-Ospina et al. 2016)	not known	• Also referred to as farnesoid X receptor deficiency • Causes loss of BSEP expression, leading to the accumulation of toxic bile and hepatocellular damage • Rapidly progressive liver disease with early onset coagulopathy, high alpha-fetoprotein and ultimately require a liver transplant
PFIC6	*MYO5B*	MYO5B (localizes canalicular membrane proteins for bile salt trafficking) (Gonzales et al. 2017)	not known	• Can present with isolated cholestasis or cholestasis with intractable diarrhea (microvillous inclusion disease that causes severe diarrhea and an inability to absorb nutrients due to hypoplasia and/or atrophy of the intestinal epithelial cells)

BSEP=bile salt export pump; GGT=gamma glutamyltransferase; PFIC=progressive familial intrahepatic cholestasis.

All PFIC types have an autosomal recessive inheritance, which leads to a relative of absolute deficiency in specific proteins involved in the hepatocellular transport system and bile formation.

Clinical presentation, diagnosis and stage/prognosis

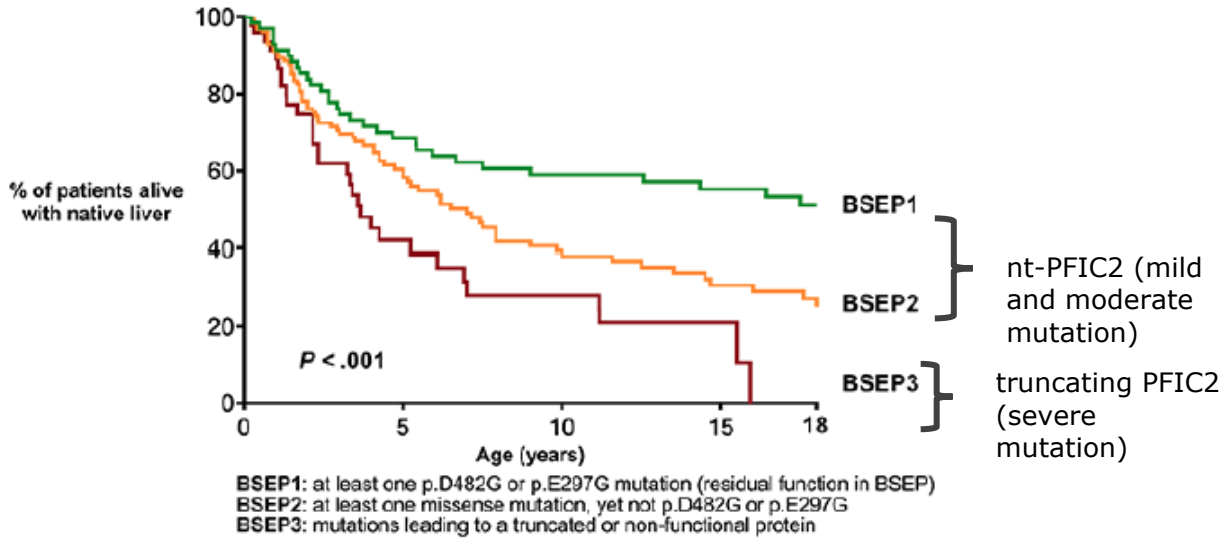
All PFIC subtypes share the main clinical manifestations of cholestasis and are associated with potential early mortality, morbidity, and severe pruritus with devastating consequences on patients' QoL. As a result of impaired bile flow, sBA levels in PFIC are severely and persistently elevated (Morris et al. 2015). The accumulation of bile acids results in progressive liver damage, and if left untreated, can lead to end-stage liver disease and death (Mehl et al. 2016; Bull and Thompson 2018). Due to a previous lack of treatment options, 70%–80% of patients ultimately require liver transplantation.

Children often present with jaundice and debilitating pruritus within the first years of life. The pruritus is often so distressing that it often requires surgical therapy. It often leads to sleep disturbances,

fatigue, irritability, cutaneous self-mutilation, poor attention, and school performance, as well as impaired QoL. Many patients will go on to receive a liver transplant in the absence of liver failure to provide relief from pruritus (Bull and Thompson 2018). In addition to pruritus, other disease manifestations include growth retardation, fat malabsorption, deficiencies in FSVs, and elevated transaminases and bilirubin (Srivastava 2014; Mehl et al. 2016). PFIC has also been associated with the development of hepatocellular carcinoma (HCC) at an early age.

All patients with PFIC, regardless of mutational status, are at risk of liver disease progression and may eventually need liver transplantation (van Wessel et al. 2020). In patients with PFIC2, only around 45% and 32% will survive with their native liver to Year 10 and Year 18, respectively (Figure 1; van Wessel et al. 2020).

Figure 2 Percent of Patients with Native Liver Survival by Genotype Severity



BSEP = bile salt export pump; PFIC = Progressive Familial Intrahepatic Cholestasis.

Note: Nontruncating mild mutation = BSEP1; Nontruncating moderate mutation = BSEP2; truncating severe mutation = BSEP3.
Source: van Wessel et al. 2020

Management

In 2021, the IBAT inhibitor odevixibat (Bylvay) became the first pharmacologic therapy approved for the treatment of PFIC in patients aged 6 months or older. Approval was based on a Phase 3, randomized, placebo-controlled study of 62 patients with PFIC1 (n=17) and PFIC2 (n=45), demonstrating a reduction in sBA levels and pruritus scores (Thompson et al. 2022).

Before the introduction of odevixibat, only off-label pharmacologic options for the treatment of PFIC have traditionally been used and were limited to treatment of pruritus as well as dietary supplementation and prevention of vitamin deficiencies. Most common off-label drugs used included UDCA, cholestyramine, and rifampicin.

Surgical Interventions

Surgical interventions to treat the pruritus and cholestasis associated with PFIC include surgical biliary diversion procedures (SBD) procedures and liver transplantation. Three types of surgical procedures have been developed for SBD: two connecting gall bladders to either skin (partial external biliary diversion – PEBD), or to colon (partial internal biliary diversion – PIBD) and one connecting ileum to colon. All three allow that re-absorption of bile acids in ileum is hindered.

SBD leads to improvement in pruritus and growth, liver histology, and better disease outcomes with longer NLS (Kurbegov et al. 2003; Arnell et al. 2010; Cielecka-Kuszyk et al. 2019).

Two systematic reviews with meta-analyses conducted by Verkade et al. (2020; 16 publications with 155 patients with PFIC) and Bolia et al. (2022; 25 publications with 424 patients with PFIC) showed that 67% patients after PEBD and 59.5% after various SBD (PEBD, PIBD, illeal exclusion) had early response in pruritus and decrease in sBA and bilirubin. Post-SBD absolute values and percentage reductions could discriminate PFIC patients with an early response (pruritus) and long-term response (native liver survival; NLS) from those with no response. Interestingly, post-SBD absolute ALT levels or percentage ALT change did not discriminate responders from non-responders (pruritus and outcomes).

In 2017, the Natural Course and Prognosis of PFIC and Effect of Biliary Diversion (NAPPED) consortium was created to collect individual data of patients with a clinical phenotype of PFIC. The research consortium includes more than 50 academic centers across the globe with data collection using a pre-specified case-record form using REDcap. The NAPPED consortium evaluated the response to SBD in BSEP and FIC1 deficiencies (van Wessel et al. 2020). In BSEP deficiency (264 patients), a clear relationship between SBD and NLS was observed with time-dependent Cox regression analysis showing that SBD was associated with significantly higher NLS (hazard ratio [HR] 0.50; 95% CI: 0.27, 0.94; p=0.03; van Wessel et al. 2020). Because sBA levels play an important role in hepatocellular damage, the authors performed ROC analyses on postsurgical sBA levels in relation to NLS. A post-SBD sBA level <102 µmol/L was associated with prolonged NLS after SBD (p<0.001, AUC sBAs: 0.778; cut-off 102 µmol/L: sensitivity 80%, specificity 75%). Additionally, a decrease of at least 75% in sBA was associated with improved NLS after SBD (p<0.001; AUC % change sBAs 0.774; cut-off 75%: sensitivity 73%; specificity 78%). In FIC1 deficiency (130 patients), time-dependent Cox regression analysis showed that SBD tended to be associated with NLS (overall HR 0.55; 95% CI: 0.28, 1.03; p=0.06; van Wessel et al. 2021). ROC analyses were performed for post-SBD sBA levels in relation to NLS after SBD. A post SBD sBA level <65 µmol/L tended to be associated with prolonged NLS after SBD (p=0.05; AUC sBAs, 0.589; sensitivity, 80%; specificity, 61%).

Figure 3 Observed native liver survival after SBD stratified for post-SBD sBA cut-offs (van Wessel et al., 2020)

Figure 3 Observed Native Liver Survival after Surgical Biliary Diversi Stratified for Post-Surgical sBA Cut-Offs

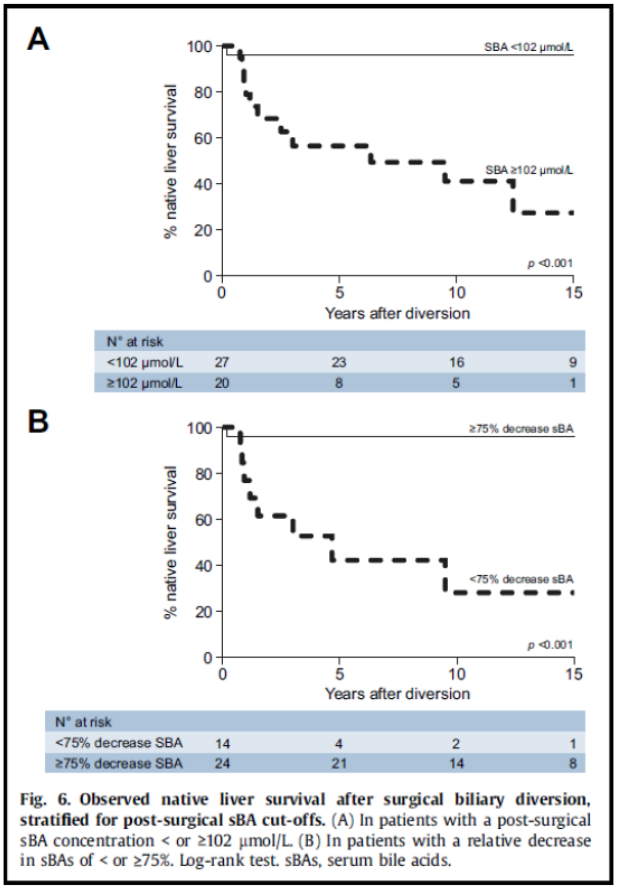


Fig. 6. Observed native liver survival after surgical biliary diversion, stratified for post-surgical sBA cut-offs. (A) In patients with a post-surgical sBA concentration < or ≥102 µmol/L. (B) In patients with a relative decrease in sBAs of < or ≥75%. Log-rank test. sBAs, serum bile acids.

sBA=serum bile acid.
(A) In patients with a post-surgical sBA concentration < or ≥102 µmol/L.
(B) In patients with a relative decrease in sBAs of < or ≥75%.
Source: van Wessel et al. 2020.

Table 1 Literature for liver-related outcomes after SBD

Publication Title	Authors	Journal	Methods	Results
Systematic reviews				
Nontransplant surgical interventions in progressive familial intrahepatic cholestasis	Davis AR, Rosenthal P, Newman TB	J Pediatr Surg 2009;44: 821–7	A systematic search of the literature for articles evaluating the outcome of nontransplant surgical interventions in PFIC patients was performed. Data from these studies was abstracted and summarized.	No trials have been performed addressing nontransplant surgical interventions in PFIC patients. In total, 11 case series and case reports were evaluated. Generally, patients had successful outcomes (81%) with cessation of progression of disease and resolution of symptoms. Treatment failures were often associated with more advanced disease.
Systematic review and meta-analysis: partial external biliary diversion in progressive familial intrahepatic cholestasis	Verkade HJ, Thompson RJ, Arnell H, et al.	J Pediatr Gastroenterol Nutr 2020;71: 176–183.	A systematic literature review and meta-analysis to evaluate relationships between liver biochemistry and pruritus relief or outcomes after PEBD.	Searches identified 175 publications and 16 met inclusion criteria. sBA could discriminate responders from nonresponders for pruritus improvement (area under the curve, 0.99; p<0.0001; this was also true for bilirubin (0.87; p=0.003), whereas ALT could not discriminate responders from nonresponders for pruritus improvement. Reductions from pre-PEBD values in sBA (0.89; p=0.0003) and bilirubin (0.98; p=0.002) but not ALT significantly discriminated decreased aggregate need for liver transplant.
Epidemiology and burden of progressive familial intrahepatic cholestasis: a systematic review	Jones-Hughes T, Campbell J, Crathorne L	Orphanet J Rare Dis 2021;16: 255	Databases including MEDLINE and Embase were searched for publications. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.	Three systematic reviews and twenty-two studies were eligible for inclusion, with a total of 2603 patients. The most detailed data come from the NAPPED study where NLS of >15 years is predicted in PFIC2 patients with a sBA below 102 µmol/L after SBD.
Biliary diversion in progressive familial intrahepatic cholestasis: a systematic review and meta-analysis	Bolia R, Goel AD, Sharma V, Srivastava A	Expert Rev Gastroenterol Hepatol 2022;16: 163–72.	PubMed, Scopus, and Google Scholar were searched for publications on PFIC and biliary diversion.	25 studies [424 children (PEBD–301, PIBD–93, IE–30)] were included. Pruritus resolved in 59.5%. Significant overlap in confidence intervals indicated no significant differences among procedures. Absolute decrease in BA (AUROC- 0.72) and bilirubin (AUROC-0.69) discriminated responders and non-responders. Overall, 27% required LT. The post-operative sBA (AUROC-0.9) and bilirubin (AUROC-0.85) determined NLS. There was no difference in ALT levels between responders and non-responders.

Publications looking at histological improvements after SBD				
Biliary diversion for progressive familial intrahepatic cholestasis: improved liver morphology and bile acid profile	Kurbegov AC, Setchell KDR, Haas JE, et al.	Gastroenterology. 2003;125: 1227–34.	Liver biopsy specimens from 3 children with low gamma-glutamyltransferase PFIC before and after PEBD were reviewed. Follow-up liver biopsies were performed 9-60 months after PEBD. Light and electron microscopic features were scored blindly.	The resolution of hepatic morphologic abnormalities following PEBD supports PEBD as an effective therapy for PFIC
Follow-up in children with progressive familial intrahepatic cholestasis after partial external biliary diversion	Arnell H, Papadogiannakis N, Zemack H, et al.	J Pediatr Gastroenterol Nutr 2010;51: 494–9.	From a total of 18 children with PFIC, 13 underwent PEBD, and 12 of these with clinical and histological follow-up.	When compared with baseline, statistically significant reductions were found in histological cholestasis 1 and 3 years after PEBD, and in fibrosis 5 and >10 years after PEBD.
Long-term follow-up in children with progressive familial intrahepatic cholestasis type 2 after partial external biliary diversion with focus on histopathological features	Cielecka-Kuszyk J, Lipiński P, Szymańska S, et al.	Pol J Pathol 2019;70: 79-83.	8 liver biopsies from 4 PFIC2 patients were assessed comparing the results from the first biopsies done at the time of PFIC diagnosis and years after PEBD.	In the follow-up biopsies after PEBD, cholestasis completely disappeared in 3 patients and decreased significantly in 1 other patient. Based on Batts and Ludwig fibrosis scoring system, the liver fibrosis had resolved in 2 out of 3 patients. Partial external biliary diversion significantly improved the clinical, anthropological, biochemical as well histological outcome of the patients.
Seminal NAPPED consortium publications				
Genotype correlates with the natural history of severe bile salt export pump deficiency	van Wessel DBE, Thompson RJ, Gonzales E, et al.	Journal of Hepatology 2020;73: j84–93	Multicenter, retrospective cohort study with 264 patients with ABCB11 mutations.	SBD was associated with significantly increased NLS (hazard ratio 0.50; 95% CI: 0.27, 0.94: p=0.03) in BSEP1 and BSEP2. sBA concentration below 102 µmol/L or a decrease of at least 75% after SBD predicted NLS of >15 years (p<0.001).
Impact of genotype, serum bile acids, and surgical biliary diversion on native liver survival in FIC1 deficiency	van Wessel DBE, Thompson RJ, Gonzales E, et al.	Hepatology 2021;74: 892–906.	Multicenter, combined retrospective and prospective study included 130 patients with predicted pathogenic *ATP8B1* variants.	Survival analysis showed an overall NLS of 44% at age 18 years. sBAs at presentation were negatively associated with NLS. SBD decreased sBAs (p=0.005). SBD (HR 0.55, 95% CI: 0.28, 1.03, p=0.06) and post-SBD sBA concentrations < 65 µmol/L (p=0.05) tended to be associated with improved NLS.

AUROC=area under receiver operating curve; BSEP=bile salt export pump; PEBD=partial external biliary diversion; PFIC=progressive familial intrahepatic cholestasis; PIBD=partial internal biliary diversion; IE=ileal exclusion; NAPPED=Natural Course and Prognosis of PFIC and Effect of Biliary Diversion; NLS=native liver survival; sBA=serum bile acid; SBD=surgical biliary diversion.

Liver transplantation is currently the only definitive treatment available for PFIC, although disease recurrence and early graft failure are not uncommon. Liver transplantation is indicated in PFIC to address both severe pruritus as well as progressive liver damage caused by bile acid accumulation (Mehl et al. 2016; Bull and Thompson 2018). It corrects the underlying bile acid excretion defect and remains the only treatment option for end-stage liver disease in PFIC (EASL 2009; Mehl et al. 2016).

2.1.2. About the product

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

This transmembrane protein transporter, localized 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. The Applicant claims that since both, SBD and maralixibat, lead to reduced bile acid re-absorption in the gut, similar disease modifying effects/impact on long-term outcomes is to be expected from maralixibat as from SBA.

Maralixibat has been approved as Livmarli on 9th December 2022 for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older.

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

The development program of maralixibat in PFIC was discussed at two Protocol Assistance meetings with the EMA.

The key regulatory advice provided by EMA supporting the development of maralixibat in PFIC and highlighted the following issues:

- The EMA agreed that there is an unmet medical need for the development of new treatment strategies for PFIC2.
- In regard to clinical efficacy, the Study LUM001-501 results and proposed Phase 3 Study MRX-502 were discussed, and it was agreed that the endpoints employed in these studies and the amount of data from Study LUM001-501 at the time would support an indication on symptomatic relief for the "treatment of pruritus associated with PFIC."
- The design of Study MRX-502 was intended to be a confirmatory trial for Study LUM001-501; thus, Study MRX-502 was conducted as a 26-week, double-blind, placebo-controlled study with a primary objective to evaluate the efficacy of maralixibat on reducing the severity of pruritus. However, the CHMP also emphasized "that for an indication of 'treatment of PFIC', even if limited to a subset (i.e., PFIC2), support/demonstration of clear benefit in terms of clinically relevant hard endpoints such as postponement or deferral of liver transplant would be ultimately required."

The applicant has completed study MRX-502, the submitted programme appears to be roughly in line with the advice given.

2.1.4. General comments on compliance with GLP, GCP

GLP

The non-clinical repeated dose toxicity study submitted with this variation procedure had been performed compliant to GLP regulations.

GCP

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

2.2. Non-clinical aspects

2.2.1. Introduction

The Applicant submits several non-clinical studies, of which only two studies had not yet been assessed before:

Study MRX-NC-016; Investigation of the Binding of Maralixibat to Cholestyramine Resin (please, see section on Pharmacokinetics, below).

Study MRX-NC-012; A 4-Week Once Daily Oral Gavage Toxicity Study with Maralixibat or Volixibat in Sprague Dawley Rats (please, see section on Toxicology, below).

All other studies submitted with the non-clinical part of the submission in the context of the variation procedure under review had already been assessed during the initial application procedure for marketing authorisation. Furthermore, an updated Environmental Risk Assessment has been provided.

This variation procedure aimed at extending the indication from presently treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older in addition to the treatment of Progressive familial intrahepatic cholestasis (PFIC) in patients 2 months of age and older. The claimed age range in PFIC was changed by the company during the procedure for the treatment of PFIC in patients 3 months and older.

Whereas the minimum age of the patients intended to treat remains almost unchanged (2 months of age vs. 3 months of age) the maximum recommended daily human therapeutic dose is increased about three times (from presently 380 µg/kg bw/day to 1140 µg/kg bw/day). Both diseases, Alagille syndrome (ALGS) and Progressive Familial Intrahepatic Cholestasis (PFIC), are cholestatic liver diseases. Maralixibat is an oral inhibitor of the ileal bile acid transporter (IBAT) inhibiting bile acid reabsorption, thereby increasing fecal bile acid (fBA) excretion and lowering serum bile acid (sBA) levels.

2.2.2. Pharmacology

Not applicable

2.2.3. Pharmacokinetics

Investigation of the Binding of Maralixibat to Cholestyramine Resin [study MRX-NC-016; non-GLP; 2022]

To investigate the binding of maralixibat to cholestyramine resin, maralixibat was tested for binding using a filtration assay. The assay conditions were based according to the Applicant upon the FDA-recommended assay for testing of cholestyramine binding capacity for bile acids. Glycocholic acid (GCA) was tested in parallel as the positive control. Analysis of the GCA binding data showed a linear response and reasonable estimates of affinity and capacity of binding of GCA by cholestyramine. The analogous analysis for maralixibat failed to fit a linear model. According to the Applicant the results suggest that any inferred binding between maralixibat and cholestyramine is nonspecific and low affinity which is agreed to.

2.2.4. Toxicology

Repeat dose toxicity

A 4-Week Once Daily Oral Gavage Toxicity Study with Maralixibat or Volixibat in Sprague Dawley Rats [study MRX-NC-012; GLP; 2022]

Maralixibat was administered once daily via oral gavage to Sprague Dawley rats (5 animals/sex/group) for 4 weeks at doses 0 or 100 mg/kg.

The following parameters and endpoints were evaluated in this study: physical examination, body weight changes, food consumption, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis prior to scheduled necropsy), gross necropsy findings, organ weights, and histopathological examinations.

No maralixibat-related mortality occurred. Maralixibat-related clinical observations included head-burrowing and excess salivation. No significant maralixibat-related changes in body weight, body weight gain, or food consumption were noted, compared with controls.

No maralixibat-related effects in hematology, coagulation, clinical chemistry, or urinalysis test results were noted for scheduled sacrifice animals. No maralixibat-related organ weight changes or macroscopic or microscopic findings were noted.

The Applicant concludes that male and female rats were administered vehicle control article or 100 mg/kg/day maralixibat via oral gavage once daily for 4 weeks. No toxicologically relevant clinical observations or clinical or anatomical pathology findings were noted. Thus, the NOAEL is 100 mg/kg/day for maralixibat.

2.2.5. Ecotoxicity/environmental risk assessment

Summary of the ERA

As required by the respective guidelines, the applicant provided an environmental risk assessment for the active ingredient maralixibat. Based on prevalence data the $PEC_{surface\ water}$ has been calculated resulting in a value of 0.00064 µg/l. As the PEC of 0.00064 µg/l is below the action limit of 0.01 µg/l no Phase II assessment was performed. Furthermore, a log K_{ow} of 1.54 was presented leading to the conclusion that no further screening for persistence, bioaccumulation and toxicity is deemed necessary.

Screening for Persistence, Bioaccumulation and Toxicity

The applicant provided an experimentally derived log K_{ow} of 1.54, i.e. a study according to OECD 123 has been performed. As the value does not exceed the trigger value of 4.5 it is concluded that no further screening for persistence, bioaccumulation and toxicity is deemed necessary.

Predicted Environmental Concentration

The Phase I of this environmental risk assessment requires the calculation of the predicted environmental concentration of maralixibat in surface water. For PEC calculation, the applicant referred to the formula given in the guideline on the environmental risk assessment of medicinal products for human use. For both indications, i.e. ALGS and PFIC Fpen was refined taking into account prevalence data. For ALGS the prevalence data were taken from the Orphanet database. Concerning PFIC, Fpen was refined based on prevalence data being available via orphan designation EU/3/20/2267. Under consideration of the refined Fpen values of 0.000008 for ALGS and 0.00002 for PFIC and the recommended maximum daily doses of 26.90 mg (ALGS) and 54.15 mg (PFIC) the calculated $PEC_{surface\ water}$ results in a value of 0.00064 µg/l. As the $PEC_{surface\ water}$ does not exceed the action limit of 0.01 µg/l the applicant concluded that Phase II testing is not triggered. Therefore, the ERA can be stopped in Phase I of the procedure.

Summary of main study results

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 data)	0.00094	µg/L	> 0.01 threshold (N)

2.2.6. Discussion on non-clinical aspects

The Applicant has submitted with this variation procedure two new non-clinical studies, one in-vitro interaction study with cholestyramine suggesting that any inferred binding between maralixibat and cholestyramine is nonspecific and low affinity and one in-vivo oral repeated dose toxicity study in rats of a rather short duration (4 weeks) and with a rather low dosing regimen (100 mg/kg bw/day) indicating the NOAEL is 100 mg/kg/day for maralixibat. The results of these studies do not change the known non-clinical safety profile of maralixibat.

In the updated Nonclinical Overview, the Applicant has adapted in a table (please, see Table 2, below) the margins of safety to the new, roughly three times higher maximum therapeutic dose in humans for treatment of PFIC. Therefore, the safety margins are reduced by a factor of about 3.

Table 2 Margins of Safety from NOAELs in Animal Toxicity Studies to Proposed Clinical Dose of 600 µg/kg Twice Daily

Species	Sex	Study Type	NOAEL (mg/kg/day)	HED based on km[a] (µg/kg/day)	HED based on BW (µg/kg/day) [b]	MOS (to 1,200 µg/kg/day)
Rat	M/F	Juvenile PND7-21	250[c]	60,000	54,000	**40 to 50**
Rat	M	Juvenile PND21-63	200	48,000	60,000	**40 to 50**
Rat	F	Juvenile PND21-63	1000	240,000	300,000	**200 to 260**
Mouse (CD-1)	M/F	13-Week	750	90,000	180,000	**70 to 150**
Rat	M	26-Week	150	36,000	63,000	**30 to 50**
Rat	F	26-Week	500	120,000	210,000	**100 to 180**
Dog	M/F	6/12-Month	20	16,000	32,000	**14 to 28**
Monkey	M	2-Week	50	24,000	61,000	**21 to 50**

NOAEL=no-observed-adverse-effect level; F=female; HED=human equivalent dose; km=factor for converting across species, the km for a human child is 25; M=male; MOS=margin of safety; BW=body weight.

[a] For this column HED = NOAEL × km ÷ 25. Conversion factor km = 3, 6, 20, 12 for mouse, rat, dog, and monkey, respectively.

[b] For this column, HEDs were calculated comparing initial animal weights in each toxicity study to a 2 kg infant using the formula: HED = Animal dose (mg/kg) × [animal weight (kg) ÷ human weight (kg)]$^{0.33}$. MOS range = HED via each method ÷ highest proposed clinical dose; note that NOAELs are presented in mg/kg/day, whereas HEDs are presented as µg/kg/day to match the clinical dosing units.

[c] No NOAEL was stated in the report, but all dose levels were well tolerated with no clear toxicity.

The Applicant has similarly actualised the margins of safety regarding the discussion of the higher bioavailability (17%) observed in rat pups at post-natal day (PND) 7 compared to that one in adult non-clinical animal species (1% or lower).

In the actualised non-clinical overview the Applicant states:

"…taking a conservative approach to the possibility that absorption could be higher in the youngest human patients based on juvenile animal toxicity studies, one can consider the extreme case of 100% bioavailability in human and use the estimated 17% bioavailability in the youngest rat pups in the juvenile toxicity study (rat PND 7) to apply a reduction in the safety margin of 6-fold (100 divided by 17) to adjust for theoretical maximum differential in oral bioavailability from rat pups to human children. Even in that very unlikely theoretical case of 100% bioavailability in the human patients, the predicted MOS would still be 7 (the lowest MOS of 40 for the juvenile rat toxicity study applying a 6-fold reduction for potential bioavailability extremes). "

The topic of the higher bioavailability in rat pups at PND7 is discussed in the present EPAR of Livmarli.

"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."

This view is from the nonclinical point of view still considered valid.

Environmental risk assessment

According to the document on orphan designation (EU/3/13/1214) Alagille syndrome affected not more than 0.3 in 10,000 people in the European Union (EU) at the time of designation. Based on this information a Fpen of 0.00003 can be derived. The Fpen refinement for the indication PFIC i.e. Fpen of 0.00002 according to orphan designation EU/3/20/2267 can be further used for $PEC_{surface\ water}$ calculation. Based on the refined Fpen values a $PEC_{surface\ water}$ of 0.00094 µg/l (PEC for ALGS: 0.0004 µg/l and PEC for PFIC: 0.00054 µg/l) can be calculated. As the PEC of 0.00094 µg/l does not exceed the action limit of 0.01 µg/l, the ERA can stop in Phase I and a Phase II ERA is deemed not necessary. This is agreed.

2.2.7. Conclusion on the non-clinical aspects

The results of the submitted non-clinical studies do not change the known non-clinical safety profile of maralixibat. There are no non-clinical concerns for the approval of the claimed PFIC indication. Maralixibat $PEC_{surface\ water}$ 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.

Therefore, the updated data do suggest that the intended use of maralixibat does not lead to a significant increase in environmental exposure.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 3 Tabulated Summary of Clinical Studies of Maralixibat for Pediatric Participants with Progressive Familial Intrahepatic Cholestasis

Study ID	Locations (# Study Centers)	Total Enrollment/ Enrollment Goal Status	Design Control Type	Study and Control Drug Route & Regimen	Study Objective	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
MRX-502	Canada, Europe, Latin America, Lebanon, Singapore, Turkey, UK (39)	Primary cohort: MRX: 14 Placebo: 17 Total: MRX: 47 Placebo: 46 Completed	Randomized, double-blind, placebo-controlled	Maralixibat 600 µg/kg twice daily or placebo	Efficacy, safety, tolerability, and PK	26 weeks	42 Males 51 Females: Median age (Range): 3 (1–17)	PFIC	ItchRO(Obs) average morning score
MRX-503	Canada, Europe, Latin America Lebanon, Singapore, Turkey, UK, US (27)	Maralixibat: up to 90 Ongoing	Open-label, extension study to MRX-502	Maralixibat 600 µg/kg twice daily	Long-term safety and tolerability, long-term efficacy	104 weeks followed by long-term extension	As of the data cutoff date for Study MRX-503, enrollment was still ongoing.	PFIC	
MRX-801	USA, UK, Poland, Belgium, France (15)	Start: 09 Sep 2022 ALGS: N≥6 (Enrolled N=8 as of 04May2022) PFIC: N≥6 (Enrolled N=4 as of 23Jun2022) Ongoing	Open label	Maralixibat ALGS: Oral once daily PFIC: Oral twice daily	Evaluation of safety and tolerability	13 weeks followed by extension period until at least 1 year of age and beyond 1 year of age to at least 1 year in the study	As of the data cutoff date for Study MRX-801, enrollment was still ongoing.	ALGS: ALGS with cholestasis PFIC: PFIC with cholestasis <12 months	
LUM001-501	France Poland UK US (10)	Enrolled N=33 Planned N=24 Completed	Phase 2, open-label, multiple-dose study	Maralixibat 280 µg/kg once daily 280 µg/kg twice daily for nonresponders during (optional) follow-up treatment period	Evaluated long-term safety and efficacy	72-week observation period optional treatment extension period	14 Males 19 Females Median Age (Range): 3.0 (1–13)	PFIC sBA > 3× ULN	Fasting sBA change from baseline to Week 13/ ET Post hoc sBA responder analysis
MRX-800	Australia, Belgium, Canada, France, Poland, Spain, UK, US (17)	Start: 16 Jan 2020 Enrolled N=52 Ongoing	Open-label extension study for participants in previous maralixibat studies	Maralixibat Oral ALGS: up to a maximum of 450 µg/kg once daily or 450 µg/kg twice daily if previously at that dose PFIC: up to a maximum of 600 µg/kg twice daily	Long-term safety, long-term efficacy	Until commercially available	26 Males 26 Females Median Age (Range): 10 (5–21)	PFIC, ALGS	Mean change from baseline in pruritus, sBA, bilirubin

ALGS=Alagille syndrome; ET=end of treatment; F=female; ID=identification; M=male; MRX=maralixibat; N=number of participants; PFIC=progressive familial intrahepatic cholestasis; PK=pharmacokinetic; sBA=serum bile acid; UK=United Kingdom; ULN=upper limit of normal; US=United States.

NOTE: The doses described in this document are of maralixibat chloride but are presented as "maralixibat." For example, 600 µg/kg maralixibat chloride is equivalent to 570 µg/kg maralixibat free base but will be referred to as 600 µg/kg maralixibat throughout this document.

2.3.2. Pharmacokinetics

With regard to pharmacokinetics, the amount of new data is very limited.

Table 4 List of additionally completed clinical studies informative for pharmacology

Study number	Study Title
Studies in Paediatric Participants with Cholestatic Disease:	
MRX-502	MARCH-PFIC: Randomized Double-Blind Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)
MRX-503	MARCH-ON: An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)
MRX-801	RISE: 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

As seen from the table, no dedicated PK study was added to the documentation of pharmacology. Addition of the PK data from the efficacy and safety studies MRX-502, MRX-503, and MRX-801, however, is considered relevant with regard to the fact that the dose used in these studies was relevantly higher than doses used in the previously submitted studies.

No new methods for the determination of maralixibat in plasma, or the determination of bile acids were used.

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 PFIC). 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 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 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

Cohort	PK Parameter	N	Geometric LSM (Fed)	Geometric LSM (Fasted)	Fed/Fasted Ratio (%)	90% CI for Geometric LS Mean Fed/Fasted Ratio
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

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 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 the 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 (which is 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 for the PFIC 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 (see below). There is literally no difference in PK between infants and older children. 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 somewhat higher exposure levels are reached in infants, these are likely not to represent a hazard.

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, PFIC, and Alagille' Syndrome. Due to the missing of data for patients with advanced liver disease (cirrhosis) and signs of decompensation, 4.2 of the SmPC informs the prescriber that close monitoring is advised in these cases and Maralixibat is contraindicated for the treatment of PFIC in severe hepatic and/or renal impairment due to the potential risk of toxicity from the excipient propylene glycol due to

the much higher dose applied compared to Alagille Syndrome. Dose reductions are applied in moderate renal and liver impairment.

The applicant 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 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 presented 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 the current SmPC has a respective warning that there is a theoretical risk of interaction with substrates of OATP2B1. This concern appears even more relevant with the dose being more than doubled as compared to the ALGS population.

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 pediatric population with PFIC or 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).

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. No patient data from newly submitted studies were included in the PBPK modelling analysis.

New data submitted within this application:

Additionally submitted PK data comprise data from clinical studies with the primary aim of demonstrating efficacy and safety. Therefore, only sparse PK sampling data are available.

Study MRX-502

Study MRX-502; MARCH-PFIC STUDY: Randomized Double-Blind Placebo Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC). This study is submitted as the pivotal evidence for efficacy for this extension of indication submission.

The MRX-502 study was open to participants with a confirmed PFIC genotype (PFIC1, PFIC2, PFIC3, PFIC4, PFIC5, or PFIC6) and also open to participants with a PFIC phenotype but no confirmed genetic diagnosis. Key readouts included sBA levels, plasma drug levels, liver enzymes and bilirubin, and pruritus. The target dose of maralixibat was 600 µg/kg BID, participants were treated for up to 26 weeks, and Study MRX-502 was followed by a long-term extension study (MRX-503), during which all participants who completed Study MRX-502 had the opportunity to be treated with maralixibat (see below).

Systemic concentrations of maralixibat in plasma were determined before dosing and at approximately 2.5 hours after the morning dose at Week 10, 14 and Week 26 (EOT/ET).

A total of 93 participants were included, and 47 were treated with maralixibat of which 44 completed the study.

The overall results showed that maralixibat was minimally absorbed, and the maralixibat concentrations ranged from 0 to 6.130 ng/ml. The median post-dose concentration at Week 26 for maralixibat participants was 0.290 ng/mL (2.5 hours postdose). The LLOQ is 0.250 ng/mL, thus, nearly 50% of the participants had values that were BLOQ.

The details of the evaluations are shown in the following tables. The analyses are divided between the primary cohort (comprising all nt-PFIC2 participants (i.e., all nt-PFIC2, except for nt-PFIC2 participants with heterozygosis, participants with low or fluctuating sBAs, or participants with previous surgery to treat PFIC); these participants were enrolled in the primary cohort and the PFIC cohort (which comprised PFIC1, nt-PFIC2, PFIC3, PFIC4, and PFIC6 participants (i.e., all known established genotypes except for t-PFIC2 participants and participants with heterozygosis, participants with low or fluctuating sBAs, participants with previous surgery to treat PFIC, or participants who had no established variant linked to PFIC disease); these participants were enrolled in the primary cohort or supplemental cohort and met the criteria to be included in the PFIC cohort. For details of this "classification" see efficacy evaluation.

Table 8: Summary of Plasma Concentrations of Maralixibat (safey population); week 10

Analysis Visit	Primary Cohort		PFIC Cohort		All Subjects	
Sample Time Point	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic	(N=14)	(N=17)	(N=33)	(N=31)	(N=47)	(N=46)
Week 10						
Pre-Dose						
n	11	16	24	21	32	32
Mean	0.6013	0.0000	0.4283	0.0000	0.3447	0.0000
(95% CI for Mean)	(-0.4021, 1.6046)	(NE, NE)	(-0.0795, 0.9361)	(NE, NE)	(-0.0353, 0.7246)	(NE, NE)
SD (SE)	1.49348 (0.45030)	0.00000 (0.00000)	1.20256 (0.24547)	0.00000 (0.00000)	1.05380 (0.18629)	0.00000 (0.00000)
CV (%)	248.4	NE	280.8	NE	305.8	NE
Median	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Q1, Q3	0.0000, 0.2530	0.0000, 0.0000	0.0000, 0.1255	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000
Min, Max	0.000, 4.990	0.000, 0.000	0.000, 4.990	0.000, 0.000	0.000, 4.990	0.000, 0.000
Geometric Mean	0.7718	NE	0.8449	NE	0.8306	NE

Analysis Visit	Primary Cohort		PFIC Cohort		All Subjects	
Sample Time Point	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic	(N=14)	(N=17)	(N=33)	(N=31)	(N=47)	(N=46)
Week 10 (Cont'd.)						
Post-Dose						
n	11	16	23	24	30	35
Mean	0.5369	0.0000	0.6960	0.0000	0.5875	0.0000
(95% CI for Mean)	(-0.1516, 1.2254)	(NE, NE)	(0.0870, 1.3049)	(NE, NE)	(0.1186, 1.0563)	(NE, NE)
SD (SE)	1.02481 (0.30899)	0.00000 (0.00000)	1.40826 (0.29364)	0.00000 (0.00000)	1.25568 (0.22925)	0.00000 (0.00000)
CV (%)	190.9	NE	202.3	NE	213.7	NE
Median	0.3420	0.0000	0.3430	0.0000	0.1710	0.0000
Q1, Q3	0.0000, 0.5170	0.0000, 0.0000	0.0000, 0.5180	0.0000, 0.0000	0.0000, 0.5180	0.0000, 0.0000
Min, Max	0.000, 3.540	0.000, 0.000	0.000, 6.130	0.000, 0.000	0.000, 6.130	0.000, 0.000
Geometric Mean	0.6554	NE	0.7320	NE	0.7418	NE

Table 9: Summary of Plasma Concentrations of Maralixibat (safety population); week 14

Analysis Visit	Primary Cohort		PFIC Cohort		All Subjects	
Sample Time Point	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic	(N=14)	(N=17)	(N=33)	(N=31)	(N=47)	(N=46)
Week 14						
Pre-Dose						
n	1	0	3	1	4	2
Mean	0.0000	--	0.0000	0.0000	0.0000	0.0000
(95% CI for Mean)	(NE, NE)	--	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)
SD (SE)	NE (NE)	--	0.00000 (0.00000)	NE (NE)	0.00000 (0.00000)	0.00000 (0.00000)
CV (%)	NE	--	NE	NE	NE	NE
Median	0.0000	--	0.0000	0.0000	0.0000	0.0000
Q1, Q3	0.0000, 0.0000	--	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000
Min, Max	0.000, 0.000	--	0.000, 0.000	0.000, 0.000	0.000, 0.000	0.000, 0.000
Geometric Mean	NE	--	NE	NE	NE	NE

Analysis Visit	Primary Cohort		PFIC Cohort		All Subjects	
Sample Time Point	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic	(N=14)	(N=17)	(N=33)	(N=31)	(N=47)	(N=46)
Week 14 (Cont'd.)						
Post-Dose						
n	1	0	3	1	4	2
Mean	0.0000	--	0.0000	0.0000	0.0000	0.0000
(95% CI for Mean)	(NE, NE)	--	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)
SD (SE)	NE (NE)	--	0.00000 (0.00000)	NE (NE)	0.00000 (0.00000)	0.00000 (0.00000)
CV (%)	NE	--	NE	NE	NE	NE
Median	0.0000	--	0.0000	0.0000	0.0000	0.0000
Q1, Q3	0.0000, 0.0000	--	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000
Min, Max	0.000, 0.000	--	0.000, 0.000	0.000, 0.000	0.000, 0.000	0.000, 0.000
Geometric Mean	NE	--	NE	NE	NE	NE

Table 10: Summary of Plasma Concentrations of Maralixibat (safety population); week 26

Analysis Visit	Primary Cohort		PFIC Cohort		All Subjects	
Sample Time Point	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic	(N=14)	(N=17)	(N=33)	(N=31)	(N=47)	(N=46)
Week 26						
Pre-Dose						
n	13	14	29	24	39	36
Mean	0.0000	0.0000	0.0103	0.0000	0.0541	0.0000
(95% CI for Mean)	(NE, NE)	(NE, NE)	(-0.0108, 0.0315)	(NE, NE)	(-0.0407, 0.1489)	(NE, NE)
SD (SE)	0.00000 (0.00000)	0.00000 (0.00000)	0.05571 (0.01034)	0.00000 (0.00000)	0.29254 (0.04684)	0.00000 (0.00000)
CV (%)	NE	NE	538.5	NE	540.7	NE
Median	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Q1, Q3	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000	0.0000, 0.0000
Min, Max	0.000, 0.000	0.000, 0.000	0.000, 0.300	0.000, 0.000	0.000, 1.810	0.000, 0.000
Geometric Mean	NE	NE	0.3000	NE	0.7369	NE

Analysis Visit	Primary Cohort		PFIC Cohort		All Subjects	
Sample Time Point	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic	(N=14)	(N=17)	(N=33)	(N=31)	(N=47)	(N=46)
Week 26 (Cont'd.)						
Post-Dose						
n	11	12	26	23	35	33
Mean	0.9927	0.0000	0.6448	0.0893	0.5197	0.0717
(95% CI for Mean)	(-0.1466, 2.1321)	(NE, NE)	(0.1780, 1.1117)	(-0.0414, 0.2200)	(0.1690, 0.8704)	(-0.0195, 0.1630)
SD (SE)	1.69594 (0.51135)	0.00000 (0.00000)	1.15575 (0.22666)	0.30215 (0.06300)	1.02090 (0.17256)	0.25739 (0.04481)
CV (%)	170.8	NE	179.2	338.3	196.4	358.9
Median	0.3310	0.0000	0.3205	0.0000	0.2900	0.0000
Q1, Q3	0.0000, 0.5760	0.0000, 0.0000	0.0000, 0.6180	0.0000, 0.0000	0.0000, 0.5440	0.0000, 0.0000
Min, Max	0.000, 5.180	0.000, 0.000	0.000, 5.180	0.000, 1.230	0.000, 5.180	0.000, 1.230
Geometric Mean	0.6839	NE	0.6264	1.0067	0.6002	0.6820

The study confirmed that even with the high doses administered in this study, a relevant proportion of the included subjects did not exhibit any measurable plasma concentrations.

Study MRX-503

MARCH-ON Study: An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC).

Study MRX-503 is an open-label extension study in participants with a diagnosis of PFIC who had previously participated in and completed the Phase 3 Study MRX-502. All participants received

maralixibat in this Study MRX 503, and the study is ongoing. The study is reported with an "Abbreviated Interim Clinical Study Report" with a cut-off as 23rd June 2022.

In this study, systemic concentrations of maralixibat in plasma were determined before dosing and at ~2.5 hours after the morning dose at Week 10 and Week 26.

Again, the observed concentrations were very low, and mostly below the LLoQ. However, the highest post-baseline concentration observed was in this case 31.0 ng/ml at week 38, a time point at which out of the total of n=8 observations the mean concentration also appeared to be relevantly increased (to 4.9388 ng/ml). In contrast to this result, the highest concentration at week 58 was 1.88 ng/ml with a mean of 0.6923 ng/ml in a cohort of altogether n=7 patients.

Study MRX-801:

RISE Study: 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

This study was designed to investigate the safety and tolerability of maralixibat in infant participants with ALGS or PFIC. Key readouts included sBA levels, plasma drug levels, liver enzymes and bilirubin, and pruritus. The study is ongoing, and two separate iCSRs are available, one for ALGS participants (data cutoff date of 04 May 2022,) and one for PFIC participants (data cutoff date of 23 June 2022). An updated data-set in PFIC population has been submitted with the responses to the RSI (data cut-off 28 June 2023).

To evaluate the pharmacokinetics of maralixibat in infant participants, plasma maralixibat concentrations were measured before and 2.5 hours after the morning dose of maralixibat on multiple study days.

For the PFIC patients (n=10), the mean (SD) concentration at 2.5 hours after maralixibat dosing was 0.5273 (1.21501). At doses of 600 µg/kg BID, 71.4% of samples were below the lower limit of detection. The highest plasma level detected was 5.78 ng/mL. These results are consistent with a minimally absorbed drug and previous results in maralixibat studies, including participants with PFIC >12 months of age.

2.3.3. 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, localized 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).

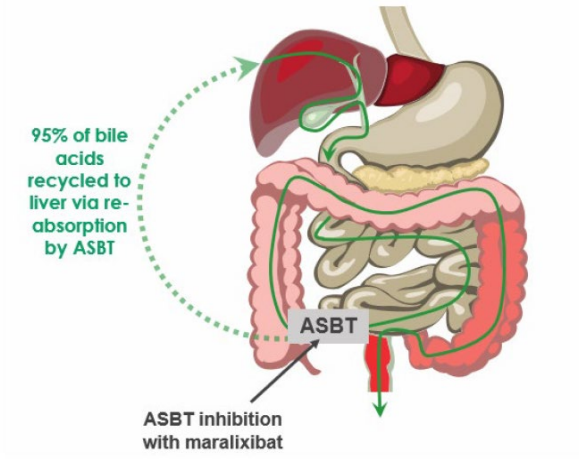


Figure 4 Interruption of enterohepatic circulation of bile acids by maralixibat

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

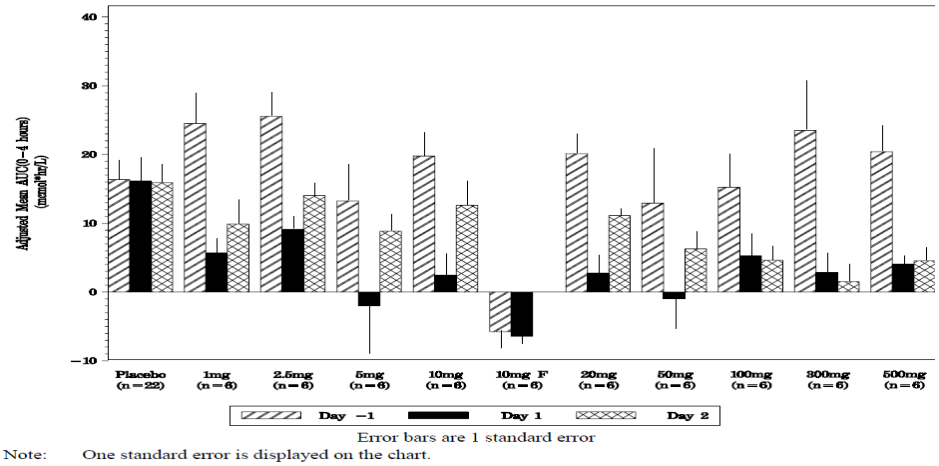
Pharmacodynamics in Healthy Adult Participants

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.



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 5 Baseline adjusted serum total bile acids concentration: Mean AUC (0-4 hours; µmoloxhr/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 11: 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.

Study LUM001-501 was conducted in patients with PFIC1 and PFIC2 using doses of maralixibat (280 µg/kg QD or 280 µg/kg BID) far below of the recommended dose in PFIC (i.e., 600 µg/kg BID). In this study, the primary outcome parameter was serum bile acid concentrations over time, but this could not achieve statistical and clinical relevance. Relevant reductions of sBAs could be shown in a sub-set of study population in the long-term extension study.

Pharmacodynamics in the target population

One study (Study LUM001-501) is presented for the target population PFIC. In this study, the primary outcome parameter was serum bile acid concentrations over time. Relevant reductions of sBAs were observed in a sub-set of study population on treatment with maralixibat. For the further assessment of this study, it is, however, referred to the chapter on efficacy.

Secondary pharmacology

The applicant has not conducted any dedicated studies 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, study NB4-00-02-006 with atorvastatin, as well as study LUM001-201 in patients with PBC provide information on PD interactions.

For atorvastatin, no additional effects on plasma lipids were detected and there was no indication for PD interactions.

For the study in PBC patients (LUM001-201), 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. UDCA interaction might be similarly relevant for the target population as for the approved indication of ALGS, as many patients are concomitantly treated with UDCA. SmPC 4.5 already informs appropriately the prescriber that this potential interaction has not been fully evaluated.

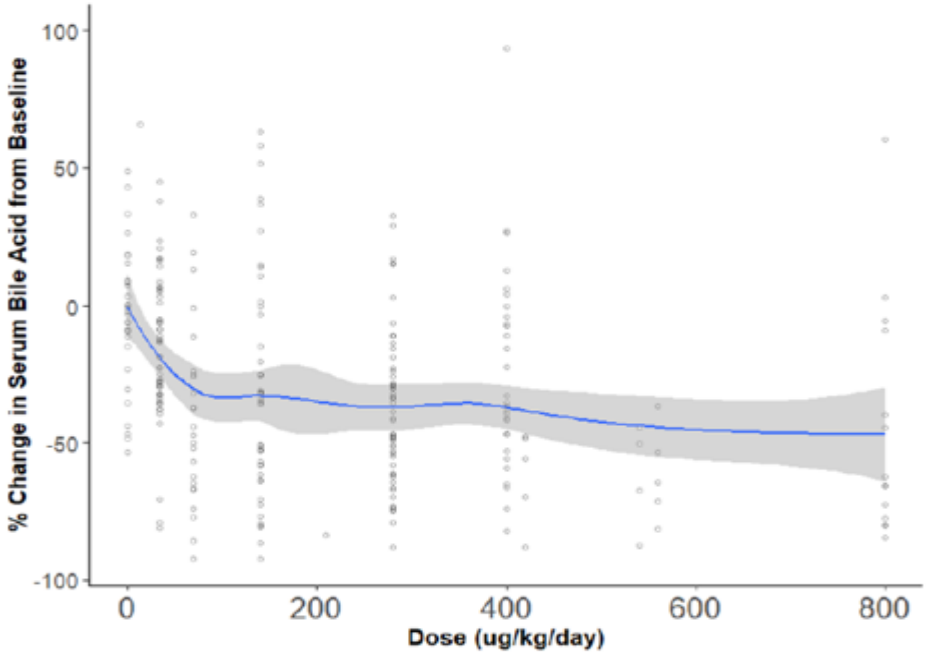
In conclusion, the PD properties of the compound have been sufficiently investigated, and overall adequately characterised. By inhibiting bile acid absorption, the compound increases the faecal excretion of bile acids, thereby inducing the potential for gastrointestinal effects (increase stool weight, 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.

No dedicated additional PD data have been submitted with the application for the extension of indication apart from the LUM001-501 study that was the first study in the PFIC population evaluating PD effect on a lower dose of maralixibat.

2.3.4. PK/PD modelling

No PK/PD modelling was done in PFIC population to evaluate dose-response. An exploratory dose-response analysis of the relationship between maralixibat dose and sBA levels in another intrahepatic cholestasis indication, i.e., ALGS (at doses from 35 µg/kg to 800 µg/kg) showed an effect of maralixibat compared to placebo (represented by a dose of 0 ug/kg/day), however, a dose-response was not defined.

Figure 6 Does of maralixibat versus percent change from baseline in sBA across studies in ALGS



Each circle represents the mean percent change from baseline in sBA for each patient at each dose level. Th blue line is a LOESS trendline with the shaded area indicating a 90% CI.
Source: Report MRX-NC-011, adapted from Figure #9

2.3.5. Discussion on clinical pharmacology

The present MAA concerns maralixibat chloride (hereafter maralixibat), an oral inhibitor of the apical sodium-dependent bile acid transporter (ASBT) which has been licensed for the treatment of Alagille's Syndrome (ALGS) and for which an extension of the indication to patients with PFIC (progressive familial intrahepatic cholestasis) is sought. 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 fecal bile acid (fBA) excretion and lowering serum bile acid (sBA) levels.

The recommended dose for the additional indication is proposed to be 570 µg/kg of maralixibat (free base equivalent to 600 µg/kg BID maralixibat chloride) twice daily with a starting dose of 285 µg/kg twice 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 leads to 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 were addressed in adequate warning statements included in the PI in the initial marketing authorisation application on Alagille Syndrome.

While some dose-finding studies in the ALGS population, and an initial efficacy (phase 2) study in PFIC population with a lower dose have been performed, the dosing schedule, including the proposed twice 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 dosing schedule is, however, acceptable (see also discussion on clinical efficacy).

Long term observations from studies MRX-502 (PFIC population 1 to 17 years of age) and MRX-801 (for the PFIC population 3 to 12 months of age) confirmed low plasma concentrations, with the majority of samples not having measurable concentrations of maralixibat. Based on available data systemic exposure to maralixibat is similar in infants from 3 to 12 months of age and older children. 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, non-clinical studies on high systemic exposure did not reveal critical safety findings. These data suggest that even if higher exposure levels are reached in infants, these are likely not to represent a hazard.

Overall, the low levels of plasma concentrations even at the high doses proposed in the new indication 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.

No new model-based data were submitted taking study MRX-801 into account. The Applicant discussed that no updated PK modelling was submitted due to low systemic exposure of maralixibat. This is agreed.

The applicant has thoroughly investigated the primary pharmacodynamic targets of IBAT inhibition through maralixibat at the time of initial marketing authorisation in ALGS population. These extend 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.

No new data concerning drug-drug interactions were submitted. Overall, potential for drug-drug interactions is considered low due to low systemic availability of the active substance. Commonly used concomitant treatments/food supplements in PFIC population are similar to those applied in the approved indication of ALGS. Therefore, the respective warnings included in the PI for ALGS are also applicable for the new indication. Additionally, the interaction potential with vitamins/food components has been evaluated in the safety assessment.

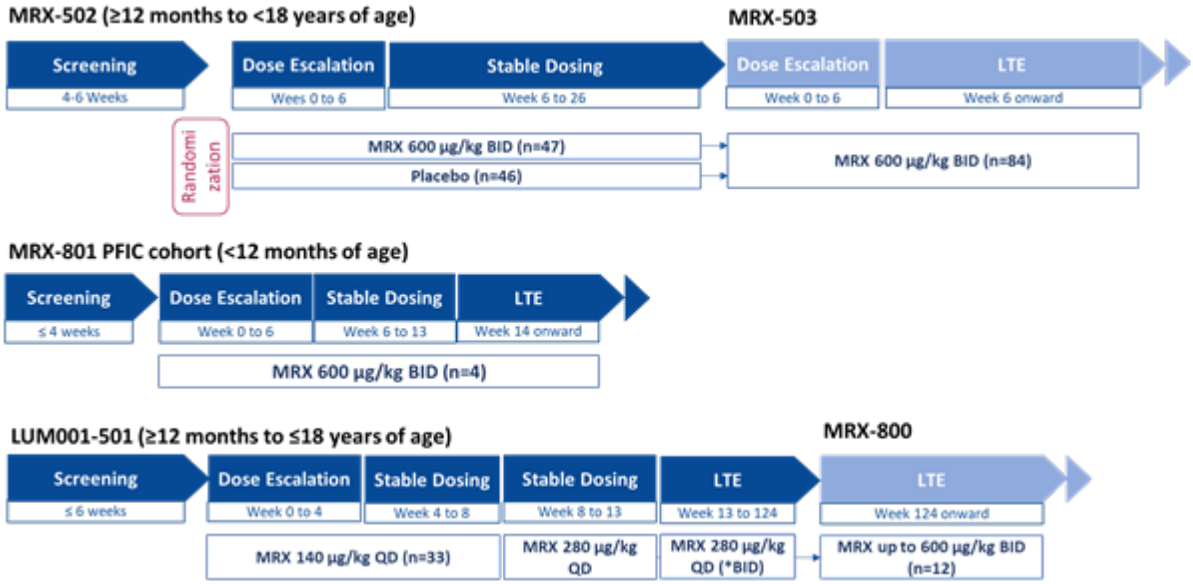
2.3.6. Conclusions on clinical pharmacology

Clinical pharmacology of maralixibat was sufficiently characterised at the time of initial marketing authorisation in ALGS. Additional sparse PK sampling with the proposed higher doses in the patients with PFIC 3 months to 17 years of age have confirmed the low absorption and erratic plasma concentrations. PK data in patients below 1 year show similarly low level of absorption as in older patients. Also, bioavailability of maralixibat in the PFIC population was in the same range as in ALGS. PK data are not available in patients below 3 months of age.

2.4. Clinical efficacy

Three clinical studies MRX-502 (pivotal study), MRX-503, MRX-801 have been submitted and are regarded as more relevant to support this variation procedure. These studies tested the recommended target dose in the patients with PFIC starting from 3 months and up-to 17 years old and present short-term effects and effects on prolonged treatment with MRX. Two further studies LUM001-501 and MRX-800 are regarded less relevant, as these studies tested lower doses of MRX in sub-population.

Figure 7 Overview of the maralixibat studies in the PFIC indication



2.4.1. Dose response study(ies)

The following dose recommendations are proposed in the SmPC: The starting dose is 285 mcg/kg orally once daily (QD) and may be increased after 1-2 weeks to 285 mcg/kg twice daily (BID, morning and evening). After 1-2 weeks, the dose can be increased to 570 mcg/kg twice daily, as tolerated. An additional table provides the dose in mL of solution to be given for each weight range. In case of poor tolerability, dose reduction or treatment interruption should be considered. Renewed dose-escalation can be attempted as tolerated. The product is to be taken 30 min prior to the respective meal or with a meal.

No dedicated dose-finding has been done. The proposed dosing regimen resembles the dosing regimens applied in the pivotal MRX-502 and infant MRX-801 studies, with dose escalation to the target dose. In the MRX-502 study the dose was selected based on the previous experience with MRX in different population (healthy volunteers, patients with hypercholesterolemia) and interim results of the studies in PFIC.

The proposed starting dose is supported by updated interim safety data of Study MRX-801 with data from 10 children <12 months of age with PFIC (data extracted on 28 June 2023) who were treated with an initial maralixibat dose of 300 µg/kg QD that was subsequently increased to 300 µg/kg BID and to 600 µg/kg BID. The starting dose of 300 µg/kg QD has not yielded safety concerns.

The maximum recommended dose and the BID have been tested in Study SHP625-101. This was a blinded, placebo-controlled, randomized, multiple-dose study in healthy volunteers, that showed that bile acids levels in faeces increased with escalating doses up to 100 mg QD and 50 mg BID of maralixibat, without any meaningful changes in the safety or tolerability profile. These doses correspond to approximately 1400 µg/kg QD and 700µg/kg BID in a 70-kg adult, respectively. It is hypothesized that twice-daily dosing has the potential to allow for more complete target engagement throughout the day at the level of the distal ileum.

The proposed therapeutic dose is three time as high as the approved maralixibat dose in ALGS patients (400 µg/kg/day). The MAH argues that PFIC and ALGS are two distinct entities and that the nature of bile flow restriction and hence the optimal dose of maralixibat may be distinct for these conditions.

Study LUM001-501 showed that lower dose of maralixibat (280 µg/kg QD) in the patients with PFIC 1 and 2 achieved serum bile acid (sBA) response in 6 participants with non-truncating progressive familial intrahepatic cholestasis Type 2 (nt PFIC2) and that doubling of this dose led to an sBA response in one further participant. Responders showed significant increases in 7α-hydroxy-4-cholesten-3-one (7αC4), a marker of bile acid synthesis, instigated by the reduction in bile acids. In addition, significantly different 7αC4 to serum bile acid ratios in responders versus non-responders were observed, suggesting that initial non-responders may benefit from increased doses of maralixibat. In the case of this 7th responder, 7αC4 was only increased upon BID dosing when reductions in sBA were observed. Improvements in growth (height and weight z-score), as well as AST, ALT, and bilirubin were also observed after increasing the dose, according to the MAH. These data indicated that responses are improved with higher maralixibat doses in patients who may require greater ileal bile acid transporter (IBAT) inhibition. For this reason and in order to maximize treatment effect, the 600-µg/kg BID dose was selected for the pivotal study MRX-502 in participants with PFIC.

In Study MRX-502, a significant reduction in LS Mean sBA and bilirubin, as well as in Itch-Reported Outcome (Observer) (ItchRO[Obs]) and Clinician Scratch Scale (CSS) severity scores from baseline was observed in the maralixibat treated group.

Differentiation from placebo in the key biomarkers of cholestasis, sBA and direct bilirubin, manifested as early as the first post-baseline assessment time point at study Week 2 (PFIC cohort). LS Mean change (SE) (95% CI) showed significant difference from placebo for sBA of -123.024 mmol/L (25.7726)(-174.634, -71.414) and for direct bilirubin of -0.945 mg/dL (0.4684)(-1.883, -0.006). 33% of patients on MRX 300 µg/kg BID vs 3% on placebo had clinically relevant sBA response (defined as sBA <102 umol/L, OR a ≤-75% average percent change from baseline) at Week 2.

Pruritus severity (assessed with CSS) also decreased significantly at Week 2 showing LS mean (SE)(95% CI) change from baseline on maralixibat of -0.942 points (0.1548) (-1.251, -0.632)(-0.697, -0.058) and difference from placebo of -0.564 points (0.2108)(-0.987, -0.142). At this time point, most participants were treated with 150 µg/kg BID followed by 300 µg/kg BID (i.e., half the recommended dose) for one week each. No data are available for ItchRO(Obs) on the 300 µg/kg BID dose.

The response (mean values) increased further at the next assessment time point (Study Week 6). At this time point, most participants had received additionally 1 week at 450 µg/kg BID and 3 weeks at 600 µg/kg BID. Additional 12% of patients (45% in total) achieved clinically relevant reduction in sBA

on the doubled dose of MRX, i.e., the recommended 600 µg/kg BID at week 6 (0% on placebo). The proportion of responders remained unchanged by the end of the 6 months treatment period.

In summary, the data indicate improvements in sBA, bilirubin and pruritus already early during dose escalation, indicating that half the recommended dose (i.e., 300 µg/kg BID) will lead to clinically relevant effects in about one third of the patients within 2 weeks of treatment. These data are supportive of use of 300 µg/kg BID dose as an alternative dose in patients at increased risk of propylene glycol toxicity (see below). However, responses further improved after dose escalation and other clinically relevant parameters (e.g., transaminases, growth) had improvements at a later time point under 600 µg/kg BID. The proposed dosing language for section 4.2 in the SmPC gives flexibility to prescribers to stop dose escalation if tolerability issues emerge.

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.

It is recommended to use fixed maximum dose of 6 mL (57 mg - base) MRX in the patients with the body weight of 50 kg and above, that corresponds to 570 µg/kg BID of pure MRX base (equivalent to 600 µg/kg BID MRX chloride)., i.e., the maximum dose used for treatment in the pivotal study. The rationale for the proposed cut-off of 50 kg is that the available safety data for the 570-µg/kg BID dose are limited to the patients who weigh <53 kg. There was only 1 participant with a weight of >50 kg at baseline (MRX-502 CSR Listing 16.4.1).

The weight bands for the weight-based dosing were selected to achieve 80% to 120% of the target dose (570 µg/kg). Thus, with stable dosing for patients >50 kg, ≥80% of the target dose is maintained up to a body weight of 62.5 kg. For a patient with a body weight of 70 kg, the fixed dose of 28.5 mg results is a calculated dose of 407 µg/kg (71% of 570 µg/kg target dose).

In participants treated with maralixibat in Study MRX-502, responses in key efficacy parameters (i.e., sBA, direct bilirubin, and pruritus severity, as measured with Clinician Scratch Scale) showed statistically and clinically meaningful improvements during the dose escalation period when patients were treated with doses lower than the target dose of 570 µg/kg BID. These data indicate that the proposed fixed dose of 28.5 mg for patients between 62.5 kg and 70 kg, which corresponds to a dose between 456 µg/kg BID and 407 µg/kg BID, will have the same or very similar efficacy.

Exposure to Propylene Glycol (PG) and the risk of PG-related toxicity

Propylene glycol is one of the main excipients of Livmarli marketed formulation. Each mL of oral solution contains 364.5 mg propylene glycol (E1520). When applied as recommended, the expected daily dose of PG in the patients with PFIC may reach 50 mg/kg/day.

Daily amount of PG intake through administration of study medication was restricted to 26 mg/kg/day in the clinical studies. This was achieved by using different formulations of study medication which had variable concentrations of MRX (e.g., 5%, 10%, 15%, 20%). Only one formulation of Livmarli oral solution (9.5% strength – MRX base) will be marketed. So that intake of the doses of Livmarli above 600 µg/kg/day will lead to a PG exposure above 26 mg/kg/day. Safety data on PG > 26 mg/kg/day in the target population are missing.

With the responses to the second RSI the Applicant has submitted safety data from the clinical studies focusing on the parameters relevant for detection of PG-related toxicity, i.e., typical AEs, osmolal gap, bicarbonate, creatinine stating that no safety signals in relation with PG were observed in the studies. Two cases of overdose of the study medication (i.e., PG) occurred, but did not result in AEs.

As a precaution, due to the propylene glycol content, the maximum proposed dose of Livmarli in patients <5 years of age and in patients with moderate hepatic and/or renal impairment (creatinine clearance CrCl ≥30 and < 60 ml/min ml/min) is 300 µg/kg BID. Livmarli is contraindicated in patients with severe renal or hepatic impairment for the same reason.

2.4.2. Main study(ies)

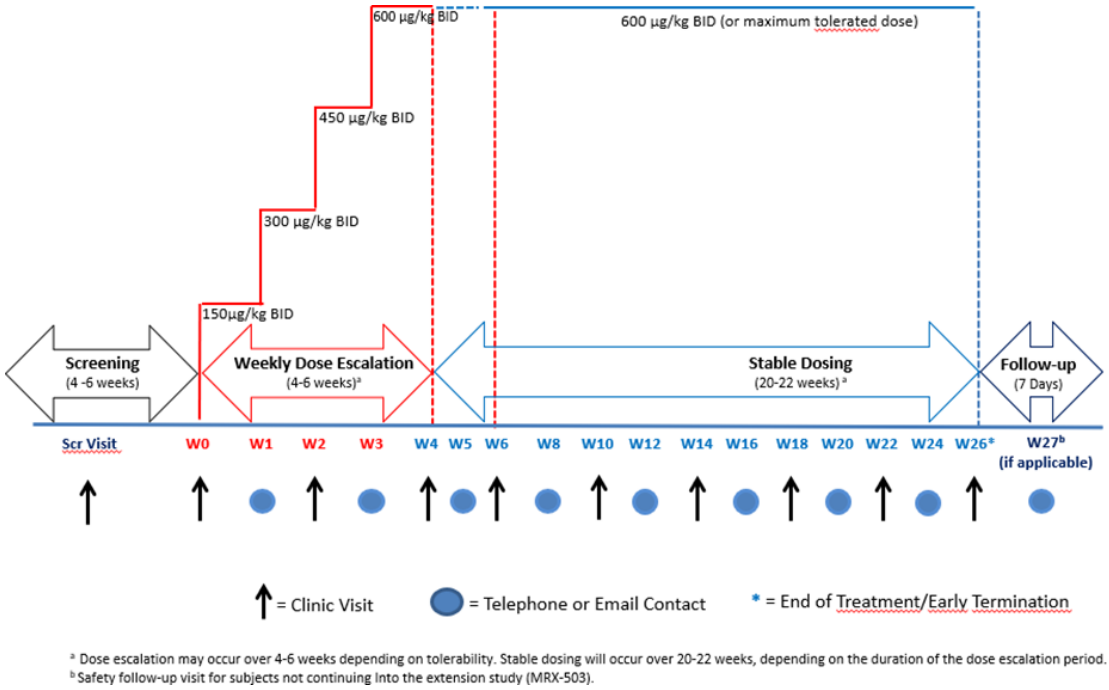
MRX-502: Randomized Double-blind Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC) – MARCH-PFIC

Methods

This was a pivotal completed 6-month international, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study that assessed the efficacy and safety of maralixibat (MRX) in participants with PFIC aged ≥12 months and <18 years.

Subject eligibility was assessed during the screening period (4-6 weeks) based on the twice daily entries in the electronic diaries for pruritus assessment and blood tests for liver function parameters, serum bile acids (sBA), C4, FGF-19, and autotaxin, assessment of prior and concomitant treatments, etc. After screening period, the selected participants were randomised either to MRX or placebo and went through a 4-6 week dose escalation period. Starting with MRX dose of 150 µg/kg BID and going through the dose steps of 300, 450 and 600 (max) µg/kg BID on a weekly basis. Escalation was stopped, if the dose was not tolerated, or safety concerns emerged. The selected maximum tolerated dose was subsequently kept unchanged over a time period of 20-22 weeks (stable dosing period; 26 weeks of treatment in total). At the end of the 26-week double-blind treatment period, participants had the opportunity to enrol in the long-term, extension Study MRX-503, or were followed-up for 7 days for safety assessment (follow-up period). Those, who discontinued from the study for safety reasons were followed up as clinically indicated or until no further improvement with an AE was expected. A participant's maximum duration of participation was expected to be up to 33 weeks.

Figure 8 Study MRX-502 – flow-chart



[a] Dose escalation may occur over 4-6 weeks depending on tolerability. Stable dosing will occur over 20-22 weeks, depending on the duration of the dose escalation period.
[b] Safety follow-up visit for subjects not continuing into the extension study (MRX-503).

BID=twice daily; Scr=screening; W=week.

Study treatment was given on top of the standard of care treatment. Safety was monitored on an ongoing basis by a data monitoring committee.

Study participants

Inclusion criteria

The study included male and female patients with PFIC

- aged ≥12 months and <18 years and with the body weight ≥5.0 kg
- with cholestasis as manifested by total sBA ≥3×ULN (applies to primary cohort only)
- with an average morning ItchRO(Obs) score ≥1.5 during 4 consecutive weeks of the screening period, leading to the baseline visit (Visit 1)
- who has completed ≥21 valid* morning ItchRO(Obs) entries during 4 consecutive weeks of the screening period, leading to the baseline visit (*valid=completed and not answered as "I don't know"; maximum allowed invalid reports=7, no more than 2 invalid reports during the last 7 days before randomization)

Diagnosis of PFIC was to be based on:

Chronic cholestasis as manifested by persistent (>6 months) pruritus in addition to biochemical abnormalities and/or pathological evidence of progressive liver disease and

- Primary Cohort:

Participants with genetic testing results consistent with biallelic disease-causing variation in ABCB11 (PFIC2, also referred to as BSEP deficiency), based on standard-of-care genotyping. Exception: the patients with predicted complete absence of BSEP function based on the type of ABCB11 mutation, those with recurrent intrahepatic cholestasis, indicated by a history of sBA levels <3×ULN or

intermittent pruritus, and those with history of surgical disruption of the enterohepatic circulation, who were excluded from this cohort.

- Supplemental Cohort:

i. Participants with genetic testing results consistent with biallelic disease-causing variation in ATP8B1 (PFIC1), ABCB4 (PFIC3), or TJP2 (PFIC4), based on standard-of-care genotyping

ii. Participants with PFIC phenotype without a known mutation or with another known mutation not described above or with intermittent cholestasis as manifested by fluctuating sBA levels

iii. Participants with PFIC after internal or external biliary diversion surgery or for whom internal or external biliary diversion surgery was reversed.

Exclusion criteria

- Current or recent history (<1 year) of atopic dermatitis or other noncholestatic diseases associated with pruritus
- Chronic diarrhea requiring intravenous fluid or nutritional intervention for the diarrhea and/or its sequelae at screening or during the 6 months prior to screening
- Previous or need for imminent liver transplant, decompensated cirrhosis (INR >1.5, and/or albumin <30 g/L, history or presence of clinically significant ascites and/or variceal hemorrhage and/or encephalopathy), ALT or total bilirubin >15×ULN at screening, or presence of other liver disease
- Presence of any other disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, including bile salt metabolism in the intestine (e.g., inflammatory bowel disease), per investigator discretion
- Other relevant conditions, such as possible liver malignancy, HIV, cancer diagnosis, alcohol or substance abuse, hypersensitivity to MRX or excipients
- Forbidden prior or concomitant treatments: bile acids or lipid binding resins or phenylbutyrates during the screening period, previous use of an IBAT inhibitor, any investigational drug, biologic, or medical device during the screening period.
- Compliance issues.

Treatments

The participants received either MRX or placebo following the dosing and titration scheme presented above. Both formulations (placebo and MRX) contained similar amounts of PG. Three different concentrations of MRX were applied to allow for PG-dose restriction to 26 mg/kg/day.

Target of the dose escalation period was to define the maximum tolerated dose for each patient. Dose escalation was stopped if major safety (e.g., liver parameters) or tolerability (e.g., GI-related TEAEs) issues emerged. Participants with such safety concerns could have had their dose reduced to a lower, previously tolerated dose level for 1 week before continuing dose escalation. The patients not tolerating 150 µg/kg BID were withdrawn.

The maximum tolerated dose of MRX was administered unchanged during the stable dosing period. MRX was to be taken 30 min prior to the morning and evening meals.

The proposed target dose was based on the preliminary data from the first interim analyses from the Phase 2 Study LUM001-501 and experience in the non-PFIC population.

Objectives

Primary Objective

- To evaluate the efficacy of MRX versus placebo on the severity of pruritus in participants with PFIC2

Secondary Objectives

- To evaluate the efficacy of MRX versus placebo on total sBA levels in participants with PFIC2
- To evaluate the efficacy of MRX versus placebo on the severity of pruritus and total sBA in participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, PFIC5, and PFIC6)
- To evaluate the efficacy of MRX versus placebo on the proportion of responders for the ItchRO(Obs) pruritus score and for sBA in participants with PFIC2 and participants with PFIC (PFIC1, PFIC2, PFIC3, PFIC4, PFIC5, and PFIC6)
- To evaluate the safety, tolerability, and pharmacokinetics (Safety Population)

Exploratory Objectives

- To evaluate the efficacy of MRX versus placebo in the primary cohort and in the PFIC cohort (PFIC1, PFIC2, PFIC3, PFIC4, PFIC5, and PFIC6) on the following parameters:
- Liver biochemistry
- Non-invasive fibrosis markers: FIB-4, APRI (AST-to-platelet ratio index), PELD (pediatric end-stage liver disease) score, MELD (model for end-stage liver disease) score
- Other measures of pruritus including ItchRO(Obs), for parameters not utilized for primary and secondary objectives, ItchRO(Pt), Clinician's Scratch Scale (CSS) and other PROs, including CIS, PIS, and EDQ
- Responder rates for pruritus severity and total sBA
- Health-related quality of life (QoL)
- Quality of sleep
- Growth
- Markers of bile acid metabolism: bile acid subspecies, C4, FGF-19, autotaxin
- Time to liver-associated events
- To evaluate the impact of maralixibat on healthcare utilization
- To evaluate the correlation between sBA and severity of pruritus in terms of levels and changes from baseline

Outcomes/endpoints

The following participant cohorts (Figure below) were used for the analysis of the various endpoints in this study. Participant cohorts were identified according to the centrally adjudicated PFIC type.

- Primary cohort: All nt-PFIC2 participants (i.e., all nt-PFIC2, except for nt-PFIC2 participants with heterozygosis, participants with low or fluctuating sBAs, or participants with previous surgery to treat PFIC); these participants were enrolled in the primary cohort.
- PFIC cohort: PFIC1, nt-PFIC2, PFIC3, PFIC4, and PFIC6 participants (i.e., all known established genotypes except for t-PFIC2 participants and participants with heterozygosis, participants with

low or fluctuating sBAs, participants with previous surgery to treat PFIC, or participants who had no established variant linked to PFIC disease); these participants were enrolled in the primary cohort or supplemental cohort and met the criteria to be included in the PFIC cohort.

- Full cohort: All participants enrolled; includes participants in the primary cohort, the PFIC cohort, and adds participants who were enrolled in the supplemental cohort and did not meet the criteria to be included in the PFIC cohort.

Figure 2 Diagram of Participant Cohorts

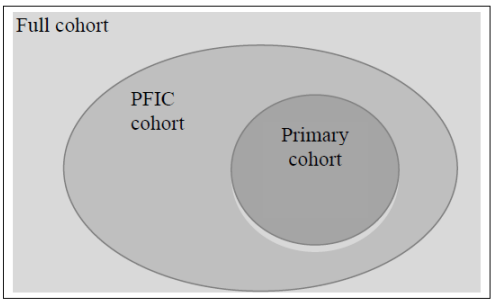


Figure 9 Diagram of participant cohorts

Study procedures and parameters

Pruritus was assessed by means of

- Exploratory Diary Questionnaire (EDQ) - Entries were made in an electronic diary over the time period of 4-6 weeks during screening and whole randomised blinded treatment phase twice daily.
- ItchPRO (Obs) - a validated tool in the patients under age of 9 years and ItchPRO(Pt) in older patients.
- Clinician's Scratch Scale (CSS) – a 5-point scale, where 0 designates no evidence of scratching and 4 designates cutaneous mutilation with bleeding, hemorrhage and scarring.
- Caregiver and Patient Impression of Severity of Pruritus (CIS and PIS, respectively. PIS only for patients of at least 9 years of age) – a scale with 1 week recall period.

Quality of life was assessed by means of

- Pediatric Quality of Life (PedQL) – a validated QoL assessment tool. PedsQL Child Report (for 8 to 12 years olds), PedsQL Teenager (for 13 to 18 years olds) and Parent PedsQL report (i.e., parents' report for Infants, Toddlers, Young Children, Children, and Teenagers) were to be completed.
- Multidimensional fatigue and family impact questionnaires
- Patient and Caregiver Impression of Change (PIC and CIC, respectively. PIC – only for patients of at least 9 years of age)

Information on healthcare utilisation was collected.

Blood samples for PK were collected under fasting condition pre-dose and 30 min post-morning dose.

Total sBA and targeted bile acid subspecies were quantified with liquid chromatography-mass spectrometry (LC-MS) methodology for exploratory assessments. C4, a key intermediate in the pathway for bile acid synthesis from cholesterol, was determined by a validated LC-MS/MS method in serum.

Primary endpoint

The mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26, using 4-week average morning ItchRO(Obs) severity scores in the primary cohort.

Secondary Efficacy Endpoints

- Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the primary cohort (considered as the key secondary endpoint)
- Mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26, using 4-week average morning ItchRO(Obs) severity scores in the PFIC cohort
- Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the PFIC cohort
- Proportion of ItchRO(Obs) and sBA responders from Week 15, or Week 18 to Week 26 in the primary and PFIC cohorts

Exploratory Efficacy Endpoints (Primary and PFIC cohorts)

- Mean change from baseline in total sBA level to Weeks 2, 6, 10, 14, 18, 22, and 26
- Mean change from baseline in liver-associated laboratory test levels (i.e., ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, albumin), FIB-4, APRI, MELD and PELD score to Weeks 2, 6, 10, 14, 18, 22, 26, and average of Weeks 18, 22, and 26
- Mean change from baseline in average morning, average evening and highest daily ItchRO(Obs) severity scores to Week 6, 10, 14, 18, 22, and 26, using 6-week average for Week 6 and 4-week average afterwards
- Mean change from baseline in average morning, average evening and highest daily ItchRO(Obs) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average morning, average evening and highest daily ItchRO(Pt) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average morning, average evening and highest daily ItchRO(Pt) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Number of days with a morning ItchRO(Obs) severity at the participant level for the last 84 days (i.e., study day 99 through 182, inclusive) of the study
- Mean change from baseline in CSS, CIS and PIS at Weeks 2, 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Mean change from baseline in average morning, average evening and highest daily EDQ(Obs) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Number and proportion of participants achieving morning ItchRO(Obs) severity scores for more than 50% of the time from post-baseline to Week 6, Weeks 7 to 10, Weeks 11 to 14, Weeks 15 to 18, Weeks 19 to 22, Weeks 23 to 26, and Week 15 to Week 26
- Mean change from baseline over time in quality of life as measured by the PedsQL (parent) total scale score at Weeks 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined

- Mean change from baseline in average morning EDQ(Obs) sleep disturbance scores to Weeks 6, 10, 14, 18, 22, and 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Proportion of participants with improvement from baseline (i.e., change from baseline <0) in morning EDQ(Obs) sleep disturbance score at Weeks 6, 10, 14, 18, 22, and 26, using 6-week average scores for Week 6 and 4-week average scores afterwards
- Proportion of morning EDQ(Obs) sleep disturbance scores ≤2 at the participant level post-baseline through Week 26
- Mean change from baseline in height z-score and weight z-score at Weeks 2, 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Mean change and % change from baseline in total sBA level to Weeks 2, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Number and proportion of subjects with total sBA % decrease from baseline to Weeks 2, 6, 10, 14, 18, 22, and 26 within the following categories: >75%, 0-75%, and <0%
- Mean change from baseline in C4, FGF-19, and autotaxin to Weeks 6, 10, 18, and 26 in the primary cohort
- Time to first liver-associated event (PEBD surgery, listing for liver transplantation, liver decompensation [hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis] events, HCC, death)

Severity scores for the EDQ were based on the EDQ(Obs) question of "How bad was your child's itch at its worst?" and on the EDQ(Pt) question of "How bad was your itch at its worst". "Non-severity" scores were based on all other EDQ questions.

For EDQ(Obs), sleep disturbance was assessed on the morning diary through the question, "Because of itch, my child had trouble staying asleep". Responses were scored on a 5-point scale, where 1=Never, 2=Rarely, 3=Sometimes, 4=Often, and 5=Almost Always.

Other Endpoints (evaluated for the primary cohort, PFIC cohort and all subjects combined – full cohort)

- Impact of maralixibat treatment on healthcare utilization (incidence of PFIC-related hospitalization, total inpatient days, selected surgical procedures, emergency room visits, and caregiver days missed from work, etc.) between clinic visits from baseline through Week 27 follow-up visit.
- Plasma levels of maralixibat at pre-dose and approximately 2.5 hours after the morning dose at Week 10 and Week 26 (EOT/ET).

Baseline

For ItchRO(Obs) and EDQ baseline was calculated from the 4 weeks twice daily entries in the e-diaries during screening period. For sBA, baseline was calculated from the sBA values measured before start of treatment (screening phase).

Sample size

The sample size was calculated to ensure enrolment of an adequate number of PFIC2 participants who fulfil criteria for the primary cohort. The following assumptions were made in estimating the sample size for Study MRX-502: between-treatment group (placebo to active) LS mean difference of 0.663; pooled SD of 0.563; effect size of 1.178 in the mean change from baseline in the 4-week average morning ItchRO(Obs) score. The estimations of LS mean difference, SD, and effect size for the sample size justification are based on ItchRO(Obs) data from the maralixibat Phase 2 studies. Maralixibat-

treated participants with PFIC2 from Study LUM001-501 were compared with placebo-treated participants with ALGS from Studies LUM001-301 and LUM001 302 because no placebo data are available from Study LUM001-501.

With the assumed values, a total of 26 complete participants (13 participants in each treatment group) for Study MRX-502 were required to provide 80% power for the comparison of the primary endpoint measure between the maralixibat treatment group and placebo, based on a 2-sample t-test at the 0.05 (2-sided) level of significance. Including a 10% dropout rate based on the previous Phase 2 PFIC study and rounding up to the next even number, approximately 30 participants (15 participants in each treatment group) were randomized in the primary cohort of the study.

Randomisation

Participants in the primary cohort were randomized in a 1:1 ratio to receive maralixibat or placebo via a computer-generated randomization schedule. Participants in the supplemental cohort were randomized in a 1:1 ratio to receive maralixibat or placebo within the following subcohorts: PFIC1, PFIC3, all other participants. Siblings were randomized in a blinded manner to the same treatment group.

Blinding (masking)

All participants, investigators, and study personnel involved in the conduct of the study, including data management, were blinded to treatment assignment. The treatment assignment was not unblinded during the study. Data that may potentially unblind treatment assignment (e.g., maralixibat serum concentrations, treatment allocation, postbaseline ItchRO(Obs) results, postbaseline sBA levels) were handled with special care during the data cleaning and review process. Prior to unblinding, any data that may have potentially unblinded study site personnel or study team personnel were presented as blinded information or otherwise were not made available. The placebo solution contained all components of the investigational product, except the active drug substance. All packaged study medication components, including the dosing dispensers, were identical to maintain the blind.

Statistical methods

Estimand (Target of estimation, Study Protocol, Amendment 4):

For this study, the primary estimand is the improvement in pruritus measured as change from baseline in the average morning ItchRO(Obs) severity score in the maralixibat treatment group relative to the placebo group. In the course of the 26-week randomized treatment period, participants may be exposed to possible known or unknown intercurrent events that could possibly impact the interpretation of the measures associated with the clinical question of interest, such as treatment discontinuation due to a specific adverse effect or perhaps a lack of effect. A treatment policy estimand will be utilized for the analysis where all data will be incorporated. Intercurrent events will be handled as follows:

- Change in or administration of any allowed concomitant medication will be handled using a treatment policy strategy.
- Administration of any prohibited concomitant medication will be handled using a hypothetical strategy assuming that the prohibited medications are not available and hence were not taken, so as to assess the treatment effect for the randomized treatment groups in addition to allowed concomitant medication.
- Discontinuation of randomized treatment due to all of the following reasons will be handled using a treatment policy strategy:
    - Lack of efficacy

    - Safety concerns
    - Lack of compliance with study treatment
- Discontinuation of randomized treatment due to other reasons (including loss to follow-up) will be handled using a hypothetical strategy, assuming that randomized treatment had not been discontinued.
- Liver transplant or death: Neither of these are expected in the study. In the unlikely event that either of these events occur, they will be analyzed using a composite strategy, assuming worst possible score for all subsequent assessments.

CSR:

For this study, the primary estimand was the improvement in pruritus measured as the change from baseline in the average morning ItchRO(Obs) severity score in the maralixibat treatment group relative to the placebo group. During the 26-week randomized treatment period, participants may have been exposed to known or unknown intercurrent events that could have possibly impacted the interpretation of the measures associated with the clinical question of interest, such as treatment discontinuation due to a specific AE or a lack of effect. The "Hypothetical Strategy" was adopted for handling all known intercurrent events in this study. To this end, a REML-based MMRM model conducted on the primary cohort in the ITT Population was used as the primary analysis method.

Statistical methods

The planned analyses, comparisons, statistical tests, and determination of sample size are described in the final version of the SAP.

The following analysis populations were planned for this study:

- Safety Population: The Safety Population consists of all participants who receive at least 1 dose of study drug.
- Intent-To-Treat (ITT) Population: The ITT Population consists of all randomized participants.
- Per Protocol (PP) Population: The PP Population consists of all participants in the ITT Population who receive at least 1 dose of study drug and do not have any important protocol violations or deviations that have a potential impact on the efficacy analysis. Important protocol violations/deviations were identified prior to database lock.

For all efficacy analyses, participants were analyzed by the randomized treatment group assignment (maralixibat or placebo).

Efficacy analyses were conducted in the ITT Population separately on the primary cohort and the PFIC cohort. The primary efficacy analysis was performed in the primary cohort for the ITT Population. Analysis of the primary efficacy endpoint and the key secondary efficacy endpoint (i.e., change from baseline in sBA level) was also performed on the primary cohort in the Per-Protocol Population.

The "Hypothetical Strategy" was adopted for handling all known intercurrent events in this study. To this end, a REML-based MMRM model conducted on the primary cohort in the ITT Population was used as the primary analysis method. The repeated measures included postbaseline time periods during the Dose Escalation period (i.e., Week 1–6) and Stable Dosing period (i.e., Weeks 7–10, 11–14, 15–18, 19–22, and 23–26), with change from baseline in the 6- or 4-week average morning ItchRO(Obs) severity score as the dependent variable. The MMRM model included the fixed, categorical effects of treatment group, time period, and treatment group-by-time period interaction as well as the continuous, fixed covariates of baseline 4-week average morning ItchRO(Obs) severity score and the

baseline score-by-time period interaction. The unstructured variance/covariance matrix was used to model the variances and covariances for the 6 time points included in the model.

The primary efficacy analysis compared maralixibat and placebo using the contrast (difference in LS means) between treatment groups across the last 12 weeks of the study (i.e., Weeks 18, 22, and 26 combined). The analytical solution of the overall treatment effect obtained from MMRM was an equally weighted average of the 3 individual visit-specific estimates over the time period of interest (i.e., the last 12 weeks of the study). Significance tests were based on LS means using a 2-sided significance level (2-sided 95% CIs).

Analyses similar to the analyses for the primary efficacy endpoint were performed for each of the change from baseline secondary efficacy endpoints. For the PFIC cohort, PFIC type was also used as a covariate in the MMRM analysis. For this analysis, due to the small sample sizes, PFIC4, PFIC5, and PFIC6 will be grouped together. For responder-type endpoints, the number and proportion of participants that were considered a "responder" were summarized by treatment group for each analysis visit or time period, as appropriate. Barnard's exact unconditional test was used to calculate the p-value for the difference between treatment groups.

A hierarchical testing procedure was used in the comparisons between maralixibat and placebo on the primary and secondary efficacy endpoints in the ITT Population.

All tests were performed at the 0.05 (2-sided) level of significance.

Sensitivity and/or supportive analyses were performed on the primary and secondary efficacy endpoints to quantify the possible impact of missing data and the use of potentially correlated sibling data and to demonstrate the robustness of the conclusions.

Sensitivity analyses were performed on the primary efficacy endpoint and key secondary efficacy endpoint in the primary cohort and PFIC cohort, individually, in the ITT Population.

Sensitivity analyses for the primary analysis (average morning ItchRO[Obs] severity score between baseline and Weeks 15–26 in the primary cohort) were conducted using only 1 sibling in the ITT Population; the choice of sibling was random.

Although the assumption of MAR, as used for the primary efficacy analysis method, is often reasonable in clinical trials, the possibility of MNAR data cannot be ruled out. Sensitivity analyses to handle missing data used MI methods where missing values were imputed individually under both a plausible MAR and MNAR scenario. Two sensitivity analysis models, one based on the standard MAR imputation approach and the other on a tipping point analysis, were used to examine robustness of the primary analysis results.

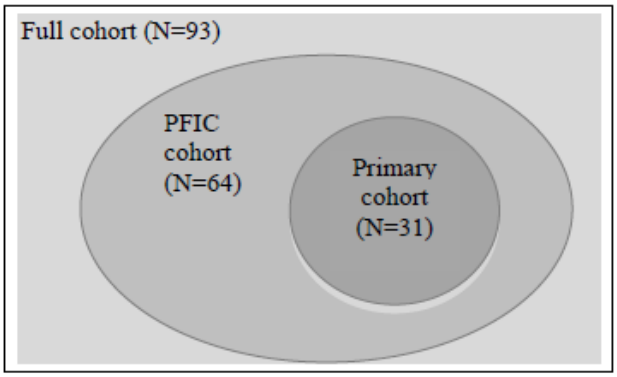
Summary statistics on the primary efficacy endpoint and the key secondary efficacy endpoint are presented descriptively by treatment group and visit, overall, and for subgroups on the primary cohort in the ITT Population. To ensure that the improvements seen in the PFIC cohort (PFIC1, nt-PFIC2, PFIC3, PFIC4, PFIC6) were not due solely to effects observed in the primary cohort (nt-PFIC2), post hoc analyses were performed in the subgroup of participants who are part of the PFIC cohort but not of the primary cohort (i.e., excluded the nt-PFIC2).

Results

A total of 90 participants were planned to be enrolled. A total of 93 participants were enrolled (full cohort) in the study (47 maralixibat and 46 placebo). A total of 86 participants (92.5%) completed the study (44 maralixibat and 42 placebo). A total of 7 participants discontinued from the study (withdrawal of consent [4 participants] and AE, liver transplantation, and disease progression [1 participant each]). In the full cohort, 5 families had siblings (10 participants) enrolled in the study.

The full cohort consists of the PFIC cohort (64 participants, including 31 participants from the primary cohort) and 29 participants who did not meet criteria for the PFIC cohort (participants with truncated BSEP mutations (t-PFIC2), heterozygosis or no variant associated with PFIC disease, low or fluctuating sBA levels, or previous surgery to treat PFIC).

- In the primary cohort, 31 participants with nt-PFIC2 were enrolled (14 maralixibat and 17 placebo). A total of 28 participants (90.3%) completed the study (13 maralixibat and 15 placebo). Three participants discontinued from the study (1 maralixibat and 2 placebo).
- In the PFIC cohort, 64 participants (PFIC1, nt-PFIC2, PFIC3, PFIC4, PFIC6) were enrolled (33 maralixibat and 31 placebo). No participant with PFIC5 was enrolled. A total of 60 participants (93.8%) completed the study (32 maralixibat and 28 placebo). Four participants discontinued from the study (1 maralixibat and 3 placebo).
- A total of additional 29 participants did not meet criteria for the PFIC cohort and were enrolled as part of the full cohort (14 maralixibat and 15 placebo). A total of 26 participants (89.7%) completed the study (12 maralixibat, 14 placebo). Three participants discontinued the study (2 maralixibat and 1 placebo).



BSEP=bile salt excretion pump; nt-PFIC=nontruncating progressive familial intrahepatic cholestasis; PFIC=progressive familial intrahepatic cholestasis; sBAs=serum bile acids; t-PFIC=truncating progressive familial intrahepatic cholestasis.
Notes: The primary cohort included participants with nt-PFIC2 (except for nt-PFIC2 participants with heterozygosis, participants with low or fluctuating sBAs, or participants with previous surgery to treat PFIC). The PFIC cohort included participants with PFIC1, nt-PFIC2, PFIC3, PFIC4, and PFIC6 participants (i.e., all known established genotypes except for t-PFIC2 participants and participants with heterozygosis, participants with low or fluctuating sBAs, participants with previous surgery to treat PFIC, or participants who had no established variant associated with PFIC disease). The full cohort included all participants enrolled: primary cohort, PFIC cohort and participants with truncated BSEP mutations (t-PFIC2), heterozygosis or no established variant associated with PFIC disease, participants with low of fluctuating sBAs and those with previous surgery to treat PFIC.

Figure 10 Diagram of participant cohorts

Participant flow

The patient disposition is presented in the table below.

Table 12 Patient disposition

	No. (%) of Participants								
	Primary Cohort			PFIC Cohort			Full Cohort		
Status or Category	Maralixibat	Placebo	Overall	Maralixibat	Placebo	Overall	Maralixibat	Placebo	Overall
Screened for eligibility									125
Screen failure									32
Randomized [a]	14	17	31	33	31	64	47	46	93
Families with siblings enrolled			1			4			5
Total no. of siblings [b]	2	0	2	4	4	8	4	6	10
Safety Population [c]	14	17	31	33	31	64	47	46	93
ITT Population [a, d]	14 (100.0)	17 (100.0)	31 (100.0)	33 (100.0)	31 (100.0)	64 (100.0)	47 (100.0)	46 (100.0)	93 (100.0)
Per-Protocol Population [e]	9 (64.3)	17 (100.0)	26 (83.9)	27 (81.8)	31 (100.0)	58 (90.6)	41 (87.2)	45 (97.8)	86 (92.5)
Completed study treatment	13 (92.9)	15 (88.2)	28 (90.3)	32 (97.0)	28 (90.3)	60 (93.8)	44 (93.6)	42 (91.3)	86 (92.5)
Discontinued early [a]	1 (7.1)	2 (11.8)	3 (9.7)	1 (3.0)	3 (9.7)	4 (6.3)	3 (6.4)	4 (8.7)	7 (7.5)
Adverse event	0	0	0	0	0	0	1 (2.1)	0	1 (1.1)
Liver transplant	0	0	0	0	0	0	1 (2.1)	0	1 (1.1)
Withdrawal of consent	1 (7.1)	1 (5.9)	2 (6.5)	1 (3.0)	2 (6.5)	3 (4.7)	1 (2.1)	3 (6.5)	4 (4.3)
Disease progression	0	1 (5.9)	1 (3.2)	0	1 (3.2)	1 (1.6)	0	1 (2.2)	1 (1.1)

IRT=interactive response technology; ITT=intent-to-treat; PFIC=progressive familial intrahepatic cholestasis.
Notes: Percentages were based on the number of participants in the Safety Population. Siblings (within the same family) were assigned in a blinded manner to the same treatment group.
[a] Participant 023004 was randomized in error within the IRT system on 14 Sep 2020, the date of the baseline visit. This participant was not dispensed study drug and was discontinued from the study due to "administrative error" on the baseline visit day. On 15 Oct 2020, this same participant was re-randomized as Participant 023005. This participant is counted only once, as Participant 023005, in the Randomized and ITT Population groups, and not counted in the Discontinued Early group.
[b] Siblings had the following PFIC types: nt-PFIC2, PFIC1, PFIC3, PFIC6, and no variant found (2 participants each; Listing 16.2.1).
[c] The Safety Population includes all participants who received ≥1 dose of study drug.
[d] The ITT Population includes all randomized participants.
[e] The Per-Protocol Population includes all participants in the ITT Population who received ≥1 dose of study drug and did not have any important protocol violations or deviations that had a potential impact on the efficacy analysis.
Source: Table 14.1.1.1.

Overall, 7 participants were not included in the Per-Protocol Population because they had an important protocol deviation that had a potential impact on the efficacy analysis including:

Primary cohort: 5 patients with nt-PFIC2 all on MRX used prohibited co-medications: hydroxyzine started on Day -11, rifampicin dose reduced 1 month prior to randomization, cholestyramine taken during the study, rifampicin started and stopped during the 4 weeks before the baseline visit; cholestyramine not stopped during screening, cholestyramine started before the study and taken during its entire duration, respectively.

PFIC cohort: one patient () due to noncompliance with study drug due to lockdown during the global pandemic.

Full cohort: one patient () used prohibited co-medication (rifampicin and UDCA dose changed during the study).

Relevant protocol deviations are presented in the table below.

Table 13 Relevant protocol deviations

Category/Type [a]	No. (%) of Participants								
	Primary Cohort			PFIC Cohort			Full Cohort		
	Maralixibat (N=14)	Placebo (N=17)	Overall (N=31)	Maralixibat (N=33)	Placebo (N=31)	Overall (N=64)	Maralixibat (N=47)	Placebo (N=46)	Overall (N=93)
Informed consent	0	0	0	0	0	0	0	1 (2.2)	1 (1.1)
Inclusion	0	1 (5.9)	1 (3.2)	1 (3.0)	1 (3.2)	2 (3.1)	1 (2.1)	2 (4.3)	3 (3.2)
Exclusion	0	0	0	0	0	0	0	1 (2.2)	1 (1.1)
Study drug	0	1 (5.9)	1 (3.2)	1 (3.0)	2 (6.5)	3 (4.7)	1 (2.1)	4 (8.7)	5 (5.4)
Prohibited comedication	5 (35.7)	1 (5.9)	6 (19.4)	6 (18.2)	2 (6.5)	8 (12.5)	6 (12.8)	3 (6.5)	9 (9.7)
Assessment-efficacy	0	1 (5.9)	1 (3.2)	1 (3.0)	1 (3.2)	2 (3.1)	1 (2.1)	3 (6.5)	4 (4.3)
Assessment-safety	0	0	0	0	0	0	1 (2.1)	1 (2.2)	2 (2.2)
Other	1 (7.1)	0	1 (3.2)	1 (3.0)	1 (3.2)	2 (3.1)	2 (4.3)	1 (2.2)	3 (3.2)

PFIC=progressive familial intrahepatic cholestasis.
Note: Percentages are 100*n/N.
[a] Important protocol deviations are grouped based on study specific protocol deviation categories as described in the Protocol Deviation Guidance Plan for the MRX-502 clinical protocol. Participants were counted only once for each category/type. Participants may appear in multiple categories.
Source: Table 14.1.2.

Recruitment

The first participant was enrolled in this study on 09 July 2019, and the last participant completed the study on 01 September 2022.

A total of 29 sites in 16 countries (Argentina, Austria, Belgium, Brazil, Canada, Columbia, France, Germany, Italy, Lebanon, Mexico, Poland, Singapore, Turkey, United Kingdom, and United States) enrolled participants in this study.

Conduct of the study

The original protocol (dated 14 Mar 2019) was amended 4 times during the study. In total 23 protocol versions were introduced in the study including the local/country-level amendments. The latest protocol amendment is dated 16 May 2022 and the latest protocol version 16 May 2022 (5F version for Germany)

The most relevant changes are summarized below by amendment.

Amendment 1 (dated 29 Apr 2019) implemented the following changes:

- Clarified expectation of chronic nature of cholestasis for participants to be allowed into the study to avoid inclusion of participants with a mild or intermittent form of cholestasis
- Clarified eligibility criteria to exclude participants with mild or intermittent form of cholestasis

Amendment 2 (dated 22 Nov 2019) implemented the following changes:

- Added urinary pregnancy test to Visits 4, 6, and 8; added PIC and CIC to EOT/ET; added CSS to screening; added lipid panel to Table 1 Schedule of Assessments
- Added additional exclusion criterion to exclude participants with recurrent intrahepatic cholestasis to avoid enrolling participants who had intermittent spontaneous near normalization of pruritus and sBA or remission of pruritus
- Added exclusion criterion to exclude participants with pruritus of noncholestatic origins, because this would directly confound the primary endpoint of the study

- Clarified exclusion criterion and discontinuation criterion from planned liver transplant to need for imminent liver transplant
- Clarified exclusion criterion regarding liver mass to possibly malignant liver mass on imaging, including screening ultrasound
- Clarified duration for contraception use after the last dose of study medication from 7 days to 30 days
- Clarified discontinuation criterion regarding use of antipruritic medications
- Clarified dose adaptations of permitted treatments if body weight changed

☐ Added option of long-term follow-up on disease progression for participants who discontinue prematurely and clarified that participants should be informed of the extension Study MRX-503 before Visit 9

☐ Added lipid panel and urinary creatinine

☐ Added PIC questionnaire to assessments to further validate ItchRO(Obs)

☐ Changed priority order of blood sample collection so sBA was prioritized over other blood samples to confirm eligibility

Amendment 3 (dated 16 Jun 2020) implemented the following changes:

- Added appendix with guidelines for study execution during a global pandemic
- Updated inclusion criterion for age to be at baseline rather than at time of consent
- Clarified definition of length of follow-up for participants who discontinue from the study
- Updated inclusion criterion of total sBA >3×ULN to apply only to the primary cohort
- Clarified that participants must have persistent pruritus to be eligible for the primary cohort and that participants with intermittent pruritus could be eligible for the supplemental cohort
- Clarified that phenylbutyrates rather than sodium phenylbutyrates were excluded during the screening period

Amendment 4 (dated 10 May 2022) implemented the following changes:

- Updated secondary objectives and endpoints to better capture clinically meaningful measures in the primary cohort and the broader PFIC population and updated hierarchical testing accordingly
- Updated exploratory objectives and endpoints to better capture clinically meaningful measures in the primary cohort, the broader PFIC population, and other subgroups of interest
- Included a blinded ItchRO validation analysis to confirm the responder definition
- Removed power calculation for endpoints other than the primary endpoint
- Clarified that the ITT Population would include all randomized participants
- Clarified the cohorts for the primary analysis of the primary and secondary efficacy endpoints
- Provided definitions for cohorts
- Included language regarding estimands and the handling of intercurrent events

Changes Due to the Global Pandemic

COVID-19 was declared a global pandemic by the World Health Organization on 11 March 2020. This study was conducted during the global pandemic.

The sponsor included management of clinical study procedures and participants during COVID19 pandemic guidelines in the protocol, Amendment 3. The sponsor worked with study centres to ensure that participants continued to have access to study drug. As necessary, site monitors used telephone or virtual visits to perform monitoring and site closeout activities. As necessary, blood sample collection could be performed at a home visit (or other agreed upon location). Due to COVID19 related restrictions, 1 participant missed 1 visit (Listing 16.3.2).

The database lock date for the MRX-502 CSR was 14 October 2022.

Baseline data

There were more females (34 [53.1%]) than males (30 [46.9%]) enrolled in the PFIC cohort (n=64). The mean (SD) age was 4.6 (3.85) years and ranged from 1 to 15 years in the PFIC cohort and 1 to 17 in the Full Cohort. The mean body weight (min; max) at the time of study entry in the PFIC cohort was 16.31 kg (5.9; 44.3) and 16.7 kg (5.9; 53.0, 48.5 in the MRX treatment group) in the full cohort. Most participants (41 [64.1%]) were 1 to <6 years of age. Most participants were White (43 [67.2%]) and not Hispanic or Latino (33 [51.6%]).

For the PFIC cohort, baseline characteristics were generally similar across treatment groups, except: There were more females in the placebo group than in the MRX group (58.1% vs. 48.5%, respectively) and participants were slightly younger in the placebo group (mean age of 4.4 vs. 4.9 years, respectively).

The mean weight and BMI z-scores were lower in participants in the MRX group than in the placebo group (weight-z-score: mean of -1.752 vs. -1.283, respectively; BMI-z-score: mean of -0.451 vs. 0.142, respectively) and median z-score for height was lower on placebo (median -2.335 vs. -1.961).

Demographic and baseline characteristics for the full cohort and the primary cohort are similar to the PFIC cohort.

Table 14 Demographics and Baseline Characteristics (Safety Population)

	No. (%) of Participants								
	Primary Cohort			PFIC Cohort			Full Cohort		
Status or category	Maralixibat (N=14)	Placebo (N=17)	Overall (N=31)	Maralixibat (N=33)	Placebo (N=31)	Overall (N=64)	Maralixibat (N=47)	Placebo (N=46)	Overall (N=93)
Age, in years [a]									
Mean	6.3	4.2	5.1	4.9	4.4	4.6	4.8	4.7	4.7
SD (SE)	5.24 (1.40)	3.56 (0.86)	4.45 (0.80)	4.10 (0.71)	3.61 (0.65)	3.85 (0.48)	4.15 (0.61)	3.57 (0.53)	3.85 (0.40)
Median	4.0	3.0	3.0	3.0	3.0	3.0	3.0	3.5	3.0
Q1, Q3	3.0, 11.0	1.0, 7.0	1.0, 8.0	2.0, 7.0	1.0, 7.0	1.0, 7.0	2.0, 7.0	1.0, 7.0	2.0, 7.0
Min, max	1, 15	1, 13	1, 15	1, 15	1, 13	1, 15	1, 17	1, 14	1, 17
Age category [a]									
1 to <6 years	9 (64.3)	11 (64.7)	20 (64.5)	22 (66.7)	19 (61.3)	41 (64.1)	32 (68.1)	29 (63.0)	61 (65.6)
6 to <13 years	2 (14.3)	5 (29.4)	7 (22.6)	8 (24.2)	11 (35.5)	19 (29.7)	11 (23.4)	15 (32.6)	26 (28.0)
13 to 18 years	3 (21.4)	1 (5.9)	4 (12.9)	3 (9.1)	1 (3.2)	4 (6.3)	4 (8.5)	2 (4.3)	6 (6.5)
Sex									
Male	7 (50.0)	6 (35.3)	13 (41.9)	17 (51.5)	13 (41.9)	30 (46.9)	20 (42.6)	22 (47.8)	42 (45.2)
Female	7 (50.0)	11 (64.7)	18 (58.1)	16 (48.5)	18 (58.1)	34 (53.1)	27 (57.4)	24 (52.2)	51 (54.8)
Race									
American Indian or Alaska Native	3 (21.4)	3 (17.6)	6 (19.4)	3 (9.1)	4 (12.9)	7 (10.9)	3 (6.4)	4 (8.7)	7 (7.5)
Asian	0	0	0	3 (9.1)	0	3 (4.7)	3 (6.4)	0	3 (3.2)
Black or African American	1 (7.1)	2 (11.8)	3 (9.7)	1 (3.0)	2 (6.5)	3 (4.7)	1 (2.1)	2 (4.3)	3 (3.2)
White	9 (64.3)	9 (52.9)	18 (58.1)	24 (72.7)	19 (61.3)	43 (67.2)	36 (76.6)	34 (73.9)	70 (75.3)
More than one race	1 (7.1)	2 (11.8)	3 (9.7)	2 (6.1)	4 (12.9)	6 (9.4)	3 (6.4)	4 (8.7)	7 (7.5)
Not reported	0	1 (5.9)	1 (3.2)	0	2 (6.5)	2 (3.1)	1 (2.1)	2 (4.3)	3 (3.2)
Ethnicity									
Hispanic or Latino	9 (64.3)	7 (41.2)	16 (51.6)	16 (48.5)	13 (41.9)	29 (45.3)	18 (38.3)	17 (37.0)	35 (37.6)
Not Hispanic or Latino	5 (35.7)	9 (52.9)	14 (45.2)	17 (51.5)	16 (51.6)	33 (51.6)	28 (59.6)	27 (58.7)	55 (59.1)
Not reported	0	1 (5.9)	1 (3.2)	0	2 (6.5)	2 (3.1)	1 (2.1)	2 (4.3)	3 (3.2)
Region									
Asia	0	0	0	2 (6.1)	0	2 (3.1)	2 (4.3)	0	2 (2.2)
Europe	3 (21.4)	5 (29.4)	8 (25.8)	7 (21.2)	7 (22.6)	14 (21.9)	14 (29.8)	10 (21.7)	24 (25.8)
Middle East	1 (7.1)	0	1 (3.2)	5 (15.2)	5 (16.1)	10 (15.6)	7 (14.9)	9 (19.6)	16 (17.2)
North America	6 (42.9)	9 (52.9)	15 (48.4)	9 (27.3)	12 (38.7)	21 (32.8)	13 (27.7)	19 (41.3)	32 (34.4)
South and Central America	4 (28.6)	3 (17.6)	7 (22.6)	10 (30.3)	7 (22.6)	17 (26.6)	11 (23.4)	8 (17.4)	19 (20.4)
Height z-score [b]									
N	14	17	31	33	31	64	47	46	93
Mean	-1.964	-2.191	-2.088	-2.081	-2.064	-2.073	-2.009	-1.913	-1.962
SD (SE)	1.3882 (0.3710)	1.4149 (0.3432)	1.3842 (0.2486)	1.2924 (0.2250)	1.4798 (0.2658)	1.3752 (0.1719)	1.3330 (0.1944)	1.3234 (0.1951)	1.3219 (0.1371)
Median	-1.979	-2.337	-2.056	-1.961	-2.335	-2.034	-1.961	-1.965	-1.961
Q1, Q3	-2.580, -1.057	-3.389, -1.812	-3.249, -1.057	-2.828, -1.189	-3.368, -0.961	-3.059, -1.123	-2.828, -1.057	-2.926, -0.961	-2.828, -1.057
Min, max	-4.92, 0.67	-4.15, 0.76	-4.92, 0.76	-4.92, 0.67	-4.54, 0.88	-4.92, 0.88	-4.92, 0.67	-4.54, 0.88	-4.92, 0.88
Weight z-score [b]									
N	14	17	31	33	31	64	47	46	93
Mean	-1.526	-1.242	-1.370	-1.752	-1.283	-1.525	-1.560	-1.224	-1.394
SD (SE)	1.3796 (0.3687)	1.4962 (0.3629)	1.4281 (0.2565)	1.2925 (0.2250)	1.3251 (0.2380)	1.3193 (0.1649)	1.3627 (0.1988)	1.2239 (0.1805)	1.2998 (0.1348)
Median	-1.430	-1.090	-1.231	-1.464	-1.090	-1.313	-1.396	-1.143	-1.231
Q1, Q3	-1.748, -1.171	-2.084, -0.648	-1.989, -0.682	-2.454, -0.946	-2.259, -0.327	-2.396, -0.703	-2.414, -0.910	-2.100, -0.327	-2.142, -0.682
Min, max	-5.08, 1.01	-3.88, 1.46	-5.08, 1.46	-5.08, 1.01	-3.88, 1.46	-5.08, 1.46	-5.08, 1.08	-3.88, 1.46	-5.08, 1.46
BMI z-score [b]									
N	14	17	31	33	31	64	47	46	93
Mean	-0.370	0.294	-0.006	-0.451	0.142	-0.164	-0.261	0.068	-0.098
SD (SE)	1.2266 (0.3278)	1.1837 (0.2871)	1.2297 (0.2209)	1.0921 (0.1901)	1.1275 (0.2025)	1.1402 (0.1425)	1.1121 (0.1622)	1.1641 (0.1716)	1.1439 (0.1186)
Median	-0.497	0.248	0.109	-0.531	0.110	-0.308	-0.473	0.117	-0.126
Q1, Q3	-0.821, 0.335	-0.568, 1.087	-0.753, 1.016	-0.884, 0.330	-0.645, 1.057	-0.791, 0.581	-0.810, 0.557	-0.660, 1.016	-0.763, 0.775
Min, max	-3.55, 1.87	-2.64, 2.34	-3.55, 2.34	-3.55, 1.87	-2.64, 2.34	-3.55, 2.34	-3.55, 2.14	-2.64, 2.34	-3.55, 2.34

BMI=body mass index; PFIC=progressive familial intrahepatic cholestasis; SD=standard deviation; SE=standard error of the mean; Q1=25th percentile; Q3=75th percentile.
Note: Percentages are 100*n/N.
[a] Age at baseline visit.
[b] Height, weight, and BMI z-scores are based on a participant's sex and age at the baseline visit. The World Health Organization (WHO) growth charts were used to derive z-scores for participants <24 months old and the Center for Disease Control (CDC) growth charts were used to derive z-scores for participants equal to or >24 months old.
Source: Table 14.1.3.

The disease history and baseline disease characteristics were generally similar between treatment groups (Table below).

No participants with PFIC5 were enrolled in the study. In the PFIC cohort, participants had nt-PFIC2, PFIC1, PFIC3, PFIC4, and PFIC6. The mean time (SD) since original diagnosis was 34.3 (34.21) and 27.5 (31.28) months in the maralixibat and placebo treatment groups, respectively. Baseline UDCA usage was lower in the maralixibat group (81.8% participants) than in the placebo group (96.8% participants), and baseline rifampicin usage was higher in the maralixibat group (54.5% participants) than in the placebo group (48.4% participants). The baseline mean ItchRO(Obs) 4-week morning average severity score was similar between groups (2.850 and 2.732 for maralixibat and placebo, respectively). The baseline mean total sBA was similar between groups (254.327 and 272.297 µmol/L for maralixibat and placebo, respectively). The baseline transaminase levels (ALT and AST) were higher in the placebo group. Values of total and direct bilirubin were similar across the treatment groups (4.1 mg/dl vs. 4.0 mg/dl and 3.0 mg/dl vs 3.0 mg/dl, respectively for MRX and Placebo). Mean and median values of FGF-19 in the placebo group were 3 and 2 times higher than those in the MRX patients. FIB-4 median values were higher in the MRX population. PELD scores showed lower levels in the placebo population.

Disease history and baseline disease characteristics for the full cohort and the primary cohort are similar to the PFIC cohort (Study MRX-502) and in general were well matched between maralixibat and placebo.

Table 15 Disease History and Baseline Disease Characteristics (Safety Population)

	Primary Cohort			PFIC Cohort			Full Cohort		
Variable Statistic or Category	Maralixibat (N=14)	Placebo (N=17)	Overall (N=31)	Maralixibat (N=33)	Placebo (N=31)	Overall (N=64)	Maralixibat (N=47)	Placebo (N=46)	Overall (N=93)
Analysis PFIC Type (genotype), No. (%) of participants									
PFIC2 (*ABCB11*) [b]	14 (100.0)	17 (100.0)	31 (100.0)	14 (42.4)	17 (54.8)	31 (48.4)	23 (48.9)	22 (47.8)	45 (48.4)
nt-PFIC2	14 (100.0)	17 (100.0)	31 (100.0)	14 (42.4)	17 (54.8)	31 (48.4)	18 (38.3)	18 (39.1)	36 (38.7)
BSEP1	2 (14.3)	6 (35.3)	8 (25.8)	2 (6.1)	6 (19.4)	8 (12.5)	4 (8.5)	6 (13.0)	10 (10.8)
BSEP2	12 (85.7)	11 (64.7)	23 (74.2)	12 (36.4)	11 (35.5)	23 (35.9)	14 (29.8)	12 (26.1)	26 (28.0)
t-PFIC2 (*BSEP3*)	0	0	0	0	0	0	5 (10.6)	4 (8.7)	9 (9.7)
PFIC1 (*ATP8B1*)	0	0	0	7 (21.2)	6 (19.4)	13 (20.3)	9 (19.1)	8 (17.4)	17 (18.3)
PFIC3 (*ABCB4*)	0	0	0	4 (12.1)	5 (16.1)	9 (14.1)	4 (8.5)	5 (10.9)	9 (9.7)
PFIC4 (*TJP2*)	0	0	0	6 (18.2)	1 (3.2)	7 (10.9)	6 (12.8)	2 (4.3)	8 (8.6)
PFIC6 (*MYO5B*)	0	0	0	2 (6.1)	2 (6.5)	4 (6.3)	2 (4.3)	2 (4.3)	4 (4.3)
Heterozygous variant[c]	0	0	0	0	0	0	0	2 (4.3)	2 (2.2)
No-variant-found	0	0	0	0	0	0	3 (6.4)	5 (10.9)	8 (8.6)
Time since original diagnosis of PFIC, in months [d]									
Mean	45.9	33.5	39.1	34.3	27.5	31.0	31.7	32.7	32.2
SD (SE)	45.73 (12.22)	36.64 (8.89)	40.76 (7.32)	34.21 (5.95)	31.28 (5.62)	32.74 (4.09)	31.50 (4.59)	30.12 (4.44)	30.66 (3.18)
Median	31.5	20.0	29.0	28.0	12.0	22.0	28.0	29.0	28.0
Q1, Q3	12.0, 48.0	4.0, 53.0	4.0, 53.0	12.0, 44.0	3.0, 39.0	5.5, 40.0	9.0, 42.0	6.0, 41.0	9.0, 41.0
Min, max	2, 136	1, 109	1, 136	2, 136	1, 109	1, 136	1, 136	1, 110	1, 136
Baseline UDCA usage, No. (%) of participants									
Yes	11 (78.6)	17 (100.0)	28 (90.3)	27 (81.8)	30 (96.8)	57 (89.1)	39 (83.0)	39 (84.8)	78 (83.9)
No	3 (21.4)	0	3 (9.7)	6 (18.2)	1 (3.2)	7 (10.9)	8 (17.0)	7 (15.2)	15 (16.1)
Baseline rifampicin usage, No. (%) of participants									
Yes	6 (42.9)	9 (52.9)	15 (48.4)	18 (54.5)	15 (48.4)	33 (51.6)	26 (55.3)	23 (50.0)	49 (52.7)
No	8 (57.1)	8 (47.1)	16 (51.6)	15 (45.5)	16 (51.6)	31 (48.4)	21 (44.7)	23 (50.0)	44 (47.3)
Liver masses detected at baseline, No. (%) of participants									
Yes	0	0	0	1 (3.0)	0	1 (1.6)	1 (2.1)	0	1 (1.1)
No	14 (100.0)	17 (100.0)	31 (100.0)	32 (97.0)	31 (100.0)	63 (98.4)	46 (97.9)	46 (100.0)	92 (98.9)

CSS Score									
Mean	2.8	2.5	2.6	2.8	2.6	2.7	2.7	2.7	2.7
SD (SE)	0.80 (0.21)	0.94 (0.23)	0.88 (0.16)	0.74 (0.13)	0.99 (0.18)	0.87 (0.11)	0.85 (0.12)	0.95 (0.14)	0.90 (0.09)
Median	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Q1, Q3	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0	2.0, 3.0
Min, max	2, 4	1, 4	1, 4	1, 4	1, 4	1, 4	0, 4	1, 4	0, 4
ItchRO(Obs) 4-wk morning avg severity score									
Mean	2.876	2.611	2.731	2.850	2.732	2.793	2.845	2.926	2.885
SD (SE)	0.9123 (0.2438)	0.8927 (0.2165)	0.8965 (0.1610)	0.8763 (0.1525)	0.8812 (0.1583)	0.8737 (0.1092)	0.8305 (0.1211)	0.8359 (0.1233)	0.8297 (0.0860)
Median	3.044	2.229	2.884	2.929	2.571	2.888	2.929	2.955	2.929
Q1, Q3	1.829, 3.625	1.821, 3.143	1.821, 3.625	2.271, 3.554	1.920, 3.714	1.964, 3.615	2.149, 3.554	2.000, 3.714	2.143, 3.625
Min, Max	1.54, 4.00	1.67, 4.00	1.54, 4.00	1.00, 4.00	1.67, 4.00	1.00, 4.00	1.00, 4.00	1.67, 4.00	1.00, 4.00
Total serum bile acid, in µmol/L									
N	12	17	29	31	31	62	45	46	91
Mean	311.879	312.278	312.113	254.327	272.297	263.312	262.615	243.306	252.854
SD (SE)	157.5957 (45.4940)	151.9863 (36.8621)	151.5160 (28.1358)	139.5156 (25.0577)	147.4035 (26.4745)	142.6205 (18.1128)	150.7223 (22.4684)	152.9405 (22.5498)	151.3137 (15.8620)
Median	352.459	312.610	330.852	246.033	262.093	250.456	254.879	226.464	234.161
Q1, Q3	219.358, 422.849	218.071, 442.306	218.071, 435.833	162.198, 362.803	183.953, 348.007	179.687, 355.932	162.198, 389.247	155.043, 336.386	155.043, 362.803
Min, Max	24.43, 503.53	25.54, 539.08	24.43, 539.08	4.25, 503.53	2.10, 549.20	2.10, 549.20	4.25, 536.39	2.10, 549.20	2.10, 549.20
Alkaline phosphatase, in U/L									
Mean	535.8	442.9	484.8	630.1	517.7	575.7	594.9	512.9	554.3
SD (SE)	320.88 (85.76)	156.33 (37.92)	244.66 (43.94)	285.81 (49.75)	290.49 (52.17)	291.34 (36.42)	292.16 (42.62)	255.11 (37.61)	276.07 (28.63)
Median	414.3	422.7	422.5	517.0	470.5	489.8	498.0	471.0	487.0
Q1, Q3	377.0, 631.5	336.0, 516.0	352.0, 553.0	422.5, 754.0	339.0, 595.5	389.0, 717.0	389.0, 732.5	339.0, 603.5	380.0, 647.0
Min, Max	317, 1575	187, 759	187, 15755	317, 1575	187, 1741	187, 1741	109, 1575	187, 1741	109, 1741

Aspartate aminotransferase, in U/L									
Mean	103.8	158.1	133.5	96.9	129.8	112.8	119.6	125.6	122.6
SD (SE)	73.84 (19.73)	125.62 (30.47)	107.40 (19.29)	54.98 (9.57)	100.90 (18.12)	81.60 (10.20)	100.46 (14.65)	95.91 (14.14)	97.75 (10.14)
Median	82.8	103.5	86.5	82.5	85.5	84.8	86.5	89.8	86.5
Q1, Q3	54.0, 109.5	77.0, 246.0	57.0, 209.7	59.5, 109.5	73.5, 157.0	60.0, 122.8	59.5, 124.0	62.0, 152.0	61.5, 134.5
Min, Max	46, 282	38, 462	38, 462	46, 282	38, 462	38, 462	26, 524	25, 462	25, 524
Alanine aminotransferase, in U/L									
Mean	98.4	154.9	129.4	87.8	127.3	107.0	107.9	121.2	114.5
SD (SE)	79.89 (21.35)	127.55 (30.94)	110.73 (19.89)	61.84 (10.77)	103.98 (18.68)	86.53 (10.82)	90.48 (13.20)	99.20 (14.63)	94.62 (9.81)
Median	82.5	119.0	86.5	72.5	92.0	82.0	80.5	84.5	81.5
Q1, Q3	49.5, 87.0	65.5, 199.0	56.0, 155.5	49.5, 101.5	58.0, 148.5	52.0, 127.3	49.5, 129.0	57.5, 142.0	53.0, 131.5
Min, Max	36, 335	34, 527	34, 527	25, 335	34, 527	25, 527	25, 381	18, 527	18, 527
Total bilirubin, in mg/dL									
Mean	3.475	2.714	3.058	4.118	4.041	4.081	4.099	3.796	3.950
SD (SE)	3.9038 (1.0433)	2.9592 (0.7177)	3.3797 (0.6070)	3.8036 (0.6621)	4.4567 (0.8004)	4.0998 (0.5125)	3.7355 (0.5449)	4.6406 (0.6842)	4.1874 (0.4342)
Median	1.725	1.850	1.850	2.800	2.550	2.725	2.800	2.375	2.550
Q1, Q3	0.600, 5.500	0.800, 3.850	0.750, 4.150	1.350, 5.500	0.800, 5.500	0.945, 5.500	1.333, 5.300	0.800, 3.950	1.150, 4.900
Min, Max	0.30, 12.05	0.30, 12.40	0.30, 12.40	0.30, 14.65	0.25, 17.00	0.25, 17.00	0.30, 14.65	0.25, 21.40	0.25, 21.40
Direct bilirubin, in mg/dL									
Mean	2.421	1.919	2.146	2.979	2.934	2.957	2.989	2.769	2.880
SD (SE)	2.9238 (0.7814)	2.1409 (0.5192)	2.4927 (0.4477)	2.8209 (0.4911)	3.3465 (0.6010)	3.0619 (0.3827)	2.7965 (0.4079)	3.5212 (0.5192)	3.1602 (0.3277)
Median	1.075	1.300	1.250	2.050	1.850	2.025	2.050	1.700	1.900
Q1, Q3	0.350, 3.200	0.450, 2.950	0.350, 2.967	0.900, 4.000	0.450, 4.300	0.650, 4.075	0.900, 3.950	0.550, 2.967	0.750, 3.450
Min, Max	0.15, 9.00	0.15, 8.70	0.15, 9.00	0.15, 10.35	0.10, 12.65	0.10, 12.65	0.15, 10.35	0.10, 16.40	0.10, 16.40

FGF-19, in pg/mL									
N	11	16	27	27	30	57	38	44	82
Mean	1051.10	3053.22	2237.54	534.28	1703.76	1149.80	1043.27	1326.15	1195.06
SD (SE)	1418.194	6465.035	5088.420	997.481	4876.849	3622.920	2759.981	4077.218	3510.651
	(427.602)	(1616.259)	(979.267)	(191.965)	(890.387)	(479.867)	(447.728)	(614.664)	(387.687)
Median	156.00	324.00	323.00	80.00	152.50	128.00	103.40	142.00	133.50
Q1, Q3	67.50,	98.90,	73.80,	41.00,	42.40,	42.20,	42.20,	50.10,	45.30,
	1593.00	2041.00	1593.00	650.00	515.00	554.00	681.00	480.50	581.00
Min, Max	35.6,	19.3,	19.3,	21.7,	19.3,	19.3,	14.1,	19.3,	14.1,
	4465.0	22267.0	22267.0	4465.0	22267.0	22267.0	16050.0	22267.0	22267.0
Autotaxin, in ng/mL									
N	12	15	27	28	29	57	41	43	84
Mean	2471.7	2363.1	2411.3	2969.9	2913.0	2940.9	2817.3	2993.0	2907.3
SD (SE)	836.12	944.04	882.43	1070.83	1705.69	1417.17	1212.79	1720.13	1487.92
	(241.37)	(243.75)	(169.82)	(202.37)	(316.74)	(187.71)	(189.41)	(262.32)	(162.35)
Median	2576.5	2255.0	2274.0	2880.5	2354.0	2673.0	2604.0	2354.0	2519.0
Q1, Q3	1898.0,	1919.0,	1919.0,	2182.5,	1973.0,	2046.0,	2010.0,	1835.0,	1974.5,
	2888.0	2648.0	2806.0	3673.0	3375.0	3601.0	3407.0	3877.0	3609.0
Min, Max	1014, 4171	1047, 5201	1014, 5201	1014, 6401	351, 7228	351, 7228	486, 6401	351, 7228	351, 7228
C4, in ng/mL									
N	12	16	28	30	30	60	43	45	88
Mean	4.263	5.808	5.145	5.914	7.060	6.487	5.440	6.366	5.913
SD (SE)	4.3075	5.2182	4.8263	9.2118	7.7223	8.4472	8.1067	6.6648	7.3762
	(1.2435)	(1.3045)	(0.9121)	(1.6818)	(1.4099)	(1.0905)	(1.2363)	(0.9935)	(0.7863)
Median	1.920	4.970	3.335	2.800	4.970	3.180	2.600	4.860	3.065
Q1, Q3	1.250,	1.250,	1.250,	1.250,	1.250,	1.250,	1.250,	1.250,	1.250,
	7.050	9.055	8.970	8.260	10.100	8.970	8.260	9.060	8.285
Min, Max	1.25, 14.20	1.25, 20.10	1.25, 20.10	1.25, 49.90	1.25, 33.20	1.25, 49.90	1.25, 49.90	1.25, 33.20	1.25, 49.90
[illegible]									
FIB-4									
N	8	13	21	22	23	45	33	33	66
Mean	0.332	0.126	0.204	0.230	0.232	0.231	0.209	0.250	0.230
SD (SE)	0.4279	0.1141	0.2871	0.3211	0.2834	0.2990	0.2731	0.3069	0.2890
	(0.1513)	(0.0317)	(0.0627)	(0.0685)	(0.0591)	(0.0446)	(0.0475)	(0.0534)	(0.0356)
Median	0.081	0.089	0.089	0.071	0.124	0.087	0.076	0.124	0.099
Q1, Q3	0.058,	0.028,	0.044,	0.057,	0.027,	0.044,	0.057,	0.033,	0.050,
	0.651	0.220	0.253	0.268	0.336	0.295	0.268	0.328	0.295
Min, Max	0.01, 1.07	0.01, 0.34	0.01, 1.07	0.01, 1.07	0.01, 1.12	0.01, 1.12	0.01, 1.07	0.01, 1.27	0.01, 1.27
PELD [e]									
N	11	16	27	29	30	59	42	44	86
Mean	-3.2	-2.4	-2.7	-1.3	-1.9	-1.6	-0.9	-2.3	-1.6
SD (SE)	8.14 (2.45)	8.34 (2.09)	8.11 (1.56)	7.01 (1.30)	7.63 (1.39)	7.28 (0.95)	7.75 (1.20)	7.05 (1.06)	7.39 (0.80)
Median	-6.7	-3.8	-5.7	-1.5	-2.6	-1.8	-2.2	-3.5	-3.0
Q1, Q3	-10.0, 4.0	-9.3, 1.7	-9.4, 2.6	-7.6, 4.0	-9.3, 2.8	-8.6, 3.4	-7.4, 4.1	-7.8, 2.4	-7.4, 3.0
Min, Max	-11, 12	-11, 18	-11, 18	-11, 12	-11, 18	-11, 18	-11, 21	-11, 18	-11, 21

Avg=average; C4=7α-hydroxy-4-cholesten-3-one; CSS=Clinician Scratch Scale; FGF-19= fibroblast growth factor-19; FIB-4=fibrosis 4; N/A=not applicable; PELD=pediatric end-stage liver disease; PFIC=progressive familial intrahepatic cholestasis; Q1=25th percentile; Q3=75th percentile; SAP=Statistical Analysis Plan; SD=standard deviation; SE=standard error of the mean; UDCA=ursodeoxycholic acid.

Notes: Percentages are 100*n/N, unless otherwise noted. Participants with PFIC1 through PFIC6 all have the biallelic disease.

[a] nt-PFIC2=nontruncated PFIC2 (primary cohort); nt-PFIC2-IsBA=nontruncated PFIC2 with low or fluctuating serum bile acids; nt-PFIC2-surg=nontruncated PFIC2 with a history of surgery; t-PFIC2=truncated PFIC2; PFIC1-surg=PFIC1 with a history of surgery; PFIC4-surg=PFIC4 with a history of surgery; nt PFIC2-het=nontruncated PFIC2 with heterozygosis; PFIC1-het=PFIC1 with heterozygosis; No-variant-found=No established variant linked to PFIC disease.

[b] nt-PFIC2=partial loss of BSEP function; t-PFIC2=complete loss of BSEP function. Only applicable for PFIC2 participants, with exception of 1 nt-PFIC2 participant (015002) with heterozygosis *ABCB11* mutation; N/A for all other participants.

[c] One participant (015002) had heterozygous *ABCB11* mutation, and another (021006) had heterozygous *ATP8B1* mutation.

[d] Partial dates were imputed based on the SAP.

[e] PELD score is calculated for children <12 years of age at the baseline visit; 11:16 and 29:30 participants, respectively, for the primary and PFIC cohorts (maralixibat:placebo).

Source: Table 14.1.4.

In the PFIC cohort, 63 participants (98.4%) received a prior medication/therapy (Study MRX 502 CSR Table 14.1.5). The most frequent (>30%) prior medications/therapies were UDCA (87.5%), rifampicin (59.4%), and tocopherol (42.2%). There were no differences in prior medications/therapies between treatment groups.

Numbers analysed

For the full cohort, 93 participants were included in the Safety/ITT populations. In the primary cohort, 31 and 26 participants were included in the Safety/ITT and Per-Protocol Populations, respectively. In the PFIC cohort, 64 and 58 participants were included in the Safety/ITT and Per-Protocol Populations, respectively.

Outcomes and estimation

Since key efficacy parameters (ItchRO(Obs) and sBA), as well as all exploratory endpoints were similarly planned for the primary (nt-PFIC2) cohort and the PFIC cohort and as the PFIC cohort is

closer to the targeted patient population, the presentation of the key efficacy results will be limited to the PFIC cohort, apart from the primary endpoint and unless otherwise specified.

Exposure/Applied MRX doses and compliance

In the full cohort, the mean (SD) maralixibat treatment duration was 177.1 (36.57) days (range: 12–256 days) and was similar between cohorts. A total of 45 of 47 study participants (95.7%) who received maralixibat dose escalated to the maximum maralixibat dose of 600 µg/kg BID.

In the primary and PFIC cohorts the mean (SD) treatment duration was 178.9 (20.69) days (range: 108-193 days) and 184.4 (18.77) days (range: 108-256 days), respectively. Information on the selected dose in this cohorts has not been provided.

Overall, treatment compliance was high in each cohort, with a mean study drug compliance of >98%, and >90% of participants had overall compliance rate of 90%–100%).

Dosing compliance was documented through caregiver completion (twice daily) of the electronic diary (eDiary). Caregivers could mark "Yes" or "No" to whether dose was administered. Some caregivers did not complete the questionnaire (left blank/unanswered) every day twice daily. With the responses to the second RSI the Applicant informed that the average percentage of days confirmed as BID dosing was similar between both the maralixibat and placebo groups and equalled 81.5% and 84.9%, respectively.

Pruritus

The primary endpoint was met. In the primary cohort, there was a statistically significant difference between maralixibat and placebo treatment groups for the average change in morning ItchRO(Obs) severity score between baseline and Weeks 15–26, with a LS mean change from placebo of -1.089 [95% CI: -1.845, -0.334], p=0.0063).

Similar results were seen in the PFIC cohort (secondary endpoint; N=64, composed of PFIC1 n=13, nt-PFIC2 n=31, PFIC3 n=9, PFIC4 n=7, and PFIC6 n=4), with a LS mean change from placebo of -1.200 (95% CI: -1.727, -0.674; p<0.0001). In both cohorts there was a statistically significant reduction (improvement) in both treatment groups. However, the reduction was smaller in the placebo group and can be attributed to the placebo effect. Reduction in ItchRO(Obs) score was meaningful on MRX.

A statistically significant improvement in the average morning ItchRO(Obs) severity score was observed in the maralixibat group compared with the placebo group as early as Weeks 1–6 (titration phase; PFIC cohort). The effect size further increased up to Weeks 11–14 and was maintained for the entire follow-up period (Weeks 23–26).

Table 16 Mean Change in Average Morning ItchRO(Obs) Severity Score between Baseline and Weeks 15–26 (ITT Population – PFIC cohort)

Postbaseline Analysis Visit Time Period Statistic [a]	Maralixibat (N=33)	Placebo (N=31)
Weeks 15–26 [b]		
LS mean (SE)	-1.811 (0.1834)	-0.610 (0.1947)
95% CI for LS mean	-2.178, -1.444	-1.000, -0.221
p-value (CFB LS mean=0)	<0.0001	0.0026
LS mean (SE) change from placebo	-1.200 (0.2630)	
95% CI for LS mean change from placebo	-1.727, -0.674	
p-value (maralixibat LS mean=placebo LS mean)	<0.0001	

CFB=change from baseline; CI=confidence interval; ItchRO(Obs)=Itch Reported Outcome (observer); ITT=intent to treat; LS=least-squares; MMRM=mixed model for repeated measures; PFIC=progressive familial intrahepatic cholestasis; SE=standard error of the mean.

[a] Estimates are from an MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction.

[b] Average of time periods Weeks 15–18, 19–22, and 23–26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

Source: Study MRX-502 CSR Table 14.2.2.1.1.

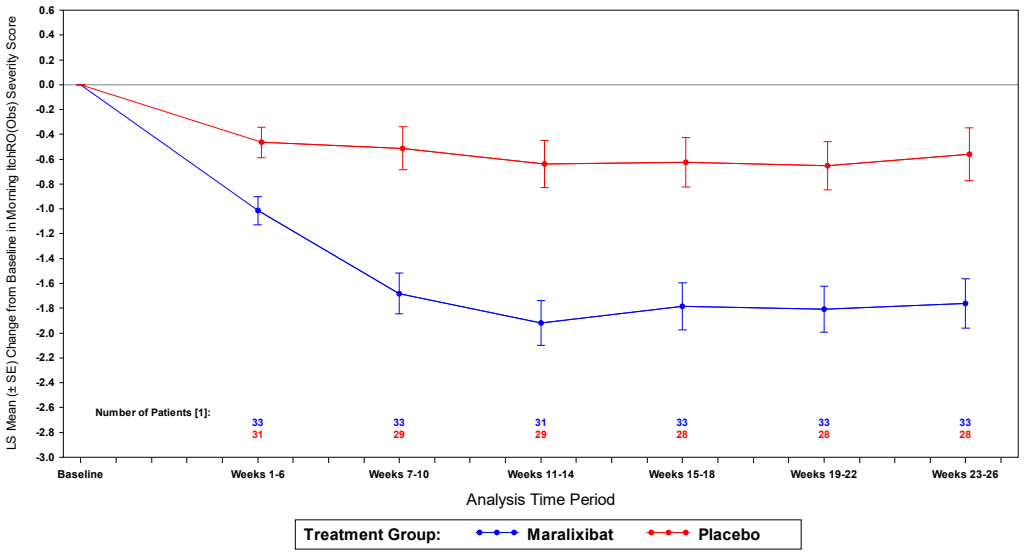


Figure 11 MMRM LS mean change from baseline in morning ItchRO(Obs) severity score over time (ITT Population - PFIC Cohort)

ItchRO(Obs)=Itch Reported Outcome(Observer); ITT=intent to treat; LS=least squares; MMRM=mixed model for repeated measures; PFIC=progressive familial intrahepatic cholestasis; SE=standard error of the mean.

Notes: Estimates are from an MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, baseline score-by-time period interaction, and PFIC type. Change from baseline at baseline visit is added for display purposes.

Sample sizes are the number of patients with nonmissing change from baseline values, at the specified time point, used in the MMRM analysis.

Source: MRX-502 CSR Table 14.2.2.1.1.

A significant treatment effect for pruritus of maralixibat compared with placebo was observed as early as Weeks 1-6, continued to improve through Weeks 11–14, and was maintained for the duration in Study MRX-502 (6 months).

Sensitivity analyses were performed in the primary cohort to test the robustness of the treatment effect. The change from baseline in weekly average morning ItchRO(Obs) severity score was assessed across subgroups for region, age at baseline, sex, race, baseline sBA, baseline UDCA usage, or baseline rifampicin usage. There were no apparent differences across the different subgroups (primary cohort).

Exploratory subgroup analyses demonstrated a significant improvement in morning ItchRO(Obs) severity with maralixibat compared with placebo in nt-PFIC2 (N=31; primary cohort), in the PFIC cohort excluding nt-PFIC2 (PFIC1, PFIC3, PFIC4, PFIC6; Figure below) and in the 8 patients with undefined PFIC. Participants with PFIC1 and PFIC3 also showed a statistically significant and clinically meaningful improvement, but difference compared with placebo did not reach statistical significance probably due to the smaller sample sizes (PFIC1 N=13, PFIC3 N=9).

No Improvement in pruritus was observed in participants with BSEP deficiency with predicted protein-truncating variants with no residual BSEP function (t-PFIC2; N=5 on MRX and 4 on placebo).

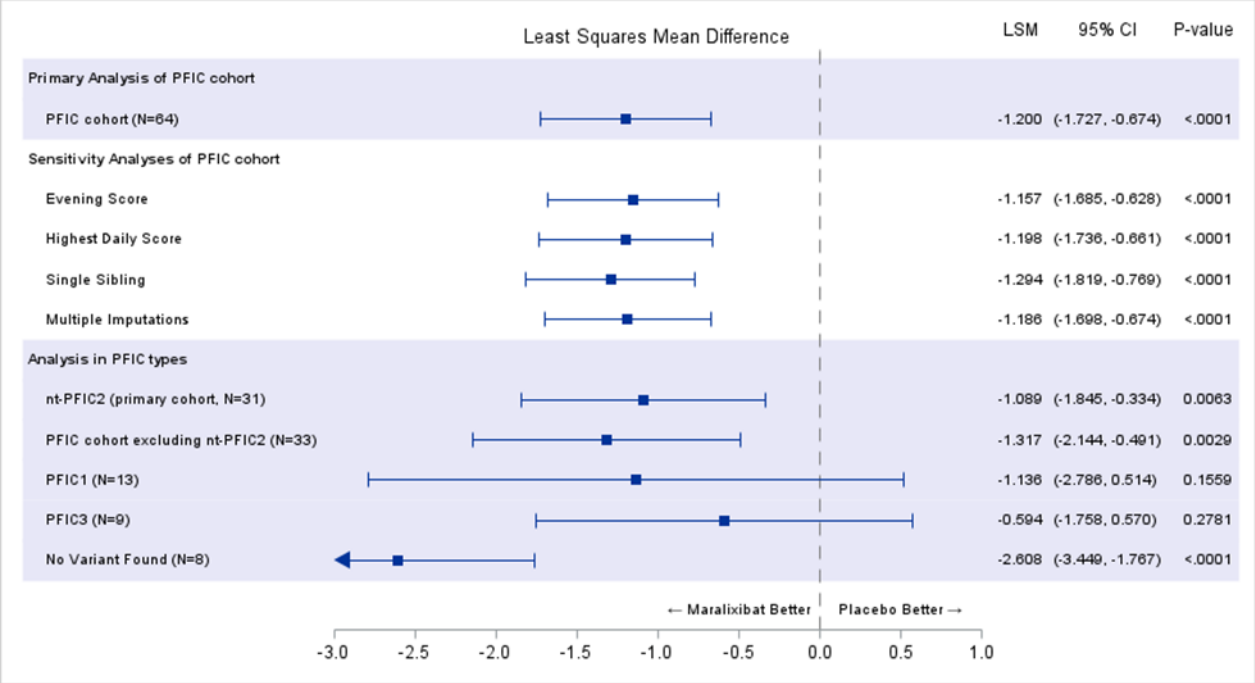


Figure 12 Sensitivity and Subgroup Analyses of Mean Change in Average Morning ItchRO(Obs) Severity Score between Baseline and Weeks 15–26 (Maralixibat vs. Placebo)–ITT Population

ItchRO(Obs)= Itch Reported Outcome – Observer; ITT=intent to treat; PFIC=progressive familial intrahepatic cholestasis; nt-PFIC=nontruncating PFIC.

PFIC cohort includes nt-PFIC2, PFIC1, PFIC3, PFIC4, PFIC6.

The improvement in pruritus with maralixibat treatment in participants with PFIC was confirmed across various pruritus scores, including morning, evening and highest daily ItchRO(Obs) severity and frequency scores, CSS scores, and morning, evening and highest daily EDQ severity scores.

The percentage of ItchRO(Obs) responders was 63.6% for maralixibat and 25.8% for placebo participants (PFIC cohort). The difference between maralixibat and placebo had a nominal p value of 0.0023.

The number of participants with morning ItchRO(Obs) severity score ≤1 for ≥50% of the time period (Weeks 15-26) was 72.7% and 35.5% in the maralixibat and placebo treatment groups, respectively (PFIC cohort). The difference between treatment groups was statistically significant; p=0.0037.

The mean number of days with a morning ItchRO(Obs) severity score ≤1, and the LS mean proportion of ItchRO(Obs) assessments with severity score decreases of ≥1 OR average score of ≤1.0 were all significantly higher in the maralixibat treatment group compared with the placebo group (PFIC cohort).

Difference between MRX and placebo treatment groups (PFIC population) in the pruritus was observed at week 2 of treatment (300 µg/kg BID dose) as per CSS. LS mean (95% CI) change from the baseline values of mean (SD) 2.8 (0.74) and 2.6 (0.99) was -0.942 (-1.251, -0.632) and -0.377 (-0.697, -0.058) for MRX and placebo, respectively, with LS mean (95% CI) difference to placebo of -0.564 (-0.987, -0.142; p=0.0097).

Total sBA

The key secondary endpoint showed significant reduction in sBA in participants with PFIC (PFIC cohort composed of PFIC1, nt- PFIC2, PFIC3, PFIC4 and PFIC6) on MRX. A significant treatment effect was observed as early as Week 2 (the first on-treatment measurement timepoint on half the recommended dose), continued to improve at Week 6 (on the recommended dose), and was maintained through Weeks 11-14 and for the follow-up period in Study MRX-502 (6 months).

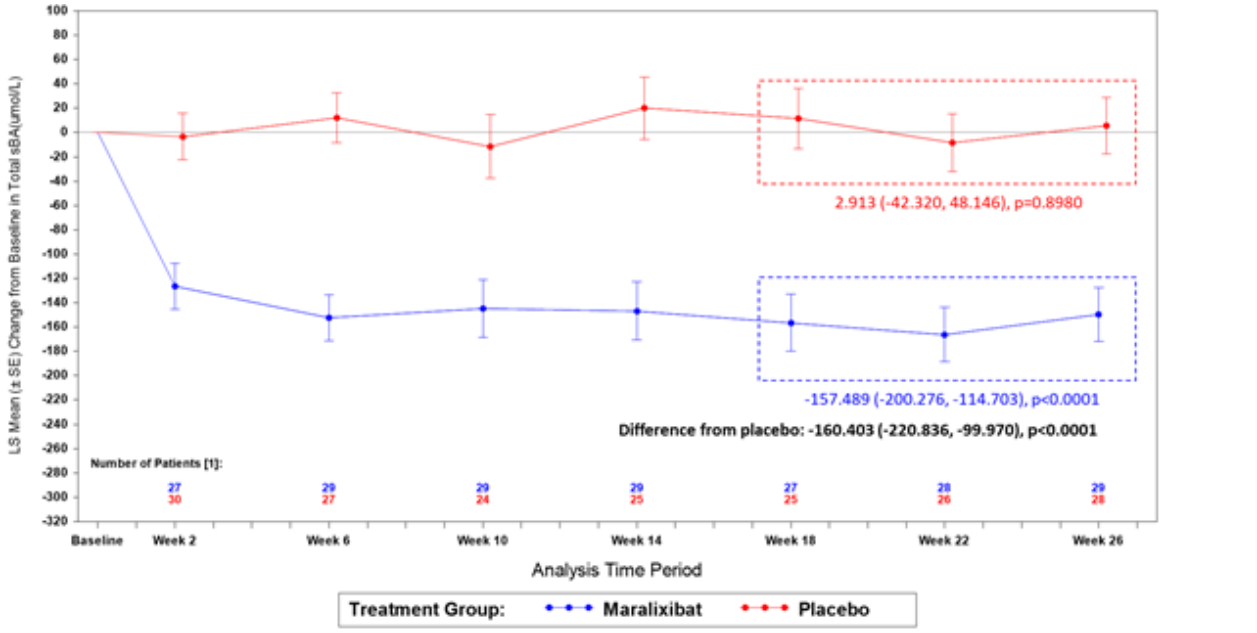


Figure 13 MMRM LS Mean Change from Baseline in Total sBA Over Time (ITT Population-PFIC Cohort)

CFB=change from baseline; ITT=intent to treat; LS=least squares; MMRM=mixed model repeated measures; sBA=serum bile acid; SE=standard error.
Notes: Estimates are from an MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit, and treatment-by-visit interaction as well as the continuous fixed covariates of baseline score, baseline score-by-visit interaction, and PFIC type.
Sample sizes are the number of participants with nonmissing CFB baseline values, at the specified time point, used in the MMRM analysis.
Numbers are the LS mean (95% CI) change from baseline in total sBA level between baseline and average of Weeks 18, 22 and 26.
Source: Study MRX-502 CSR Table 14.2.2.2.1.

Changes in the sBA in the Primary cohort were consistent with the changes in the PFIC cohort.

The change from baseline in total sBA was assessed across subgroups for region, age at baseline, sex, race, baseline median sBA, baseline UDCA usage, or baseline rifampicin usage. There were no apparent differences across the different subgroups (primary cohort). However, the subgroups were too small and partly imbalanced.

Exploratory subgroup analyses demonstrated a significant reduction in total sBA levels with maralixibat compared with placebo in participants with nt-PFIC2 (N=31; primary cohort), in the PFIC cohort excluding nt-PFIC2 (PFIC1, PFIC3, PFIC4, PFIC6), and in participants with PFIC1 (Figure below). Participants with PFIC3 treated with maralixibat also showed a statistically significant reduction from baseline, but not compared to placebo probably due to the smaller sample size (PFIC3 N=9).

In the patients without defined PFIC variant a decrease in total sBA in the maralixibat treatment group did not reach statistical significance and showed only numerical difference to placebo (Figure below). Subgroup analyses in PFIC4 and PFIC6 was not conducted.

No sBA reductions were observed in participants with BSEP deficiency with predicted protein-truncating variants with no residual BSEP function (t-PFIC2).

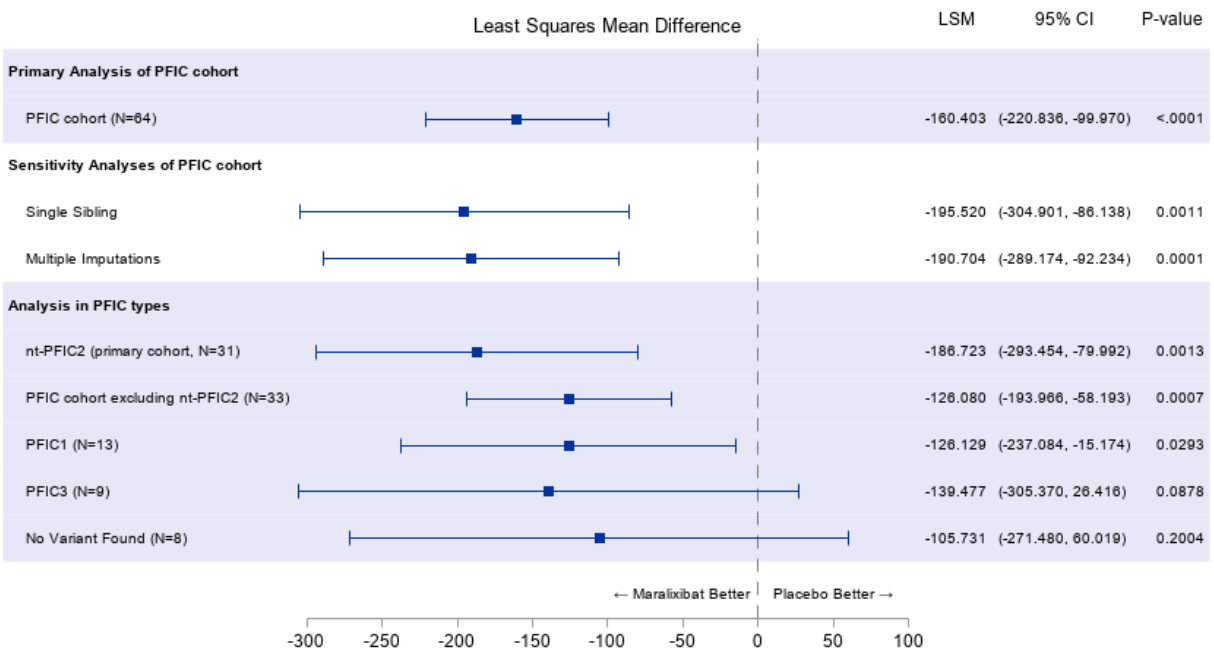


Figure 14 Sensitivity and Subgroup Analyses of Mean Change in sBA Between Baseline and Average of Weeks 18, 22, and 26 (Maralixibat vs. Placebo) - ITT Population

ITT=intent to treat; nt-PFIC=nontruncating PFIC; PFIC=progressive familial intrahepatic cholestasis; sBA=serum bile acid.

Note: PFIC cohort includes nt-PFIC2, PFIC1, PFIC3, PFIC4, PFIC6.

In the maralixibat group of the PFIC cohort, 45.5% reached sBA thresholds found to be predictive of TFS beyond 15 years in patients with PFIC2 (average sBA level of <102 µmol/L OR at least a 75% average percent reduction; van Wessel et al. 2020). In the placebo group, only 6.5% reached these thresholds. The difference between the treatment groups was statistically significant (p=0.0004).

Caregiver Impression of Severity

In the PFIC cohort, there was a statistically significant reduction (improvement) in CIS between baseline and average of Weeks 18, 22, and 26 in the maralixibat treatment group (ITT Population); the LS mean reduction was -1.897 (95% CI: -2.276, -1.519), p<0.0001. A smaller LS mean reduction in CIS of -0.657 (95% CI: -1.068, -0.247), p=0.0022; was observed in the placebo group. The difference between maralixibat and placebo treatment groups was statistically significant; the LS mean reduction was -1.240 (95% CI: -1.792, -0.688), p<0.0001. The reduction in CIS was rapid, with a statistically significant change from baseline observed in the maralixibat treatment group as early as Week 4.

EDQ(Obs) Sleep Disturbance Scores

Sleep disturbance was scored in the morning using a 5-point scale, in which 1 designates because of itch my child never had trouble staying asleep and 5 designates because of itch my child almost always has trouble staying asleep.

In the PFIC cohort, there was a statistically significant reduction (improvement) in morning EDQ(Obs) sleep disturbance score between baseline and average of Weeks 18, 22, and 26 in the maralixibat treatment group (ITT Population); the LS mean reduction was -1.741 (95% CI: -2.149, -1.333), p<0.0001. A smaller LS mean reduction of -0.550 (95% CI: -0.990, -0.111), p=0.0151 was observed

in the placebo group. The difference between maralixibat and placebo treatment groups was statistically significant (LS mean change from placebo of -1.190 [95% CI: -1.783, -0.597], p=0.0002). The reduction in morning EDQ(Obs) sleep disturbance score was rapid, with a statistically significant change from baseline observed as early as Weeks 1–6.

Fatigue and Sleep

There was a statistically significant reduction (improvement) in morning EDQ(Obs) sleep disturbance score between baseline and average of Weeks 15–26 and in PedsQL (parent) multidimensional fatigue scale score between baseline and average of Weeks 18, 22, and 26 in the maralixibat group compared with the placebo group (PFIC cohort; p=0.0002 and p=0.0208, respectively).

Pediatric Quality of Life

Both treatment groups showed a significant improvement in QoL (assessed by the PedsQL(parent) Total Scale Score) between Baseline and Average of Weeks 18, 22, and 26. Improvements were slightly larger in the maralixibat group compared with the placebo group, but the difference was not statistically significant. The lack of a significant effect on QoL despite a significant improvement in pruritus severity may partially be explained by the lower average baseline scores in the maralixibat group compared with the placebo group and the large placebo effect in self- and caregiver-reported measures. Of note, although PedsQL is a common instrument of choice for measurement of HRQoL in healthy pediatric population, PedsQL has not been optimized for pediatric patients with cholestatic disease (Kamath et al. 2018).

Liver Chemistry

Changes in the liver function tests are presented in the tables below.

Treatment with maralixibat led to reductions from baseline in total and direct bilirubin (PFIC cohort; MRX-503). In Study MRX-502, there was a mean reduction in total bilirubin in the maralixibat group and an increase in the placebo group, with a statistically significant difference between maralixibat and placebo of -2.003 mg/dL (95% CI: -3.980, -0.027; p=0.0471). Total bilirubin responses to maralixibat treatment in Study MRX-503 in participants previously exposed to placebo in Study MRX-502 were very similar to the responses in Study MRX-502 (PFIC cohort).

There were 43 participants with elevated total bilirubin at baseline (>ULN), of which 25 were in the maralixibat group and 18 were in the placebo group. In the maralixibat group, 40% of participants with elevated total bilirubin at baseline showed normalization in total bilirubin levels versus 0% in the placebo group (PFIC cohort). The Applicant claims, that these results suggest that maralixibat treatment leads to bilirubin normalization and thus demonstrates a potential for improving underlying liver health in patients with PFIC.

A trend in numerical difference to placebo in total bilirubin and small difference in direct bilirubin was observed at Week 2 of study treatment on half the recommended MRX dose.

There were no statistically significant changes from baseline in ALT, AST, ALP, GGT, albumin, and FIB-4 in the maralixibat or placebo treatment groups (PFIC cohort; MRX-502).

Growth

Height z-Score

There was an increase (improvement) in height z-score between baseline and average of Weeks 18, 22, and 26 in the maralixibat-treatment group in the primary and PFIC cohorts; the LS mean was 0.095 (95% CI: -0.174, 0.364), p=0.4734 (primary cohort) and 0.078 (95% CI: -0.093, 0.248), p=0.3652 (PFIC cohort). In the placebo group there was a decrease (worsening) in height z-score in

the primary and PFIC cohorts. For both the maralixibat and placebo groups, the changes from baseline were not statistically significant. In the primary and PFIC cohorts, the differences between maralixibat and placebo treatment groups were not statistically significant.

Weight z-Score

In the PFIC cohort, there was a statistically significant increase (improvement) in weight z-score between baseline and average of Weeks 18, 22, and 26 in the maralixibat treatment group (ITT Population). In the placebo group, there was a small increase that was not statistically significant. The difference between maralixibat and placebo treatment groups was statistically significant; the LS mean change from placebo was 0.227 (95% CI: 0.012, 0.442), p=0.0391. The increase in weight z-score in the maralixibat group was rapid, with a statistically significant change from baseline in the maralixibat treatment group observed as early as Week 4.

Table 17 Liver function tests and growth parameters for maralixibat vs. placebo over the 26-week treatment period in participants with PFIC in the pivotal trial (ITT Population)

Efficacy endpoint	**Placebo (n=31)**	**Maralixibat (n=33)**
Alanine aminotransferase (U/L)		
Baseline (mean [SE])	127.3 (18.68)	87.8 (10.77)
LS mean change [SE] to weeks 18-26	-7.0 (11.13)	10.0 (10.36)
LS mean difference vs. placebo (95% CI); p-value		16.6 (-13.31, 46.60); 0.2707
Aspartate aminotransferase (U/L)		
Baseline (mean [SE])	129.8 (18.12)	96.9 (9.57)
LS mean change [SE] to weeks 18-26	-0.4 (14.91)	13.6 (14.05)
LS mean difference vs. placebo (95% CI); p-value		14.1 (-26.57, 54.69); 0.4914
Total bilirubin (µmol/L)		
Baseline (mean [SE])	69.1 (13.69)	70.4 (11.32)
LS mean change [SE] to weeks 18-26	15.9 (12.37)	-18.3 (11.65)
LS mean difference vs. placebo (95% CI); p-value		-34.3 (-68.06, -0.05); 0.0471
Direct bilirubin (µmol/L)		
Baseline (mean [SE])	50.2 (10.28)	50.9 (8.40)
LS mean change [SE] to weeks 18-26	13.5 (9.52)	-12.9 (8.97)
LS mean difference vs. placebo (95% CI); p-value		-26.4 (-52.46, -0.26); 0.0480
Height z-score		

Efficacy endpoint	Placebo (n=31)	Maralixibat (n=33)
Baseline (mean [SE])	-2.06 (0.27)	-2.08 (0.23)
LS mean change [SE] to weeks 18-26	-0.131 (0.0909)	0.078 (0.0851)
LS mean difference vs. placebo (95% CI); p-value		0.208 (-0.036, 0.453); 0.0939
Weight z-score		
Baseline (mean [SE])	-1.28 (0.24)	-1.75 (0.23)
LS mean change [SE] to weeks 18-26	0.120 (0.0779)	0.347 (0.0738)
LS mean difference vs. placebo (95% CI); p-value		0.227 (0.012, 0.442); 0.0391

SE=standard error; LS = least-squares; CI=confidence interval. Baseline values are observed values. LS mean values are averages of weeks 18, 22, and 26 using an equally weighted average of the 3 individual visit-specific estimates obtained from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, PFIC type, analysis visit and treatment-by-visit interaction as well as the continuous fixed covariates of baseline score and baseline score-by-visit interaction.

Markers of bile acid synthesis (fibroblast growth factor-19 [FGF-19] and 7αC4)

Baseline FGF-19 levels were elevated in the majority of participants, varied ranging from 19.3 pg/mL to 22267.0 pg/mL and were closer to a log-normal distribution. The geometric mean (95% CI) FGF-19 baseline levels tended to be slightly higher in the placebo group (212.38 [106.44, 423.75]) compared with the maralixibat group (149.65 [80.71, 277.50]) (PFIC cohort).

A post-hoc analysis assessing the geometric mean changes to account for baseline variable population showed that inn the placebo group, the geometric mean FGF-19 levels remained stable over the course of the study. In contrast, on maralixibat the average FGF-19 levels significantly dropped and 7αC4 levels significantly increased by the first analysis time point at Week 6 and then remained stable over the remaining course of the studychanging from 149.65 (80.71, 277.50) at baseline to 46.72 (24.62, 88.66) pg/mL at Week 26.

Baseline 7αC4 levels were also variable, ranging from below the lower limit of detection (LLOD; for samples < LLOD, a value of 1.25 ng/mL [½ of the LLOD of 2.5 ng/mL] was assigned) to 49.90 ng/mL and were closer to being log-normally distributed. The geometric mean (95% CI) 7αC4 levels of the PFIC cohort was 3.614 (2.748, 4.753). 33 of 60 participants (55%) in the PFIC cohort with available 7αC4 results at baseline had fully suppressed bile acid synthesis (<4 ng/mL). In line with the FGF-19 levels, geometric mean 7αC4 levels at baseline tend to be slightly higher in the placebo group (3.959 [95% CI: 2.603, 6.023]) compared with the maralixibat group (3.299 [95% CI: 2.267, 4.799]). The number of participants with 7αC4 levels below the LLOD was comparable between the treatment groups (12 of 30 participants [40%] in the maralixibat group and 13 of 30 participants [43%] in the placebo group).

A statistically significant increase in 7αC4 was observed in the maralixibat treatment group ($p<0.0001$; PFIC cohort). The increase in 7αC4 was rapid, with a statistically significant change from baseline observed as early as Week 6 that was maintained throughout the treatment period. At Week 26, 7αC4

levels in the maralixibat group ranged from 1.25 ng/mL to 274 ng/mL with a geometric mean of 17.72 (95% CI: 9.248, 33.960). At Week 26, 5 of 27 participants (19%) had fully suppressed bile acid synthesis (<4 ng/mL) and 7 of 27 participants (26%) in the maralixibat group had elevated 7αC4 levels (>66.5 ng/mL). No significant change from baseline was observed in the placebo group; p=0.3656 (PFIC cohort). There was a statistically significant increase in 7αC4 between baseline and the average of Weeks 18, 22, and 26 in the maralixibat treatment group compared with the placebo group (least squares [LS] mean change from placebo was 37.977 ng/mL (95% CI:13.934, 62.020), p=0.0025; PFIC cohort).

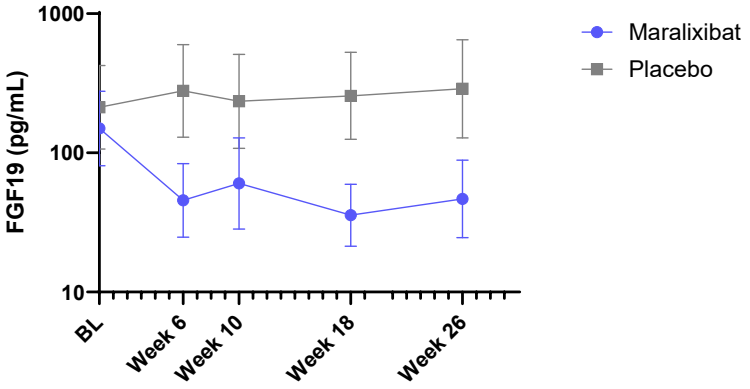


Figure 15 MRX-502 – Geometric Mean (95% CI) FGF-19 Levels over Time (PFIC Cohort)

FGF-19=fibroblast growth factor 19; PFIC=progressive familial intrahepatic cholestasis.

No significant correlation was observed between FGF-19 or 7αC4 baseline levels and changes in sBA from baseline to the average of Week 18, 22, and 26 in the maralixibat treatment group. In the majority of maralixibat-treated participants, the bile acid synthesis rate was not increased beyond the normal range of healthy individuals. This is also reflected by the fact that despite the increase in de-novo bile acid synthesis with maralixibat treatment, the overall bile acid pool (measured as sBA) is significantly and sustainably reduced.

Autotaxin

In Study MRX-502, baseline levels of autotaxin were very variable, ranging from 351 to 7228 ng/mL, and were log-normal distributed. The geometric mean concentrations at baseline were comparable in the maralixibat (2788.8 ng/mL [95% CI: 2416.3, 3218.6]) and the placebo group (2439.2 ng/mL [95% CI: 1906.1, 3121.4]). Given that normal ranges for the study population are unknown and the observed effect of age on normal levels of autotaxin in teenagers, it is difficult to conclude on the clinical meaningfulness of the observed baseline levels.

In Study MRX-502, there was a statistically significant reduction (improvement) in autotaxin levels observed in the maralixibat treatment group; p=0.0002 (PFIC cohort). The decrease was rapid, with a statistically significant change from baseline observed as early as Week 6. Levels further decreased during the treatment period. At Week 26, autotaxin levels in the maralixibat group ranged from 766 ng/mL to 4934 ng/mL with a geometric mean of 1747.46 (95% CI: 1423.09, 2145.76). In contrast, in the placebo group, there was an increase (worsening) that was not statistically significant; p=0.6603. There was a statistically significant reduction (improvement) in autotaxin between baseline and average of Weeks 18, 22, and 26 in the maralixibat treatment group compared with the placebo group (LS mean change from placebo of -1057.528 ng/mL [95% CI: -1724.827, -390.230]), p=0.0025.

The clinical relevance of the observed reduction in autotaxin is supported by the strong positive correlation between ItchRO(Obs) severity score for observed average values from Week 18, 22, and 26 and for change from baseline to average of Week 18, 22, and 26 (r=06287; p=0.0003 and r=0.7479 with p<0.0001, respectively). Based on a simple linear regression, a 578.6-ng/mL reduction in autotaxin corresponds to a 1-point reduction in ItchRO(Obs).

FIB-4

FIB-4 scores at baseline ranged from 0.01 to 1.12, indicating no advanced fibrosis in any participant at study baseline. FIB-4 baseline levels are log-normal distributed and are comparable between the placebo and the maralixibat group.

In the placebo group, a statistically significant increase in FIB-4 scores was observed with a LS mean (standard error [SE]) change from baseline to Week 18–26 of 0.101 (0.0358, p=0.0062). Increases in FIB-4 are indicative of disease progression over time. In contrast, no significant change in FIB-4 was observed in the maralixibat group with a LS mean (SE) change from baseline to Week 18–26 of 0.016 (0.0328, p=0.6242). The LS mean change from baseline between the two groups did not reach statistical significance with an LS mean (SE) of -0.085 (0.0484, p=0.0838). At Week 26, all participants of both treatment groups had a FIB-4 score <1.45 indicating no advanced fibrosis.

The maintained FIB-4 scores in maralixibat-treated participants are indicative of stabilization of disease progression and fibrosis staging.

APRI

APRI scores at baseline ranged from 0.17 to 4.40 and followed more a log-normal distribution. In the PFIC cohort, the geometric mean APRI score at baseline was 0.542 (95% CI: 0.4184, 0.7017). Overall, 11 of 45 participants (24.4%) in the PFIC cohort had a score of >0.99 at baseline, predictive of a severe fibrosis (F3-F4) (Shiau et al. 2020). APRI scores at baseline tended to be slightly higher in the placebo group compared with the maralixibat group. The number of participants with a score >0.99 were comparable; 5 of 22 participants (23%) in the maralixibat group and 6 of 23 participants (26%) in the placebo group.

APRI scores in the placebo group tended to increase over time with a LS mean (SE) change from baseline at Week 18-26 of 0.462 (0.2341; p=0.0570). In contrast, in the maralixibat treatment group, APRI scores tended to be maintained with a LS mean (SE) change from baseline of -0.039 (0.2189; p=0.8605). The difference between the treatment groups was not statistically significant (LS mean [SE] difference in the maralixibat group compared to placebo of -0.501 [0.3211; p=0.1287]). Following 26 weeks of treatment, no meaningful changes in the number of participants with APRI scores >0.99 were observed in the maralixibat or placebo group.

The maintained APRI scores in maralixibat-treated participants are indicative of stabilization of disease progression and fibrosis staging.

PELD

Pediatric end-stage liver disease (PELD) is a noninvasive marker based on patient age, albumin, total bilirubin, international normalized ratio, and weight z-score to estimate the 90-day waitlist mortality for pediatric liver transplant candidates (<12 years of age). PELD is commonly used to assign priority to most liver transplant candidates on the basis of medical urgency. It can also be considered as a marker for end-stage liver disease severity.

Study participants of the PFIC cohort of Study MRX-502 generally had low PELD scores (mean (SD) -1.6 (7.28); range -11 to 18), indicating very low probability of death within the next 90 days and liver disease that was not advanced. The scores were comparable across the treatments.

For PELD in Study MRX-502 the LS mean (SE) change from baseline to Week 18-26 in the placebo group was 1.981 (1.0760; p=0.0708). In contrast, a small decrease from baseline was observed in the maralixibat group (LS mean (SE) of -1.805 (1.0377; p=0.0879). The LS mean (SE) difference compared with placebo was -3.785 (1.4752; p=0.0131).

Data extrapolation to PFIC5 population and efficacy of MRX in t-PFIC2

PFIC5:

No participants with PFIC5 were enrolled in the study, and therefore, the treatment effect of maralixibat in this disease type could not be evaluated. However, the data collected in PFIC1, PFIC2, PFIC3, PFIC4, and PFIC6 can be extrapolated to the broader PFIC patient population, including PFIC5. Of note, a treatment response was observed in participants with only clinically diagnosed PFIC for whom no PFIC variant was identified, indicating the benefit of maralixibat treatment in the broader PFIC population regardless of PFIC type. For this reason, the proposed SmPC was not changed to mention lack of experience of MRX treatment/effectiveness in PFIC5.

Extrapolation of efficacy to patients with PFIC5 is based on the following:

A) Patients with PFIC, including PFIC5, share the same disease pathophysiology pathway.

PFIC5 is caused by loss of function mutations in farnesoid X receptor (FXR deficiency). FXR is a nuclear bile acid-sensing receptor activated by bile acids and directly involved in the expression of both BSEP and MDR3, proteins affected in PFIC2 (BSEP deficiency) and PFIC3 (MDR3 deficiency), respectively (Huang et al. 2003; Gomez-Ospina et al. 2016). FXR deficiency results in secondary BSEP and MDR3 deficiency. BSEP is a bile acid transporter expressed at the canalicular membrane of hepatocytes and responsible for exporting bile acids from the hepatocyte in the bile canaliculi (Henkel et al. 2019). Impaired expression of BSEP, as a result of FXR deficiency, leads to in impairment of bile acid excretion capabilities, resulting in accumulation of toxic levels of bile acids within the hepatocyte. MDR3 transports phosphatidyl-choline from the hepatocyte to the bile canaliculi. Impaired expression of MDR3, due to FXR deficiency, impairs transportation of phosphatidyl-choline, resulting in the presence of insoluble bile salts and cholesterol in the biliary canaliculi, which damages the cholangiocytes (Sticova et al 2020). Data from Study MRX-502 demonstrated that maralixibat has a significant effect in reducing sBA and pruritus severity in patients with PFIC2 (BSEP deficiency) and showed strong trends in patients with PFIC3 (MDR3 deficiency); therefore, there is a strong rationale that the efficacy can be extrapolated to patients with PFIC5.

B) Maralixibat inhibits the IBAT receptor, which is universally shared in all patients with PFIC, including patients with PFIC5.

C) Patients with PFIC5 are encountered so rarely that it is not feasible to study this PFIC type separately.

t-PFIC2:

The mechanism of action of maralixibat requires that some degree of enterohepatic circulation of bile acids is preserved. For this reason, patients with complete absence or lack of function of BSEP protein are not expected to respond to maralixibat. However, the prediction of complete absence of BSEP protein (t-PFIC2 or BSEP3) by interpretation of genetic test results is not 100% conclusive and therefore some residual BSEP function could be present. Data of 9 patients with t-PFIC2 have been submitted and discussed stating that some patients had improvement on MRX.

Efficacy Data from the Full Cohort

The Full Cohort consists of the PFIC cohort (64 participants, including 31 participants from the primary cohort) and 29 participants who did not meet criteria for the PFIC cohort; 9 participants with biallelic

protein-truncating bile salt excretion pump (BSEP) mutations (truncating PFIC Type 2 [t-PFIC2]), 2 participants with heterozygous mutations, 8 participants with PFIC phenotype but no genetic variant associated with PFIC disease identified, 2 participants with nt-PFIC2 and low or fluctuating sBA levels, and 8 participants with previous surgery to treat PFIC (3 nt-PFIC2, 4 PFIC1, 1 PFIC4; MRX-502 CSR).

Demographics and baseline characteristics were generally similar between the PFIC cohort and the Full Cohort.

Efficacy outcomes in the Full Cohort were comparable to the outcomes in the PFIC cohort. Key efficacy data are being summarized in the tables and figures below.

Table 18 MRX-502 – Demographics and Baseline Characteristics (Safety Population – PFIC Cohort and Full Cohort)

	PFIC Cohort			Full Cohort		
Status or Category	Maralixibat (n=33)	Placebo (n=31)	Overall (N=64)	Maralixibat (n=47)	Placebo (n=46)	Overall (N=93)
Age, in years [a]						
Mean	4.9	4.4	4.6	4.8	4.7	4.7
SD (SE)	4.10 (0.71)	3.61 (0.65)	3.85 (0.48)	4.15 (0.61)	3.57 (0.53)	3.85 (0.40)
Median	3.0	3.0	3.0	3.0	3.5	3.0
Min, max	1, 15	1, 13	1, 15	1, 17	1, 14	1, 17
Age category [a]						
1 to <6 years	22 (66.7)	19 (61.3)	41 (64.1)	32 (68.1%)	29 (63.0%)	61 (65.6%)
6 to <13 years	8 (24.2)	11 (35.5)	19 (29.7)	11 (23.4%)	15 (32.6%)	26 (28.0%)
13 to 18 years	3 (9.1)	1 (3.2)	4 (6.3)	4 (8.5%)	2 (4.3%)	6 (6.5%)
Sex						
Male	17 (51.5)	13 (41.9)	30 (46.9)	20 (42.6%)	22 (47.8%)	42 (45.2%)
Female	16 (48.5)	18 (58.1)	34 (53.1)	27 (57.4%)	24 (52.2%)	51 (54.8%)
Race						
American Indian or Alaska Native	3 (9.1)	4 (12.9)	7 (10.9)	3 (6.4%)	4 (8.7%)	7 (7.5%)
Asian	3 (9.1)	0	3 (4.7)	3 (6.4%)	0	3 (3.2%)
Black or African American	1 (3.0)	2 (6.5)	3 (4.7)	1 (2.1%)	2 (4.3%)	3 (3.2%)
White	24 (72.7)	19 (61.3)	43 (67.2)	36 (76.6%)	34 (73.9%)	70 (75.3%)
More than one race	2 (6.1)	4 (12.9)	6 (9.4)	3 (6.4%)	4 (8.7%)	7 (7.5%)
Not reported	0	2 (6.5)	2 (3.1)	1 (2.1%)	2 (4.3%)	3 (3.2%)
Ethnicity						
Hispanic or Latino	16 (48.5)	13 (41.9)	29 (45.3)	18 (38.3%)	17 (37.0%)	35 (37.6%)
Not Hispanic or Latino	17 (51.5)	16 (51.6)	33 (51.6)	28 (59.6%)	27 (58.7%)	55 (59.1%)
Not reported	0	2 (6.5)	2 (3.1)	1 (2.1%)	2 (4.3%)	3 (3.2%)
Region						
Asia	2 (6.1)	0	2 (3.1)	2 (4.3%)	0	2 (2.2%)
Europe	7 (21.2)	7 (22.6)	14 (21.9)	14 (29.8%)	10 (21.7%)	24 (25.8%)
Middle East	5 (15.2)	5 (16.1)	10 (15.6)	7 (14.9%)	9 (19.6%)	16 (17.2%)
North America	9 (27.3)	12 (38.7)	21 (32.8)	13 (27.7%)	19 (41.3%)	32 (34.4%)
South and Central America	10 (30.3)	7 (22.6)	17 (26.6)	11 (23.4%)	8 (17.4%)	19 (20.4%)
Height z-score [b]						
Mean	-2.081	-2.064	-2.073	-2.009	-1.913	-1.962
SD (SE)	1.292 (0.225)	1.480 (0.266)	1.375 (0.172)	1.333 (0.194)	1.323 (0.195)	1.322 (0.137)
Median	-1.961	-2.335	-2.034	-1.961	-1.965	-1.961
Min, max	-4.92, 0.67	-4.54, 0.88	-4.92, 0.88	-4.92, 0.67	-4.54, 0.88	-4.92, 0.88
Weight z-score [b]						
Mean	-1.752	-1.283	-1.525	-1.560	-1.224	-1.394
SD (SE)	1.293 (0.225)	1.325 (0.238)	1.319 (0.1650)	1.363 (0.199)	1.224 (0.181)	1.300 (0.135)
Median	-1.464	-1.090	-1.313	-1.396	-1.143	-1.231
Min, max	-5.08, 1.01	-3.88, 1.46	-5.08, 1.46	-5.08, 1.08	-3.88, 1.46	-5.08, 1.46
BMI z-score [b]						
Mean	-0.451	0.142	-0.164	-0.261	0.068	-0.098
SD (SE)	1.092 (0.190)	1.128 (0.203)	1.140 (0.143)	1.112 (0.162)	1.164 (0.172)	1.144 (0.119)
Median	-0.531	0.110	-0.308	-0.473	0.117	-0.126
Min, max	-3.55, 1.87	-2.64, 2.34	-3.55, 2.34	-3.55, 2.14	-2.64, 2.34	-3.55, 2.34

BMI=body mass index; max=maximum; min=minimum; PFIC=progressive familial intrahepatic cholestasis; SD=standard deviation; SE=standard error of the mean.
Note: Percentages are 100*n/N.
[a] Age at baseline visit.
[b] Height, weight, and BMI z-scores are based on a participant's sex and age at the baseline visit. The World Health Organization growth charts were used to derive z-scores for participants <24 months old, and the Centers for Disease Control and Prevention growth charts were used to derive z-scores for participants ≥24 months old.
Source: MRX-502 CSR Table 14.1.3, Appendix 2 Q16 Table 1.

Table 19 MRX-502 – Disease History and Baseline Disease Characteristics (Safety Population – PFIC Cohort and Full Cohort)

Variable Statistic or Category	PFIC Cohort Maralixibat (n=33)	PFIC Cohort Placebo (n=31)	PFIC Cohort Overall (N=64)	Full Cohort Maralixibat (n=47)	Full Cohort Placebo (n=46)	Full Cohort Overall (N=93)
Analysis PFIC Type (genotype), no. (%) of participants						
PFIC2 (*ABCB11*) [a]	14 (42.4)	17 (54.8)	31 (48.4)	23 (48.9%)	22 (47.8%)	45 (48.4%)
nt-PFIC2	14 (42.4)	17 (54.8)	31 (48.4)	18 (38.3%)	18 (39.1%)	36 (38.7%)
t-PFIC2 (BSEP3)	NA	NA	NA	5 (10.6%)	4 (8.7%)	9 (9.7%)
PFIC1 (*ATP8B1*)	7 (21.2)	6 (19.4)	13 (20.3)	9 (19.1%)	8 (17.4%)	17 (18.3%)
PFIC3 (*ABCB4*)	4 (12.1)	5 (16.1)	9 (14.1)	4 (8.5%)	5 (10.9%)	9 (9.7%)
PFIC4 (*TJP2*)	6 (18.2)	1 (3.2)	7 (10.9)	6 (12.8%)	2 (4.3%)	8 (8.6%)
PFIC6 (*MYO5B*)	2 (6.1)	2 (6.5)	4 (6.3)	2 (4.3%)	2 (4.3%)	4 (4.3%)
Heterozygous variant[b]	NA	NA	NA	0	2 (4.3%)	2 (2.2%)
No-variant-found	NA	NA	NA	3 (6.4%)	5 (10.9%)	8 (8.6%)
Time since original diagnosis of PFIC, in months [c]						
Mean	34.3	27.5	31.0	31.7	32.7	32.2
SD (SE)	34.21 (5.95)	31.28 (5.62)	32.74 (4.09)	31.50 (4.59)	30.12 (4.44)	30.66 (3.18)
Median	28.0	12.0	22.0	28.0	29.0	28.0
Min, max	2, 136	1, 109	1, 136	1, 136	1, 110	1, 136
Baseline UDCA usage, no. (%) of participants						
Yes	27 (81.8)	30 (96.8)	57 (89.1)	39 (83.0%)	39 (84.8%)	78 (83.9%)
No	6 (18.2)	1 (3.2)	7 (10.9)	8 (17.0%)	7 (15.2%)	15 (16.1%)
Baseline rifampicin usage, no. (%) of participants						
Yes	18 (54.5)	15 (48.4)	33 (51.6)	26 (55.3%)	23 (50.0%)	49 (52.7%)
No	15 (45.5)	16 (51.6)	31 (48.4)	21 (44.7%)	23 (50.0%)	44 (47.3%)
Liver masses detected at baseline, no. (%) of participants						
Yes	1 (3.0)	0	1 (1.6)	1 (2.1%)	0	1 (1.1%)
No	32 (97.0)	31 (100.0)	63 (98.4)	46 (97.9%)	46 (100.0%)	92 (98.9%)
CSS Score						
Mean	2.8	2.6	2.7	2.7	2.7	2.7
SD (SE)	0.74 (0.13)	0.99 (0.18)	0.87 (0.11)	0.85 (0.12)	0.95 (0.14)	0.90 (0.09)
Median	3.0	3.0	3.0	3.0	3.0	3.0
Min, max	1, 4	1, 4	1, 4	0, 4	1, 4	0, 4
ItchRO(Obs) 4-wk morning avg severity score						
Mean	2.850	2.732	2.793	2.842	2.921	2.881
SD (SE)	0.8763 (0.1525)	0.8812 (0.1583)	0.8737 (0.1092)	0.8345 (0.1217)	0.8364 (0.1233)	0.8318 (0.0863)
Median	2.929	2.571	2.888	2.929	2.951	2.929
Min, max	1.00, 4.00	1.67, 4.00	1.00, 4.00	1.00, 4.00	1.67, 4.00	1.00, 4.00
ItchRO(Obs) 4-wk highest daily avg severity score						
Mean	3.010	2.881	2.947	2.995	3.051	3.023
SD (SE)	0.8218 (0.1431)	0.8329 (0.1496)	0.8232 (0.1029)	0.7761 (0.1132)	0.7889 (0.1163)	0.7787 (0.0807)
Median	3.071	2.857	3.036	3.036	3.057	3.042
Min, max	2.429, 3.679	2.036, 3.857	2.071, 3.798	1.00, 4.00	1.68, 4.00	1.00, 4.00
Total serum bile acid, in µmol/L						
Mean	254.327	272.297	263.312	262.615	243.306	252.854
SD (SE)	139.5156 (25.0577)	147.4035 (26.4745)	142.6205 (18.1128)	150.7223 (22.4684)	152.9405 (22.5498)	151.3137 (15.8620)
Median	246.033	262.093	250.456	254.879	226.464	234.161
Min, max	4.25, 503.53	2.10, 549.20	2.10, 549.20	4.25, 536.39	2.10, 549.20	2.10, 549.20
Alkaline phosphatase, in U/L						
Mean	630.1	517.7	575.7	594.9	512.9	554.3
SD (SE)	285.81 (49.75)	290.49 (52.17)	291.34 (36.42)	292.16 (42.62)	255.11 (37.61)	276.07 (28.63)
Median	517.0	470.5	489.8	498.0	471.0	487.0
Min, max	317, 1575	187, 1741	187, 1741	109, 1575	187, 1741	109, 1741
Aspartate aminotransferase, in U/L						
Mean	96.9	129.8	112.8	119.6	125.6	122.6
SD (SE)	54.98 (9.57)	100.90 (18.12)	81.60 (10.20)	100.46 (14.65)	95.91 (14.14)	97.75 (10.14)
Median	82.5	85.5	84.8	86.5	89.8	86.5
Min, max	46, 282	38, 462	38, 462	26, 524	25, 462	25, 524

Variable Statistic or Category	PFIC Cohort Maralixibat (n=33)	PFIC Cohort Placebo (n=31)	PFIC Cohort Overall (N=64)	Full Cohort Maralixibat (n=47)	Full Cohort Placebo (n=46)	Full Cohort Overall (N=93)
PELD [d]						
Mean	-1.3	-1.9	-1.6	-0.9	-2.3	-1.6
SD (SE)	7.01 (1.30)	7.63 (1.39)	7.28 (0.95)	7.75 (1.20)	7.05 (1.06)	7.39 (0.80)
Median	-1.5	-2.6	-1.8	-2.2	-3.5	-3.0
Min, max	-11, 12	-11, 18	-11, 18	-11, 21	-11, 18	-11, 21

APRI=AST-to-platelet ratio index; Avg=average; 7αC4=7α-hydroxy-4-cholesten-3-one; CSS=Clinician Scratch Scale; FGF-19= fibroblast growth factor-19; FIB-4=fibrosis 4; ItchRO(Obs)=Itch-Related Outcome (Observer); max=maximum; min=minimum; NA=not applicable; PELD=pediatric end-stage liver disease; PFIC=progressive familial intrahepatic cholestasis; SAP=Statistical Analysis Plan; SD=standard deviation; SE=standard error of the mean; UDCA=ursodeoxycholic acid.

Notes: Percentages are 100*n/N, unless otherwise noted.

Participants with PFIC1 through PFIC6 all have genetic test results consistent with biallelic disease.

[a] nt-PFIC2=partial loss of BSEP function; t-PFIC2=complete loss of BSEP function. Only applicable for PFIC2 participants, with exception of 1 nt-PFIC2 participant (015002) with heterozygosis *ABCB11* mutation; NA for all other participants.

[b] One participant (015002) had heterozygous ABCB11 mutation, and another (021006) had heterozygous ATP8B1 mutation.

[c] Partial dates were imputed based on the SAP.

[d] PELD score is calculated for children <12 years of age at the baseline visit; 11:16 and 29:30 participants, respectively, for the primary and PFIC cohorts (maralixibat:placebo).

Source: MRX-502 CSR Table 14.1.4, Appendix 2 Q16 Table 2.

Table 20 MRX-502 – Overview of Change from Baseline for Efficacy Endpoints (MMRM analyses, PFIC Cohort and Full Cohort)

Parameter	Analysis Visit Statistic	PFIC Cohort Maralixibat (n=33)	PFIC Cohort Placebo (n=31)	Full Cohort Maralixibat (n=47)	Full Cohort Placebo (n=46)
Total sBA (µmol/L) Weeks 18-26 [1] [2]	LS Mean (SE)	-157.489 (21.3609)	2.913 (22.6264)	-123.447 (22.1449)	4.715 (20.9051)
	(95% CI for LS Mean)	-200.276, -114.703	-42.320, 48.146	(-167.373, -79.521)	(-36.748, 46.178)
	p-value (CFB LS Mean = 0)	<0.0001	0.8980	<0.0001	0.8220
	LS Mean Change from Placebo (SE)	-160.403 (30.1827)		-128.162 (23.7026)	
	(95% CI for LS Mean Change from Placebo)	-220.836, -99.970		(-175.331, -80.992)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	<0.0001		<0.0001	
ItchRO(Obs) Morning Severity Score Weeks 15-26 [1] [3]	LS Mean (SE)	-1.811 (0.1834)	-0.610 (0.1947)	-1.469 (0.1936)	-0.275 (0.1812)
	(95% CI for LS Mean)	(-2.178, -1.444)	(-1.000, -0.221)	(-1.852, -1.085)	(-0.634, 0.085)
	p-value (CFB LS Mean = 0)	<0.0001	0.0026	<0.0001	0.1327
	LS Mean Change from Placebo (SE)	-1.200 (0.2630)		-1.194 (0.2223)	
	(95% CI for LS Mean Change from Placebo)	(-1.727, -0.674)		(-1.636, -0.752)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	<0.0001		<0.0001	
Clinician Scratch Score Weeks 18-26 [1] [2]	LS Mean (SE)	-1.827 (0.1835)	-0.698 (0.1966)	-1.591 (0.1935)	-0.296 (0.1824)
	(95% CI for LS Mean)	(-2.194, -1.460)	(-1.091, -0.305)	(-1.975, -1.208)	(-0.657, 0.066)
	p-value (CFB LS Mean = 0)	<0.0001	0.0007	<0.0001	0.1079
	LS Mean Change from Placebo (SE)	-1.129 (0.2623)		-1.296 (0.2163)	
	(95% CI for LS Mean Change from Placebo)	(-1.654, -0.604)		(-1.726, -0.865)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	<0.0001		<0.0001	
EDQ (Obs) Morning Average Sleep Disturbance Scores Weeks 15-26 [1] [3]	LS Mean (SE)	-1.741 (0.2027)	-0.550 (0.2191)	-1.345 (0.2099)	-0.224 (0.2072)
	(95% CI for LS Mean)	-2.149, -1.333	-0.990, -0.111	(-1.762, -0.928)	(-0.636, 0.188)
	p-value (CFB LS Mean = 0)	<0.0001	0.0151	<0.0001	0.2826
	LS Mean Change from Placebo (SE)	-1.190 (0.2951)		-1.121 (0.2599)	
	(95% CI for LS Mean Change from Placebo)	-1.783, -0.597		(-1.639, -0.603)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0002		<0.0001	
PedsQL Total Scale Score – Parent Weeks 18-26 [1] [2]	LS Mean (SE)	15.255 (3.2703)	11.306 (3.5029)	11.929 (3.7087)	5.198 (3.3391)
	(95% CI for LS Mean)	(8.698, 21.811)	(4.297, 18.315)	(4.566, 19.292)	(-1.431, 11.827)
	p-value (CFB LS Mean = 0)	<0.0001	0.0020	0.0018	0.1228
	LS Mean Change from Placebo (SE)	3.948 (4.7035)		6.731 (4.0810)	
	(95% CI for LS Mean Change from Placebo)	(-5.478, 13.374)		(-1.395, 14.856)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.4049		0.1031	
Multidimensional Fatigue Scale Score – Parent Weeks 18-26 [1] [2]	LS Mean (SE)	21.253 (2.6512)	11.277 (3.1807)	18.839 (3.7606)	1.774 (3.1994)
	(95% CI for LS Mean)	15.862, 26.644	4.824, 17.729	(11.309, 26.370)	(-4.630, 8.177)
	p-value (CFB LS Mean = 0)	<0.0001	0.0011	<0.0001	0.5815
	LS Mean Change from Placebo (SE)	9.976 (4.1156)		17.066 (4.0839)	
	(95% CI for LS Mean Change from Placebo)	1.614, 18.338		(8.855, 25.276)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0208		0.0001	

Height z-score Weeks 18-26 [1] [2]	LS Mean (SE)	0.078 (0.0851)	-0.131 (0.0909)	0.176 (0.0819)	-0.019 (0.0783)
	(95% CI for LS Mean)	-0.093, 0.248	-0.312, 0.051	(0.013, 0.338)	(-0.174, 0.136)
	p-value (CFB LS Mean = 0)	0.3652	0.1555	0.0340	0.8073
	LS Mean Change from Placebo (SE)	0.208 (0.1223)		0.195 (0.0959)	
	(95% CI for LS Mean Change from Placebo)	-0.036, 0.453		(0.004, 0.385)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0939		0.0454	
Weight z-score Weeks 18-26 [1] [2]	LS Mean (SE)	0.347 (0.0738)	0.120 (0.0779)	0.292 (0.0681)	0.027 (0.0660)
	(95% CI for LS Mean)	0.199, 0.494	-0.036, 0.275	(0.157, 0.427)	(-0.104, 0.158)
	p-value (CFB LS Mean = 0)	<0.0001	0.1301	<0.0001	0.6853
	LS Mean Change from Placebo (SE)	0.227 (0.1075)		0.265 (0.0868)	
	(95% CI for LS Mean Change from Placebo)	0.012, 0.442		(0.092, 0.437)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0391		0.0031	
Total Bilirubin (mg/dL) Weeks 18-26 [1] [2]	LS Mean (SE)	-1.073 (0.6813)	0.931 (0.7236)	-0.686 (0.6168)	0.714 (0.5840)
	(95% CI for LS Mean)	(-2.448, 0.303)	(-0.528, 2.389)	(-1.911, 0.539)	(-0.447, 1.875)
	p-value (CFB LS Mean = 0)	0.1231	0.2051	0.2689	0.2247
	LS Mean Change from Placebo (SE)	-2.003 (0.9786)		-1.400 (0.7283)	
	(95% CI for LS Mean Change from Placebo)	(-3.980, -0.027)		(-2.855, 0.055)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0471		0.0590	
Direct Bilirubin (mg/dL) Weeks 18-26 [1] [2]	LS Mean (SE)	-0.755 (0.5247)	0.787 (0.5566)	-0.634 (0.4569)	0.516 (0.4334)
	(95% CI for LS Mean)	-1.816, 0.306	-0.337, 1.911	(-1.543, 0.274)	(-0.346, 1.378)
	p-value (CFB LS Mean = 0)	0.1582	0.1651	0.1686	0.2371
	LS Mean Change from Placebo (SE)	-1.542 (0.7548)		-1.151 (0.5437)	
	(95% CI for LS Mean Change from Placebo)	-3.068, -0.015		(-2.238, -0.063)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0480		0.0385	
ALT (U/L) Week 26 [4]	Mean	5.9	-1.6	3.213	-0.829
	(95% CI for Mean)	(-16.4, 28.2)	(-18.0, 14.9)	(-16.155, 22.580)	(-12.930, 11.271)
	Median	-3.5	1.5	-2.250	1.000
	Q1, Q3	-19.8, 21.3	-23.3, 24.0	-19.750, 20.250	-21.000, 21.500
	Min, Max	0.5947	-144, 68	-136.50, 214.00	-143.50, 68.00
AST (U/L) Week 26 [4]	Mean	11.8	7.8	8.725	12.654
	(95% CI for Mean)	(-24.1, 47.8)	(-14.7, 30.2)	(-20.622, 38.072)	(-5.142, 30.451)
	Median	-9.0	0.5	-5.000	5.500
	Q1, Q3	-36.8, 10.3	-15.5, 32.3	-36.500, 11.500	-10.000, 30.000
	Min, Max	-82, 458	-122, 141	-111.00, 457.50	-122.00, 179.50
Fibrosis-4 Weeks 18-26 [1] [2] [5]	LS Mean (SE)	0.016 (0.0328)	0.101 (0.0358)	0.021 (0.0512)	0.108 (0.0545)
	(95% CI for LS Mean)	(-0.049, 0.082)	(0.030, 0.173)	(-0.084, 0.125)	(-0.003, 0.219)
	p-value (CFB LS Mean = 0)	0.6242	0.0062	0.6911	0.0562
	LS Mean Change from Placebo (SE)	-0.085 (0.0484)		-0.087 (0.0747)	
	(95% CI for LS Mean Change from Placebo)	(-0.182, 0.012)		(-0.240, 0.065)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0838		0.2504	

APRI Weeks 18-26 [1] [2] [5]	LS Mean (SE)	-0.039 (0.2189)	0.462 (0.2341)	0.245 (0.1704)	0.421 (0.1732)
	(95% CI for LS Mean)	(-0.485, 0.407)	(-0.015, 0.939)	(-0.098, 0.588)	(0.073, 0.769)
	p-value (CFB LS Mean = 0)	0.8605	0.0570	0.1580	0.0189
	LS Mean Change from Placebo (SE)	-0.501 (0.3211)		-0.176 (0.2348)	
	(95% CI for LS Mean Change from Placebo)	(-1.155, 0.153)		(-0.650, 0.297)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.1287		0.4565	
PELD Weeks 18-26 [1] [2]	LS Mean (SE)	-1.805 (1.0377)	1.981 (1.0760)	-2.088 (1.0293)	0.864 (0.9761)
	(95% CI for LS Mean)	(-3.887, 0.277)	(-0.173, 4.135)	(-4.130, -0.047)	(-1.070, 2.797)
	p-value (CFB LS Mean = 0)	0.0879	0.0708	0.0450	0.3781
	LS Mean Change from Placebo (SE)	-3.785 (1.4752)		-2.952 (1.1213)	
	(95% CI for LS Mean Change from Placebo)	(-6.743, -0.827)		(-5.185, -0.720)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0131		0.0102	
7 alpha-hydroxy-4-cholesten-3-one (C4) (ng/mL) Weeks 18-26 [1] [2]	LS Mean (SE)	46.216 (8.4796)	8.239 (9.0364)	36.084 (9.7308)	1.576 (8.7155)
	(95% CI for LS Mean)	29.227, 63.206	-9.843, 26.321	(16.741, 55.426)	(-15.738, 18.890)
	p-value (CFB LS Mean = 0)	<0.0001	0.3656	0.0004	0.8569
	LS Mean Change from Placebo (SE)	37.977 (12.0053)		34.508 (9.8120)	
	(95% CI for LS Mean Change from Placebo)	13.934, 62.020		(14.974, 54.041)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0025		0.0007	
FGF-19 (pg/mL) Weeks 18-26 [1] [2]	LS Mean (SE)	NE (NE)	NE (NE)	-511.057 (586.8566)	419.636 (519.1426)
	(95% CI for LS Mean)	(NE, NE)	(NE, NE)	(-1678.836, 656.722)	(-613.258, 1452.529)
	p-value (CFB LS Mean = 0)	NE	NE	0.3864	0.4213
	LS Mean Change from Placebo (SE)	NE (NE)		-930.692 (571.5965)	
	(95% CI for LS Mean Change from Placebo)	(NE, NE)		(-2070.593, 209.208)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	NE		0.1079	
Autotaxin (ng/mL) Weeks 18-26 [1] [2]	LS Mean (SE)	-947.273 (237.3048)	110.255 (249.3570)	-855.105 (287.4080)	-89.761 (259.8937)
	(95% CI for LS Mean)	-1424.452, -470.095	-390.674, 611.185	(-1426.476, -283.733)	(-605.718, 426.195)
	p-value (CFB LS Mean = 0)	0.0002	0.6603	0.0038	0.7306
	LS Mean Change from Placebo (SE)	-1057.528 (331.9651)		-765.343 (288.0026)	
	(95% CI for LS Mean Change from Placebo)	-1724.827, -390.230		(-1340.204, -190.482)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	0.0025		0.0098	

APRI=AST to platelet ratio index; CFB=change from baseline; EDQ(Obs)=exploratory diary questionnaire (observer); FGF-19=fibroblast growth factor 19; ItchRO(Obs)=Itch-Reported Outcome (Observer); LS=least squares; MMRM=mixed effect model for repeated measures; NE=not estimable; PELD= pediatric end-stage liver disease; PedsQL=Pediatric Quality of Life Inventory; PFIC=progressive familial intrahepatic cholestasis; Q1=25th percentile; Q3=75th percentile; sBA=serum bile acid; SE=standard error of the mean.

[1] Estimates are from a MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit and treatment-by-visit interaction as well as the continuous fixed covariates of baseline score and baseline score-by-visit interaction, and PFIC Type.

[2] Average of Weeks 18, 22, and 26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

[3] Average of time periods Weeks 15-18, 19-22, and 23-26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

[4] Median Changes from Baseline to Week 26. MMRM analysis was not applied due to non-normal distribution.

[5] Platelet count of MRX-502 study participant 037002 at Week 18 was incorrect due to an error in the reported unit of the local laboratory value (0.423 instead of 423). The correct value was hardcoded for this analysis.

Sources: MRX-502 CSR Table 14.2.2.1.1, Table 14.2.2.2.1, Table 14.2.4.7.1, Table 14.2.4.8.1, Table 14.2.4.13.1, Table 14.2.4.20.1, Table 14.2.4.24.1, Table 14.2.4.27.1, Table 14.2.4.28.1, Table 14.2.4.29.1, Table 14.2.4.31.1, Table 14.2.4.32.1, Table 14.2.4.33.1, Table 14.2.4.35.1. Appendix 2 Q1a Table 3.6.4 and Table 3.7.4. Appendix 2 Q16 Table 4.1, Table 4.2, Table 4.3, Table 4.4, Table 4.5, Table 4.6, Table 4.7, Table 4.8, Table 4.9, Table 4.10, Table 4.11, Table 4.12, Table 4.13, Table 4.14, Table 4.15, Table 4.16, Table 4.17, Table 4.18.

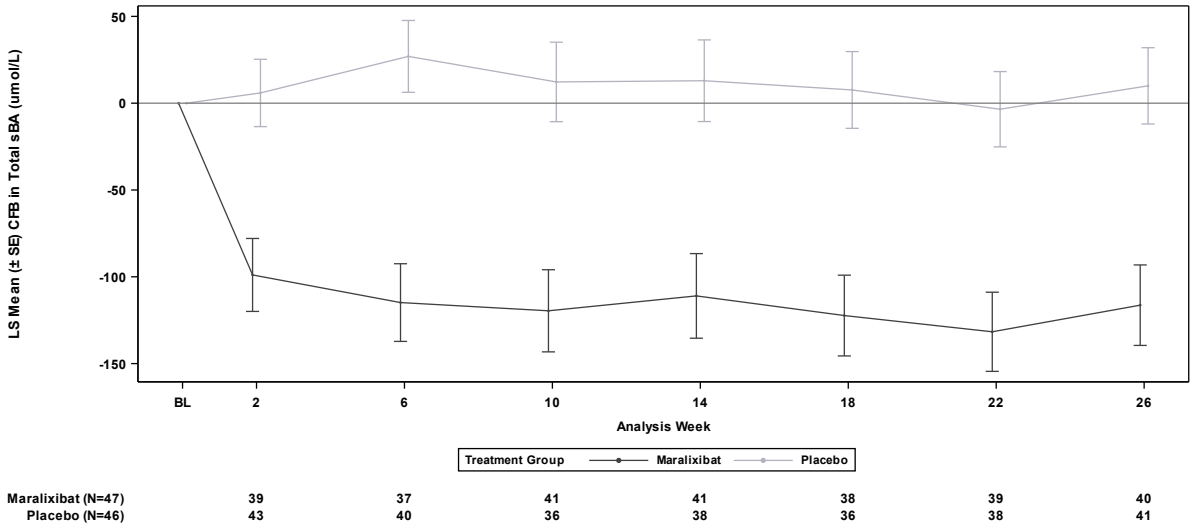


Figure 16 MRX-502 – MMRM LS Mean (±SE) Change from Baseline in sBA (µmol/L) Over Time (Full Cohort)

BL=baseline; CFB=change from baseline; LS=least squares; MMRM=mixed model for repeated measures; PFIC=progressive familial intrahepatic cholestasis; sBA=serum bile acid; SE=standard error.

Notes: Estimates are from a MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction, and PFIC type. Change from baseline at baseline visit is added for display purposes.
Sample sizes are the number of participants with non-missing change from baseline values, at the specified time point, used in the MMRM analysis.

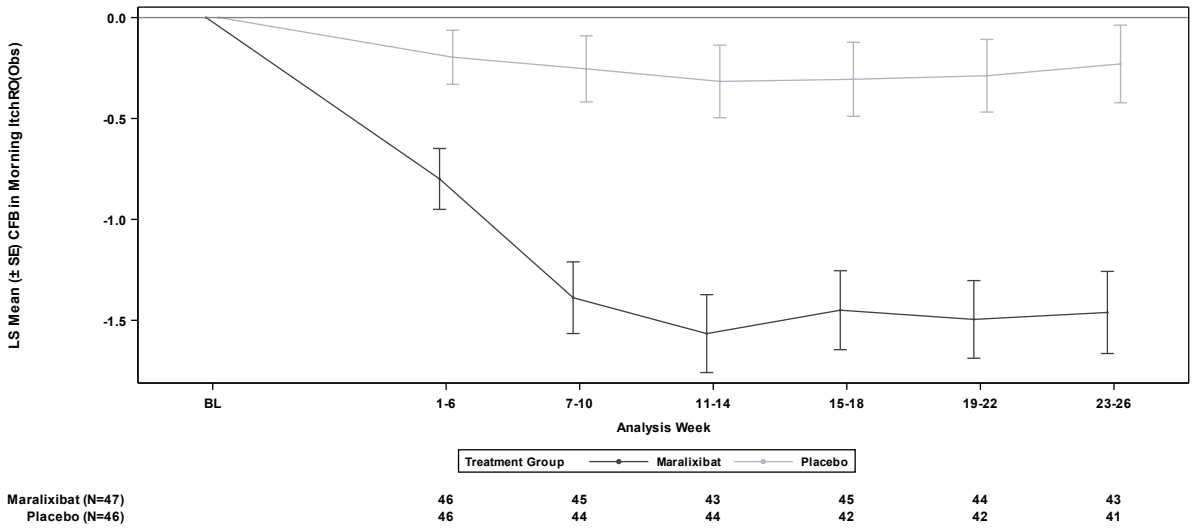


Figure 17 MRX-502 – MMRM LS Mean (±SE) Change from Baseline in Morning ItchRO(Obs) Severity Score Over Time (Full Cohort)

BL=baseline; CFB=change from baseline; ItchRO(Obs)=Itch-Reported Outcome (Observer); LS=least squares; MMRM=mixed model for repeated measures; PFIC=progressive familial intrahepatic cholestasis; SE=standard error.

Notes: Estimates are from a MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction, and PFIC type. Change from baseline at baseline visit is added for display purposes.

Sample sizes are the number of participants with non-missing change from baseline values, at the specified time point, used in the MMRM analysis.

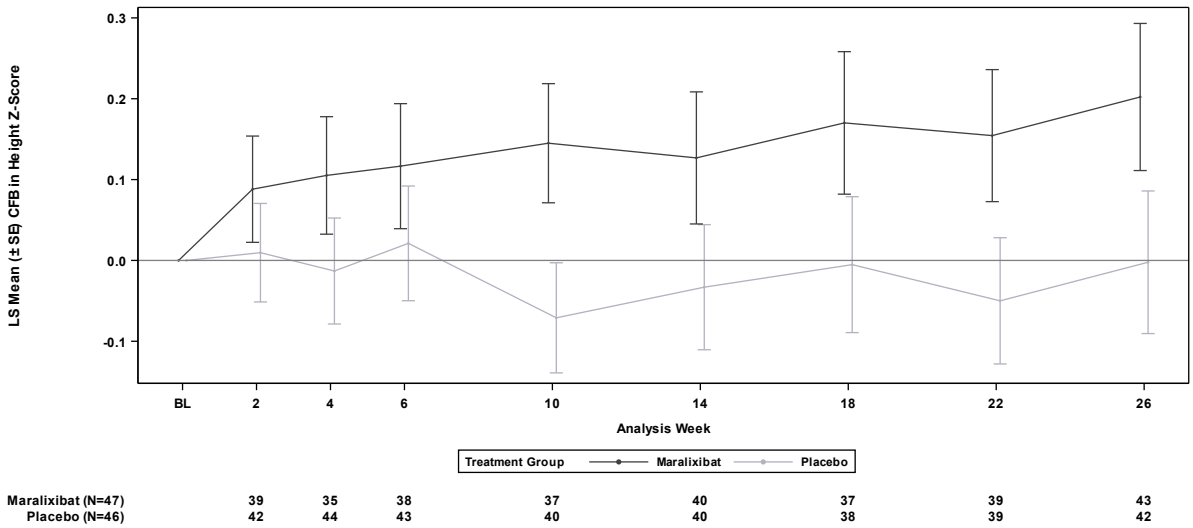


Figure 18 MRX-502 – MMRM LS Mean (±SE) Change from Baseline in Height Z-Score Over Time (Full Cohort)

BL=baseline; CFB=change from baseline; LS=least squares; MMRM=mixed model for repeated measures; PFIC=progressive familial intrahepatic cholestasis; SE=standard error.

Notes: Estimates are from a MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction, and PFIC type. Change from baseline at baseline visit is added for display purposes.
Sample sizes are the number of participants with non-missing change from baseline values, at the specified time point, used in the MMRM analysis.

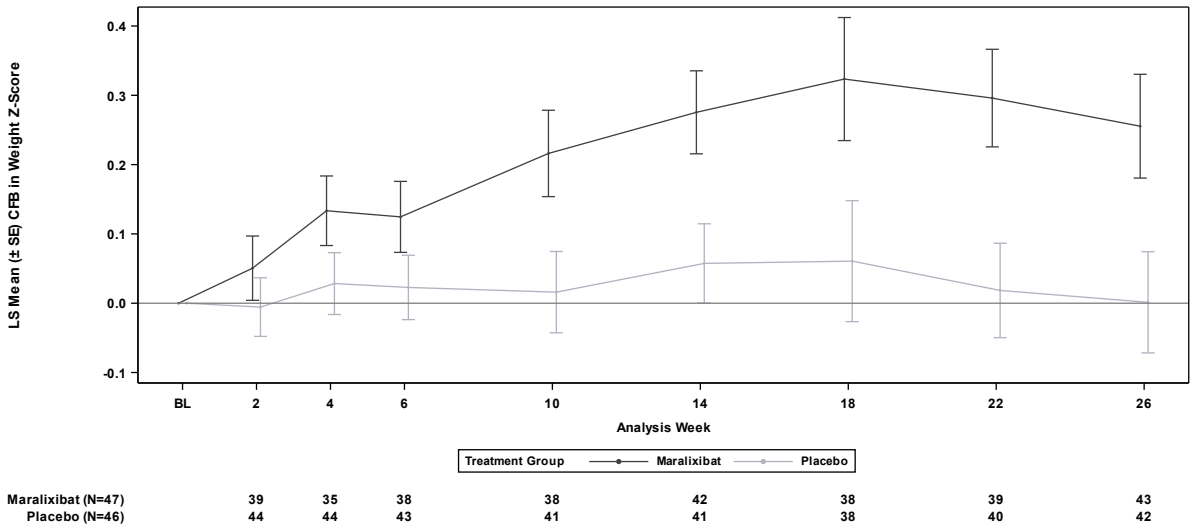


Figure 19 MRX-502 - MMRM LS Mean (±SE) Change from Baseline in Weight Z-Score Over Time (Full Cohort)

BL=baseline; CFB=change from baseline; LS=least squares; MMRM=mixed model for repeated measures; PFIC=progressive familial intrahepatic cholestasis; SE=standard error.

Notes: Estimates are from a MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction, and PFIC type. Change from baseline at baseline visit is added for display purposes.

Sample sizes are the number of participants with non-missing change from baseline values, at the specified time point, used in the MMRM analysis.

Table 21 MRX-502 – Proportion of ItchRO(Obs) and sBA Responders (PFIC Cohort and Full Cohort)

	PFIC Cohort		Full Cohort	
Responder Type Category	Maralixibat (n=33)	Placebo (n=31)	Maralixibat (n=47)	Placebo (n=46)
ItchRO Responders [1]				
Responder	21 (63.6%)	8 (25.8%)	27 (57.4%)	10 (21.7%)
Non-Responder	12 (36.4%)	23 (74.2%)	20 (42.6%)	36 (78.3%)
p-value vs. Placebo [3]	0.0023		0.0004	
sBA Responders [2]				
Responder	15 (45.5%)	2 (6.5%)	18 (38.3%)	3 (6.5%)
Non-Responder	18 (54.5%)	29 (93.5%)	29 (61.7%)	43 (93.5%)
p-value vs. Placebo [3]	0.0004		0.0002	

Number of Days Morning ItchRO(Obs) Severity Score ≤1 Over the Last 84 Study Days and Morning ItchRO(Obs) Severity Score ≤1 for >50% of Time Period showed roughly similar effects on MRX in PFIC and Full cohorts that were significantly better than the results on placebo.

Shift from baseline in the total and direct bilirubin levels averaged over the weeks 18, 22 and 26 also showed decrease in the % of patients with "high" levels of these parameters on MRX, whereas on placebo either the proportion of such patients increased or decreased to much lesser extent than on MRX. The observed effects were very similar in the PFIC and Full cohorts.

Ancillary analyses

See above.

Summary of main study(ies)

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

Table 22 Summary of Efficacy for trial MRX-502

Title: MRX-502: Randomized Double-Blind Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)–MARCH-PFIC			
Study identifier	MRX-502 EudraCT number: 2019-001211-22 INDs: 119916		
Design	Double-blind, randomised, placebo-controlled, parallel-group, Phase III, multicentre, 6-months study in the patients with PFIC of 1-17 years of age. Patients were titrated to the target dose of 600 µg/kg BID by the end of Week 6 after randomisation. Escalation was stopped, if tolerability/safety issues emerged. The selected dose was subsequently administered over further 20 weeks duration. After completion of 26-week treatment period, patients were rolled over to the extension study MRX-503, or were followed-up for 7 days.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 weeks titration and 20 weeks fixed dosing not applicable not applicable
Hypothesis	Superiority		
Treatments groups	MRX		MRX administered for 26 weeks. randomised: 33, completed:32.
	PBO		PBO administered for 26 weeks. Randomised: 32, Completed: 29
Endpoints and definitions	Primary endpoint	Morning ItchRO(Obs) (Primary cohort)	mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26, using 4-week average morning ItchRO(Obs) severity scores in the primary cohort.
	Key Secondary	sBA (Primary cohort)	Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the primary cohort
	Secondary	Morning ItchRO(Obs) (PFIC cohort)	Mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26, using 4-week average morning ItchRO(Obs) severity scores in the PFIC cohort
	Secondary	sBA (PFIC cohort)	Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the PFIC cohort
Database lock	Not specified in the study report		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat in the Primary cohort population (nt-PFIC2) Weeks 15-26		
Descriptive statistics and estimate variability	Treatment group	MRX	PBO
	Number of subject	14	17
	Morning average ItchRO(Obs) score - change LS mean	-1.718 (0.2708)	-0.628 (0.2479)

	95% CI *for LS mean* P value vs baseline LS mean (SE) change from placebo 95% CI for LS mean change from placebo p-value (maralixibat LS mean=placebo LS mean)	-2.272, -1.163 <0.0001 -1.089 (0.3691) -1.845, -0.334 0.0063	-1.136, -0.121 0.0171
Notes	<free text>		
Analysis description	**Secondary analysis in the Primary cohort and PFIC cohort**		

CFB in Total sBA Level, in µmol/L, to Average of Weeks 18, 22, and 26 (Primary Cohort-ITT Population)		
N	14	17
LS mean (SE)	-175.536 (39.4850)	11.187 (33.7413)
LS mean (SE) change from placebo	-186.723 (51.9501)	
95% CI for LS mean change from placebo	-293.454, -79.992	
p-value (maralixibat LS mean=placebo LS mean)	0.0013	
CFB in Average Morning ItchRO(Obs) Severity Score to Weeks 15–26 (PFIC Cohort-ITT Population)		
N	33	31
LS mean (SE)	-1.811 (0.1834)	-0.610 (0.1947)
LS mean (SE) change from placebo	-1.200 (0.2630)	
95% CI for LS mean change from placebo	-1.727, -0.674	
p-value (maralixibat LS mean=placebo LS mean)	<0.0001	
CFB in Total sBA Level, in µmol/L, to Average of Weeks 18, 22, and 26 (PFIC Cohort-ITT Population)		
N	33	31
LS mean (SE)	-157.489 (21.3609)	2.913 (22.6264)
LS mean (SE) change from placebo	-160.403 (30.1827)	
95% CI for LS mean change from placebo	-220.836, -99.970	
p-value (maralixibat LS mean=placebo LS mean)	<0.0001	
ItchRO(Obs) Responders (PFIC Cohort)		
N	33	31
Responder, No. (%)	21 (63.6)	8 (25.8)
Nonresponder, No. (%)	12 (36.4)	23 (74.2)
p-value vs. placebo c,d	0.0023	
sBA Responders (PFIC Cohort)		
N	33	31
Responder, No. (%)	15 (45.5)	2 (6.5)
Nonresponder, No. (%)	18 (54.5)	29 (93.5)
p-value vs. placebo	0.0004	

Supportive study(ies)

Extension to Study MRX-502 – Study MRX-503

This is an ongoing open-label extension (LTE) to the pivotal study MRX-502. Participants who completed the 6-month treatment in the MRX-502 study had the option to continue treatment in the open-label LTE Study MRX-503. All participants received maralixibat at the proposed commercial dose of 600 µg/kg BID.

The key objectives of the study were: 1) to assess the maintenance of effect and long-term safety and tolerability of MRX in participants beyond 6 months of treatment and 2) to substantiate the short term treatment effect and safety upon initiation of treatment with maralixibat in the participants who had received placebo in Study MRX-502. The study design of Study MRX-503 (the first 26 weeks) including dose escalation, study visit schedule, and schedule of assessments was designed to be comparable to Study MRX-502.

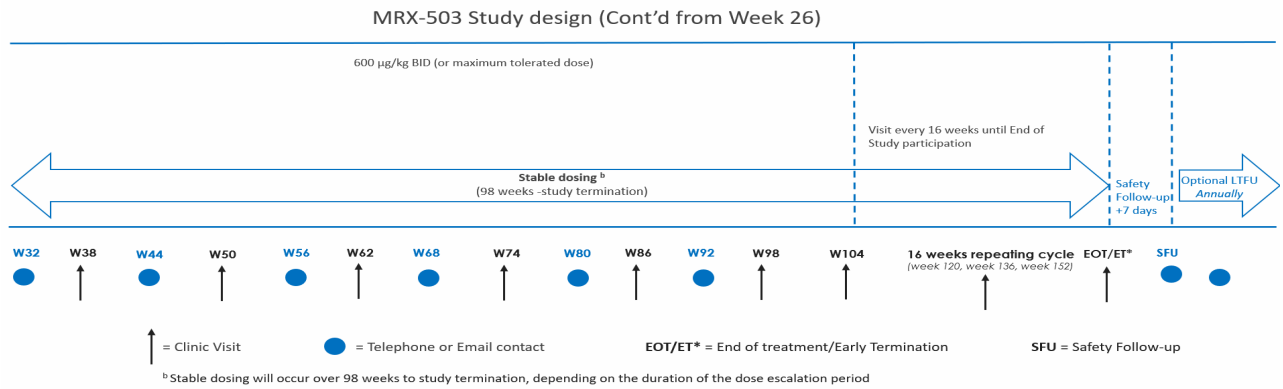


Figure 20 MRX-503 study design

The same efficacy parameters as those applied in the MRX-502 were utilised.

A planned interim analysis for Study MRX-503 with a data cut of 23 June 2022 was performed for the purpose of supporting this application. For the report, combined data from MRX-502 and MRX-503 were analyzed. Weeks presented in the efficacy results are relative to maralixibat baseline (defined as the time point when the first dose of maralixibat was received in Study MRX-502 or Study MRX-503).

Analyses were performed for the same cohorts as defined in Study MRX-502 and for the subgroups MRX MRX, PBO MRX, and All MRX.

Results:

At the end of Study MRX-502, 86 participants (92%) completed the study: 44 in the maralixibat group, 42 in the placebo group. At the data cutoff for Study MRX-503 (23 June 2022), 74 participants transitioned from Study MRX-502 to Study MRX-503: 36 from MRX and 38 from placebo treatment. Ten were still participating in the MRX-502 at the time of data cut-off.

The MRX-MRX analysis group comprises all 47 participants who had received maralixibat in Study MRX-502. The PBO-MRX analysis group comprises the 38 participants who had enrolled in Study MRX-503 as of the data cutoff date and who had received placebo in Study MRX-502.

The Overall analysis group (N=85) comprises all participants who enrolled in Study MRX-502 except participants who received placebo in Study MRX-502 and had not yet enrolled in Study MRX-503 (N=3)

or participants who received placebo in Study MRX-502 and discontinued early from Study MRX-502 (N=4) as of the cutoff date for the interim analysis.

Table 23 Patient disposition

Status or Category	No. (%) of Participants								
	Primary Cohort			PFIC Cohort			All Participants		
	MRX-MRX (n=14)	PBO-MRX (n=13)	All MRX (n=27)	MRX-MRX (n=33)	PBO-MRX (n=24)	All MRX (n=57)	MRX-MRX (n=47)	PBO-MRX (n=38)	All MRX (n=85)
Families with siblings enrolled	1		1	2	1	3	2	2	4
Total no. of siblings	2		2	4	2	6	4	4	8
Safety Population [a]	14	13	27	33	24	57	47	38	85
ITT Population [b]	14 (100.0)	13 (100.0)	27 (100.0)	33 (100.0)	24 (100.0)	57 (100.0)	47 (100.0)	38 (100.0)	85 (100.0)
Per-Protocol Population [c]	9 (64.3)	13 (100.0)	22 (81.5)	27 (81.8)	24 (100.0)	51 (89.5)	41 (87.2)	37 (97.4)	78 (91.8)
Completed study treatment				1 (3.0)[d]		1 (1.8)	1 (2.1)		1 (1.2)
Discontinued early [a]	2 (14.3)		2 (7.4)	5 (15.2)	3 (12.5)	8 (14.0)	10 (21.3)	3 (7.9)	13 (15.3)
Adverse event	1 (7.1)		1 (3.7)	3 (9.1)		3 (5.3)	4 (8.5)		4 (4.7)
Liver transplant					1 (4.2)	1 (1.8)	2 (4.3)	1 (2.6)	3 (3.5)
Withdrawal of consent[d]				1 (3.0)		1 (1.8)	1 (2.1)		1 (1.2)
Withdrawal by participant/guardian[e]	1 (7.1)		1 (3.7)	1 (3.0)	2 (8.3)	3 (5.3)	3 (6.4)	2 (5.3)	5 (5.9)

ITT=intent-to-treat; PFIC=progressive familial intrahepatic cholestasis.
Notes: Percentages were based on the number of participants in the Safety Population. Siblings (within the same family) were assigned in a blinded manner to the same treatment group. Data are presented in an integrated manner for Studies MRX-502 and MRX-503.

[a] The Safety Population includes all participants who received at least 1 dose of study drug.
[b] The ITT Population includes all randomized participants.
[c] The Per Protocol Population includes all participants in the ITT Population who received at least 1 dose of study drug and did not have any important protocol violations or deviations that had a potential impact on the efficacy analysis.
[d] Study MRX-502 only.
[e] Study MRX-503 only.

Sources: Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.3.

Demographic and baseline characteristics are similar to those of the patients in MRX-502 and the same patients are being recruited.

For all participants, the mean (SD) treatment compliance was 98.78% (2.873%). Most participants (97.6%) had an overall compliance rate of 90%–100%.

Baseline values collected at the baseline for study MRX-502 were utilised for MRX-MRX group and those before, or on day of the start of MRX in MRX-503 study for the PBO-MRX group.

The submitted interim report includes available results for changes in pruritus (ItchRO[Obs]); sBA level; growth (height and weight z-scores); time to first liver-associated event; total bilirubin and direct bilirubin; liver chemistry levels (ALT, AST, ALP, GGT, and albumin); CSS scores; biomarkers; healthcare utilization; caregiver burden; and pharmacokinetics.

Data presented have been collected in the patients with mean/median (range) treatment duration of around 1 year (mean and median: range: 10 to 837 days) on MRX including the exposure in the predecessor MRX-502 study.

Pruritus

The mean changes from maralixibat baseline over time in the average morning ItchRO(Obs) severity score in Study MRX-503 showed 1) maintenance of treatment effect in participants previously exposed to maralixibat in Study MRX-502 (MRX-MRX) and 2) statistically significant and clinically meaningful improvements in the pruritus score in participants previously exposed to placebo in Study MRX-502 (PBO-MRX) (Figure below).

Overall, there were clinically and statistically significant (mean decrease ≥1 point from baseline in the ItchRO[Obs] score) reductions (improvement) from maralixibat baseline over time in average morning

ItchRO(Obs) severity scores in the first 26 weeks on maralixibat in both the MRX-MRX and PBO-MRX groups in Study MRX-502 and Study MRX-503, respectively.

Changes from maralixibat baseline over time in both the MRX-MRX and PBO-MRX groups combined (All MRX group), demonstrated statistically significant improvements in average morning ItchRO(Obs) severity scores throughout the follow-up for up to 75–78 weeks until the number of participants with assessments at the time point is 9 (PFIC cohort).

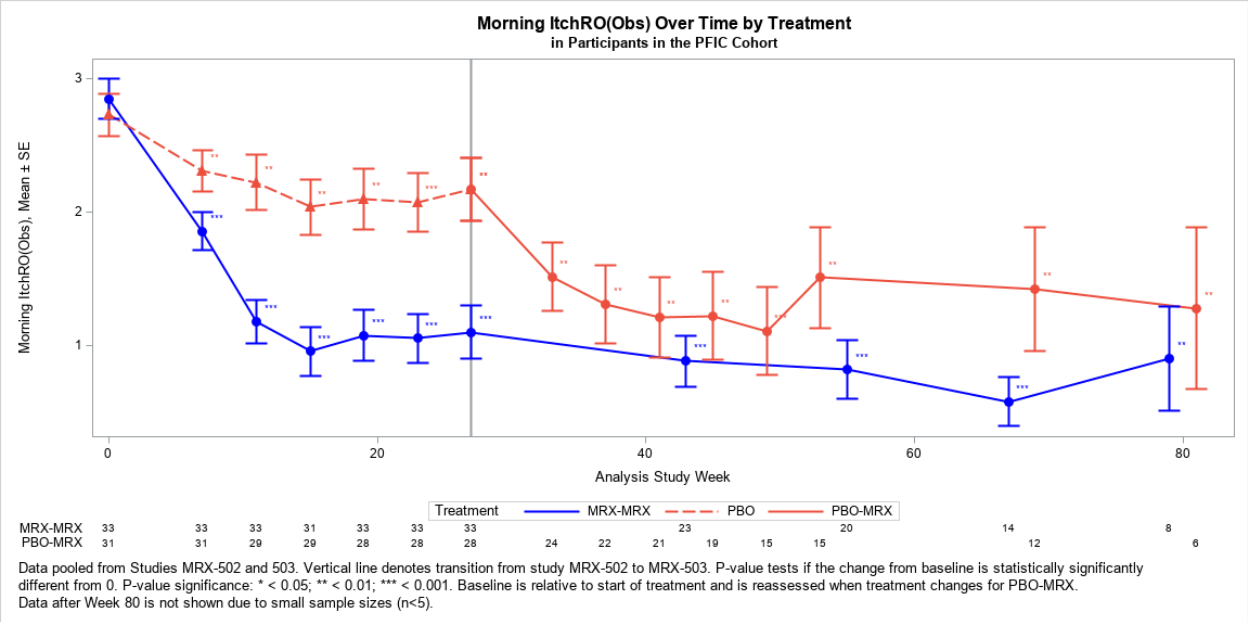


Figure 21 Mean Weekly Average Morning ItchRO(Obs) Severity Score over Time (ITT – PFIC Cohort)

iCSR=interim clinical study report; ITT=intent to treat; MRX-MRX=participants who were assigned maralixibat during Study MRX-502 and received maralixibat in Study MRX-503; PBO=participants who were assigned placebo during Study MRX-502; PBO-MRX=participants who were assigned placebo during Study MRX-502 and received maralixibat during Study MRX-503; PFIC=progressive familial intrahepatic cholestasis; SE=standard error of the mean.

Notes: Weeks along the x-axis are relative to the start of Study MRX-502.

Time points with data from <5 participants in the All MRX group are not shown (for these time points, data are summarized in the source table).

Source: Study MRX-503 iCSR Table 14.2.1.2.

Improvement in pruritus severity with maralixibat treatment was further demonstrated by statistically significant reduction (improvement) in the first 26 weeks on maralixibat in both MRX-MRX and PBO-MRX groups in Study MRX-502 and Study MRX-503, respectively, across different pruritus assessments, including ItchRO(Obs) evening and highest daily severity scores; ItchRO(Obs) morning, evening, and highest daily frequency scores;, and CSS scores.

Serum Bile Acid Endpoints

The mean change from maralixibat baseline over time in total sBA levels in Study MRX-503 showed 1) maintenance of treatment effect in participants previously exposed to maralixibat in Study MRX-502 (MRX-MRX) and 2) statistically significant decrease (improvement) in total sBA levels in participants previously exposed to placebo in Study MRX-502 (PBO-MRX).

Overall, there were statistically significant reductions (improvement) from maralixibat baseline over time in total sBA levels in the first 26 weeks on maralixibat in both MRX-MRX and PBO-MRX groups in Study MRX-502 and Study MRX-503, respectively.

Changes from maralixibat baseline over time in both MRX-MRX and PBO-MRX groups combined (All MRX group) demonstrate significant improvements in total sBA levels throughout the follow-up, up to 94 weeks in the PFIC cohort, after which the number of participants with assessments at the time point was 4 (PFIC cohort).

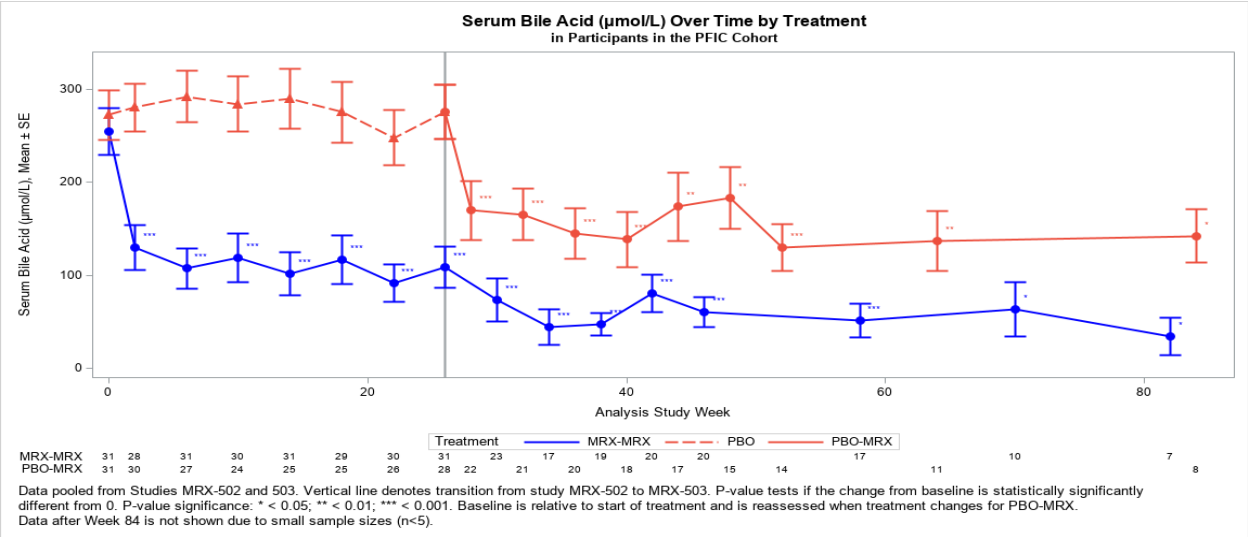


Figure 22 Mean Serum Bile Acid over Time (ITT – PFIC Cohort)

iCSR=interim clinical study report; ITT=intent to treat; MRX-MRX=participants who were assigned maralixibat during Study MRX-502 and received maralixibat in Study MRX-503; PBO=participants who were assigned placebo during Study MRX-502; PBO-MRX=participants who were assigned placebo during Study MRX-502 and received maralixibat during Study MRX-503; PFIC=progressive familial intrahepatic cholestasis; SE=standard error of the mean.

Notes: Weeks along the x-axis are relative to the start of Study MRX-502.

Time points with data from <5 participants in the All MRX group are not shown (for these time points, data are summarized in the source table).

Source: Study MRX-503 iCSR Table 14.2.2.2.

Bilirubin

The mean change from maralixibat baseline over time in total and direct bilirubin in Study MRX-503 showed 1) maintenance of reductions (improvement) in total and direct bilirubin levels in participants previously exposed to maralixibat in Study MRX-502 (MRX-MRX) and 2) reductions (improvement) in total and direct bilirubin in participants previously exposed to placebo in Study MRX-502 (PBO-MRX) (PFIC cohort).

The mean changes from maralixibat baseline in total and direct bilirubin in the All MRX group ranged from -0.692 to -4.275 mg/dL and -0.553 to -3.238, respectively, and were statistically significant at various time points up to Week 70 (PFIC cohort). After this time point, the sample size was <12 participants due to data cutoff for the interim analysis.

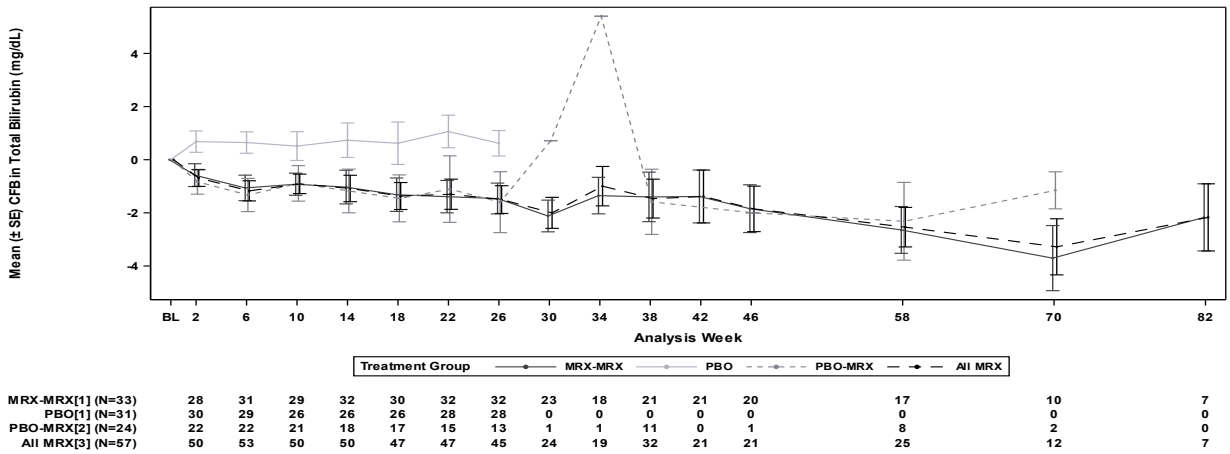


Figure 23 Mean Change from Maralixibat Baseline in Total Bilirubin (ITT – PFIC Cohort)

CFB=change from baseline; iCSR=interim clinical study report; ITT=intent to treat; MRX-MRX=participants who were assigned maralixibat during Study MRX-502 and received maralixibat in Study MRX-503; PBO=participants who were assigned placebo during Study MRX-502; PBO-MRX=participants who were assigned placebo during Study MRX-502 and received maralixibat during Study MRX-503; SE=standard error of the mean.

[1] Change from Study MRX-502 baseline.

[2] Change from Study MRX-503 baseline.

[3] Combines MRX-MRX and PBO-MRX treatment groups. Baseline for MRX-MRX is from Study MRX-502 and for PBO-MRX from Study MRX-503.

Note: Time points with data from <5 participants in the All MRX group are not shown (for these time points, data are summarized in the source table).

Sources: Study MRX-503 iCSR Figure 14.2.3.1.2, Table 14.2.3.3.2.

Similar effects were seen for direct bilirubin.

Liver Chemistry and Liver Markers Endpoints

No trends for clinically meaningful changes from baseline in ALT, AST, ALP, GGT, and albumin levels were observed, and no statistically significant differences were observed between groups.

Growth

Slight increases (improvement) in height and weight z-scores over time in the MRX-MRX and PBO-MRX groups were observed.

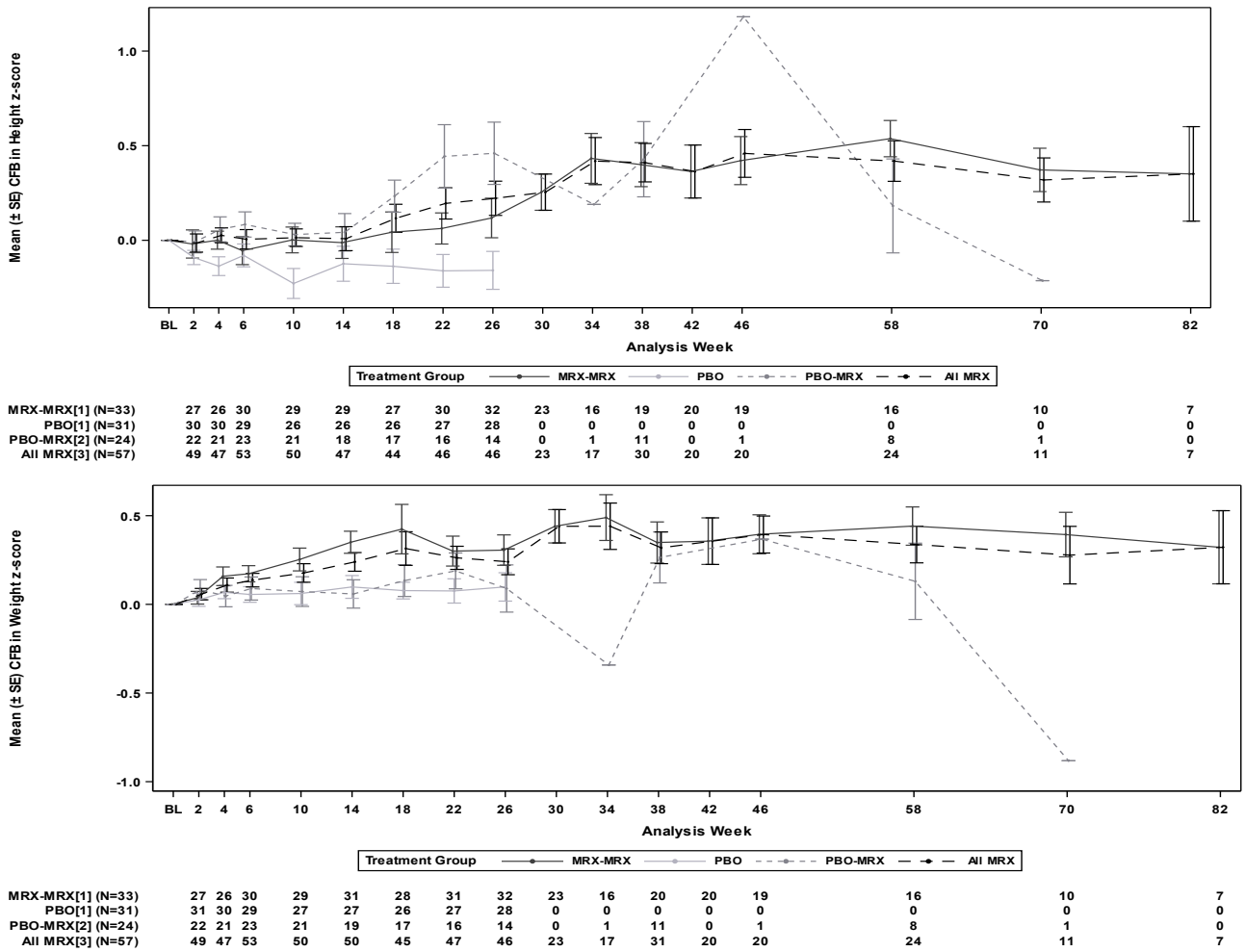


Figure 24 Mean Change from Maralixibat Baseline in Height (upper figure) and Weight (lower figure) z-Scores (ITT – PFIC Cohort)

CFB=change from baseline; iCSR=interim clinical study report; ITT=intent to treat; MRX-MRX=participants who were assigned maralixibat during Study MRX-502 and received maralixibat in Study MRX-503; PBO=participants who were assigned placebo during Study MRX-502; PBO-MRX=participants who were assigned placebo during Study MRX-502 and received maralixibat during Study MRX-503; PFIC=progressive familial intrahepatic cholestasis; SE=standard error of the mean. Sources: Study MRX-503 iCSR

Biomarkers of Bile Acid Synthesis

7αC4 levels increased from maralixibat baseline and were maintained throughout the follow-up (up to 106 weeks) in all analysis groups (MRX-MRX, PBO-MRX, and All MRX).

FGF-19 levels tended to decrease (mean values. Less change observed for median) from maralixibat baseline in all analysis groups (MRX-MRX, PBO-MRX, and All MRX).

Autotaxin

The effect of maralixibat treatment on autotaxin levels, as a potential mediator of pruritus through the production of LPA, was assessed.

Decreases from maralixibat baseline in autotaxin concentrations were observed throughout the follow-up (up to 82 weeks) in all analysis groups (MRX-MRX, PBO-MRX, and All MRX).

Similar effects were seen in the primary and PFIC cohorts for changes in pruritus, growth, sBA, bilirubin, bile synthesis biomarkers, and autotaxin.

Updated interim analysis of MRX-503 (data cut-off 10 June 2023) and cross-study comparisons

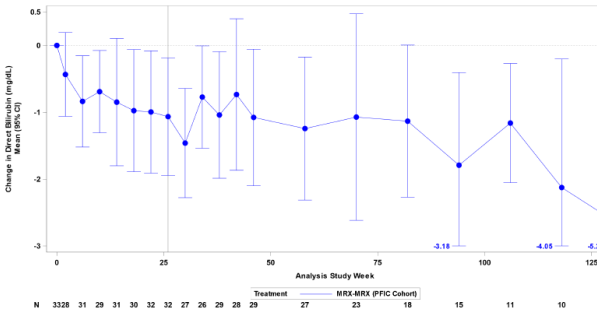
The Applicant has submitted more recent interim analysis of the ongoing Study MRX 503 (data extract date: 10 June 2023), providing additional long-term data of patients treated long term with maralixibat.

Efficacy of MRX - liver parameters

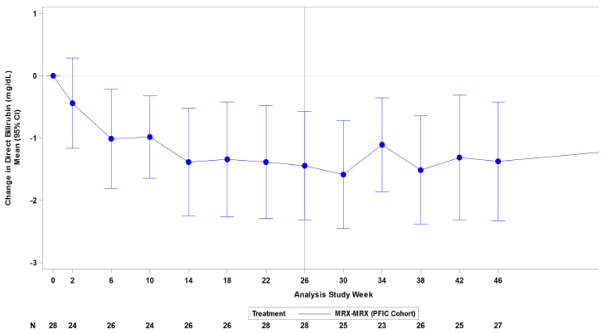
sBA and total bilirubin

Data show statistically significant decrease in mean values of bilirubin (total and direct) compared to baseline and to placebo on MRX. Newly conducted analyses contain a sensitivity analysis in the patients (n=28) who remained in the LTE study to MRX-502 (i.e., MRX-503) up-to 2 years and had data-set up-to 58 weeks on MRX. These data confirmed similar level of maintenance of effects on bilirubin (total and direct) over prolonged treatment period as the pre-planned analyses.

Figure 25 MRX-502 and MRX-503 - Mean (95% CI) Change in Direct Bilirubin (mg/dL) Over Time up to Week 58 (MRX-MRX, PFIC Cohort, all Participants [left-side figure] and Participants with Complete Follow-Up to Week 58 [right-side figure])



MRX-MRX=participants treated with maralixibat in MRX-503 who previously received maralixibat in MRX-5
N=number of participants with applicable data at specified analysis visit; PFIC=progressive familial intrahe
cholestasis.
Notes: Data extract date: 10-Jun-2023.
Data pooled from Studies MRX-502 and MRX-503.
Vertical line denotes transition from Study MRX-502 to MRX-503. Dashed horizontal line denotes no chang
Week 118 is used as a cutoff because the sample size drops below 5 after this point.
Upper confidence limits capped at 0.5 for readability, with actual values noted.
Lower confidence limits capped at -3.0 for readability, with actual values noted.



MRX-MRX=participants treated with maralixibat in MRX-503 who previously received maralixibat in MRX-5
N=number of participants with applicable data at specified analysis visit; PFIC=progressive familial intrahe
cholestasis.
Notes: Data extract date: 10-Jun-2023.
Data pooled from studies MRX-502 and MRX-503.
Vertical line denotes transition from study MRX-502 to MRX-503. Dashed horizontal line denotes no chang

Table 24 Overview of Treatment Effects on Total and Direct Bilirubin (SAP Predefined Analyses)

		MRX-502 Change from Baseline to Week 18-26 (MMRM) [a] (PFIC Cohort)			**MRX-503** Change from Baseline to Week 26 [b] (PFIC Cohort)	**MRX-801** Change from Baseline to Week 13 (PFIC Cohort)
	Statistic	Maralixibat (N=33)	Placebo (N=31)	Statistic	PBO-MRX [c] (N=27)	Maralixibat (N=10)
Total Bilirubin (mg/dL)				n	24	9
	LS mean (SE)	-1.073 (0.6813)	0.931 (0.7236)	Mean	-0.773	-1.171
	95% CI for LS mean	-2.448, 0.303	-0.528, 2.389	(95% CI for Mean)	(-2.319, 0.773)	(-2.006, -0.336)
	p-value (CFB LS mean=0)	0.1231	0.2051	p-value [d]	0.3116	0.0120
	LS mean (SE) change from placebo	-2.003 (0.9786)				
	95% CI for LS mean change from placebo	-3.980, -0.027				
	p-value (maralixibat LS mean=placebo LS mean)	0.0471				
Direct Bilirubin (mg/dL)				n	24	7
	LS mean (SE)	-0.755 (0.5247)	0.787 (0.5566)	Mean	-0.698	-1.064
	95% CI for LS mean	-1.816, 0.306	-0.337, 1.911	(95% CI for Mean)	(-1.814, 0.418)	(-1.883, -0.245)
	p-value (CFB LS mean=0)	0.1582	0.1651	p-value [d]	0.2084	0.0191
	LS mean (SE) change from placebo	-1.542 (0.7548)				
	95% CI for LS mean change from placebo	-3.068, -0.015				
	p-value (maralixibat LS mean=placebo LS mean)	0.0480				

CI=confidence interval; LS=least-squares; MMRM=mixed model for repeated measures; PBO-MRX=participants treated with maralixibat in MRX-503 who previously received placebo in MRX-502; PFIC=progressive familial intrahepatic cholestasis; SE=standard error of the mean.

[a] Estimates are from an MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit, and treatment-by-visit interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-visit interaction. PFIC type is included in the model as an additional covariate. Average of Weeks 18, 22, and 26 are obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

[b] Baseline for PBO-MRX is from MRX-503.

[c] Participants from Study MRX-503 treated with maralixibat, that previously had received placebo in MRX-502.

[d] Student's t-test used to test if mean change from baseline is statistically significant.

Sources: MRX-502 CSR Table 14.2.4.7.1, Table 14.2.4.8.1; Appendix 1 Q1a Table 5.3.2 and Table 5.4.2, Appendix 1 Q1b Table 6.4 and Table 6.5.

Correlation analysis conducted for the PFIC cohort showed positive correlation between percent reduction in sBA and percent reduction in total bilirubin (Spearman r 0.620, p=0.0003) and direct bilirubin (Spearman r 0.686, p<0.0001) in maralixibat-treated participants. In contrast, no correlation was observed in participants treated with placebo. A comparable positive correlation between sBA and bilirubin responses was also observed in maralixibat-treated participants in Study MRX-503 who previously received placebo.

Table 25 MRX-502 and MRX-503 - Spearman Correlation Analysis of sBA against Liver Parameters - Average Percent Change at Weeks 18, 22, and 26 (New Post Hoc Analysis)

	Spearman Correlation Coefficient (p-Value)							
	Maralixibat				Placebo			
Study Population Parameter	ALT	AST	Total Bilirubin	Direct Bilirubin	ALT	AST	Total Bilirubin	Direct Bilirubin
MRX-502 Primary Cohort								
sBA	0.891 (0.0002)	0.873 (0.0005)	0.518 (0.1025)	0.582 (0.0604)	-0.032 (0.9095)	0.268 (0.3344)	0.186 (0.5075)	0.161 (0.5672)
PFIC Cohort								
sBA	0.339 (0.0666)	0.515 (0.0036)	0.620 (0.0003)	0.686 (<0.0001)	0.094 (0.6337)	0.250 (0.1992)	0.129 (0.5124)	0.109 (0.5820)
	PBO-MRX							
	ALT	AST	Total Bilirubin	Direct Bilirubin				
MRX-503 Primary Cohort								
sBA	0.908 (<0.0001)	0.829 (0.0003)	0.560 (0.0371)	0.741 (0.0024)				
PFIC Cohort								
sBA	0.578 (0.0020)	0.696 (<0.0001)	0.355 (0.0750)	0.456 (0.0191)				

MRX=maralixibat; PBO-MRX=participants treated with maralixibat in MRX-503 who previously received placebo in MRX-502; sBA=serum bile acid.
Sources: Appendix 1 Q1a Table 4.1, Table 4.3.

Transaminases

As per the statistical analysis plan (SAP)–defined mixed model for repeated measures (MMRM) based analysis, no statistically significant changes from baseline in ALT or AST in the maralixibat or placebo treatment group were found. In the dataset, ALT and AST baseline levels and the change from baseline values in the maralixibat treatment group were not normally distributed and the MMRM LS mean change from baseline was largely affected by outlier values. To account for the non-normal distribution, median changes from baseline at Week 26 were assessed and showed small increases in ALT and AST for the placebo group in Study MRX-502 (see the table below with new Post hoc analysis). In contrast, small decreases (not statistically significant) were observed in the maralixibat treated groups in Study MRX-502 and in study MRX-503 (participants switched from placebo). Improvement in transaminases tended to increase over time with continued treatment with maralixibat (Figures).

Table 26 Overview of Treatment Effects on ALT and AST (SAP predefined analyses; LS mean)

	Statistic	MRX-502 Change from Baseline to Week 18-26 (MMRM) [a] (Primary Cohort) Maralixibat (N=14)	Placebo (N=17)	MRX-502 Change from Baseline to Week 18-26 (MMRM) [a] (PFIC Cohort) Maralixibat (N=33)	Placebo (N=31)	Statistic	MRX-503 Change from Baseline to Week 26 [b] (Primary Cohort) PBO-MRX [c] (N=14)	(PFIC Cohort) PBO-MRX [c] (N=27)	MRX-801 Change from Baseline to Week 13 (PFIC Cohort) Maralixibat (N=10)
ALT (U/L)						n	14	24	9
	LS mean (SE)	3.913 (19.6890)	-8.067 (18.1493)	9.670 (10.3639)	-6.977 (11.1283)	Mean	-24.75	-7.00	-15.2
	95% CI for LS mean	(-36.760, 44.586)	(-45.575, 29.441)	(-11.058, 30.398)	(-29.212, 15.259)	95% CI for Mean	(-69.10, 19.60)	(-34.50, 20.50)	(-47.8, 17.4)
	p-value (CFB LS mean=0)	0.8442	0.6608	0.3545	0.5329	p-value [d]	0.2495	0.6035	0.3127
	LS mean (SE) change from placebo	11.980 (27.1064)		16.647 (14.9716)		Median	-22.00	-9.25	-19.0
	95% CI for LS mean change from placebo	(-44.055, 68.015)		(-13.309, 46.603)		Q1, Q3	-75.50, 4.00	-32.50, 19.25	-34.0, 0.0
	p-value (maralixibat LS mean=placebo LS mean)	0.6626		0.2707		Min, max	-156.0, 142.0	-156.0, 142.0	-73, 79
AST (U/L)						n	14	24	8
	LS mean (SE)	42.510 (25.2941)	14.420 (23.2001)	13.621 (14.0490)	-0.439 (14.9083)	Mean	-36.46	-17.40	-27.6
	95% CI for LS mean	(-8.479, 93.500)	(-32.364, 61.205)	(-14.482, 41.725)	(-30.234, 29.357)	95% CI for Mean	(-103.64, 30.71)	(-55.98, 21.19)	(-53.5, -1.8)
	p-value (CFB LS mean=0)	0.1000	0.5375	0.3362	0.9766	p-value [d]	0.2619	0.3607	0.0393
	LS mean (SE) change from placebo	28.090 (34.5201)		14.060 (20.3049)		Median	-18.50	-6.00	-9.5
	95% CI for LS mean change from placebo	(-41.533, 97.713)		(-26.572, 54.693)		Q1, Q3	-54.50, 10.50	-34.75, 10.75	-58.5, -5.0
	p-value (maralixibat LS mean=placebo LS mean)	0.4203		0.4914		Min, max	-283.5, 186.5	-283.5, 186.5	-74, -1

CI=confidence interval; LS=least-squares; max=maximum; min=minimum; MMRM=mixed model for repeated measures; PFIC=progressive familial intrahepatic cholestasis; SAP=statistical analysis plan; SE=standard error of the mean.

[a] Estimates are from an MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit, and treatment-by-visit interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-visit interaction. PFIC type is included in the model as an additional covariate. Average of Weeks 18, 22, and 26 are obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

[b] Baseline for PBO-MRX is from MRX-503.

[c] Participants from Study MRX-503 treated with maralixibat, that previously had received placebo in MRX-502.

[d] Student's t-test used to test if mean change from baseline is statistically significant.

Sources: MRX-502 CSR Table 14.2.4.5.1, Table 14.2.4.6.1; Appendix 1 Q1a Table 5.1.1, Table 5.2.1, Table 5.1.2, Table 5.2.2; Q1b Table 6.4 and Table 6.5.

Table 27 MRX-502 and MRX-503 – Median Changes from Baseline in ALT and AST at Week 26 (New Post Hoc Analysis)

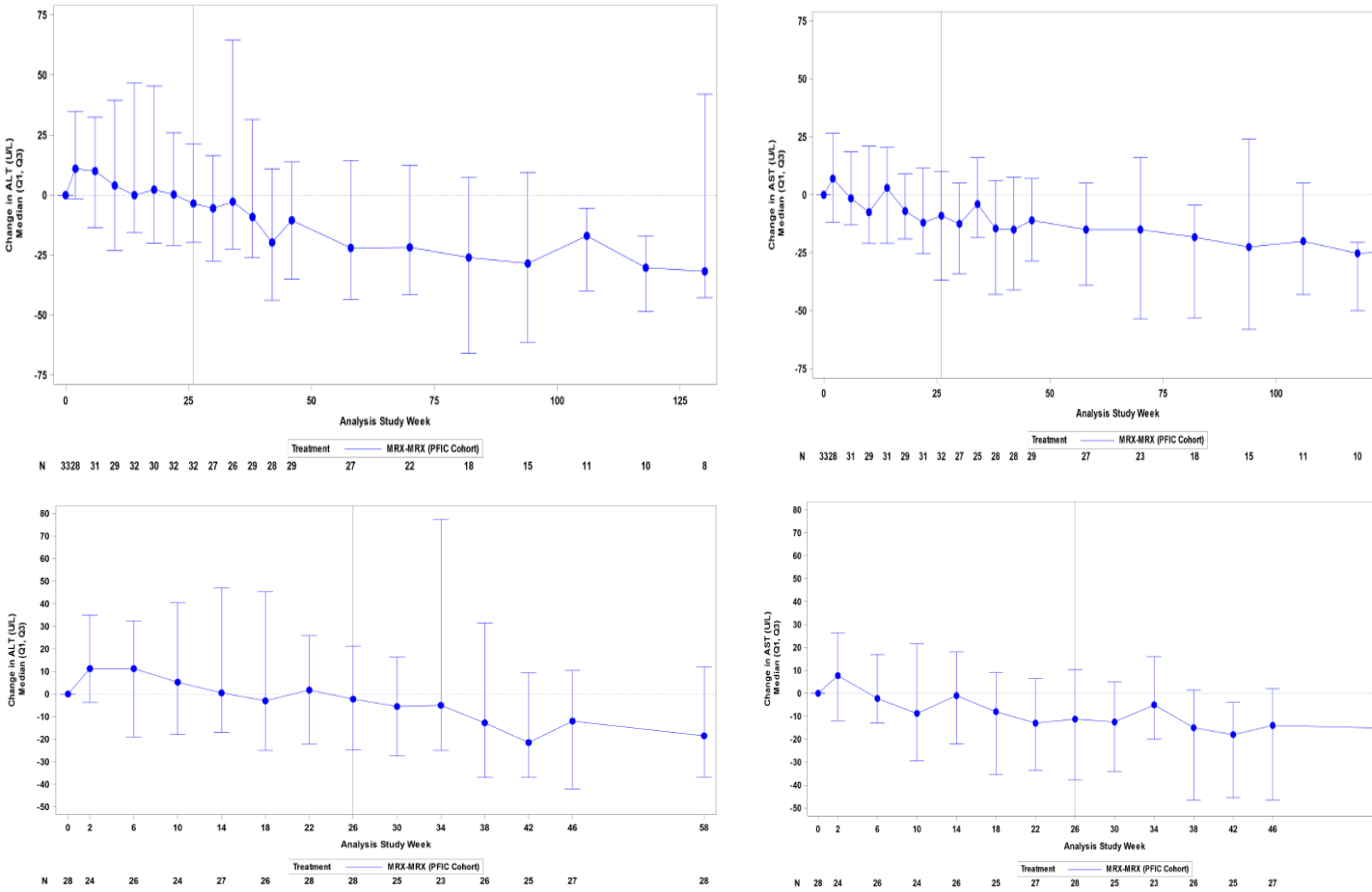
	Statistic	Primary Cohort Maralixibat (n=33)	Placebo (n=31)	PFIC Cohort Maralixibat (n=33)	Maralixibat (n=33)	Placebo (n=31)
ALT (U/L)		Week 26	Week 26	Week 26	Week 58	Week 26
	n	12	15	31	28	28
	Mean	4.583	8.800	6.548	-15.143	-1.554
	(95% CI for Mean)	(-44.468, 53.635)	(-8.661, 26.261)	(-16.457, 29.554)	(-35.884, 5.599)	(-18.009, 14.901)
	Median	**-19.000**	**4.000**	**-3.000**	**-18.500**	**1.500**
	Q1, Q3	-43.750, 35.500	-12.000, 34.000	-21.500, 24.000	-36.750, 12.000	-23.250, 24.000
	Min, max	-66.00, 214.00	-34.00, 68.00	-102.00, 214.00	-170.00, 130.00	-143.50, 68.00
AST (U/L)		Week 26	Week 26	Week 26	Week 58	Week 26
	n	12	15	31	28	28
	Mean	34.417	19.056	12.742	-7.732	7.762
	(95% CI for Mean)	(-65.678, 134.512)	(-17.347, 55.458)	(-24.432, 49.915)	(-30.330, 14.866)	(-14.699, 30.223)
	Median	**-18.0000**	**4.500**	**-8.000**	**-15.250**	**0.500**
	Q1, Q3	-47.250, 21.000	-15.500, 35.500	-37.500, 11.500	-38.000, 1.000	-15.500, 32.250
	Min, max	-81.50, 457.50	-114.00, 140.50	-81.50, 457.50	-86.50, 157.00	-122.00, 140.50

CFB=change from baseline; CI=confidence interval; max=maximum; min=minimum; Obs=observed values; SD=standard deviation; SE=standard error of the mean; Q1=25th percentile; Q3=75th percentile.

Sources: Appendix 1 Q1a Table 1.1.1, Table 1.2.1, Table 1.1.4, Table 1.2.4; Q23 Table 5.5 and Table 5.6.

Sensitivity analyses for the change from baseline in participants treated with maralixibat for ≥2 years with continuous follow-up to Week 58 (MRX MRX PFIC Cohort, n=28) confirmed that improvements in ALT and AST are observed following long term treatment with maralixibat.

Figure 26 MRX-502 and MRX-503 - Median (Q1, Q3) Change in ALT (U/L)(Left) and AST (U/L) (Right) Over Time in PFIC cohort (figures on top) and in the subgroup of patients treated at least for 2 years and with follow-up up-to 58 weeks (figures at the bottom).



MRX-MRX=participants treated with maralixibat in MRX-503 who previously received maralixibat in MRX-502; N=number of particip with applicable data at specified analysis visit; PFIC=progressive familial intrahepatic cholestasis; Q1=Quartile 1; Q3=Quartile 3.

Notes: Data extract date: 10-Jun-2023.

Data pooled from Studies MRX-502 and MRX-503.

Vertical line denotes transition from study MRX-502 to MRX-503. Dashed horizontal line denotes no change.

Week 118 is used as a cutoff since the sample size drops below 5 after this point

Transaminase normalization rates in ALT and AST by Week 26 were evaluated in those participants with abnormal values at baseline. In Study MRX-502, in the PFIC cohort, maralixibat-treated participants with elevated transaminase levels at baseline had normalized ALT (≤30 U/L) and AST (55 U/L) in 22.6% (7/31) and 25.9% (7/27) of participants, respectively. In contrast, in the placebo group, 7.1% (2/28) and 4.2% (1/24) showed normalization of ALT and AST, respectively. Higher normalization rates with maralixibat treatment were also observed for the primary cohort. In participants of the primary cohort, 53.8% (7/13) and 44.4% (4/9) on MRX and 6.7% (1/15) and 7.7% (1/13) of participants on placebo showed normalization of ALT and AST, respectively.

In Study MRX-502, in maralixibat-treated participants in the primary cohort, there was a positive correlation between percent reduction in sBA and percent reduction in ALT (Spearman r 0.891, p=0.0002) and AST (Spearman r 0.873, p=0.0005). In the PFIC cohort, there was a trend indicating a similar correlation, albeit less strong. In contrast, no correlation was observed in participants treated with placebo in both groups. Importantly, a comparable positive correlation between sBA and

transaminase responses was also observed in participants treated with maralixibat in Study MRX-503 who previously received placebo.

The median decreases in transaminases in maralixibat-treated participants observed in Studies MRX-502, MRX-503, and MRX-801 are in line with data regarding SBD outcomes (Verkade et al. 2020; Bolia et al. 2022).

With the responses to the second RSI, additional analyses were submitted for AST and ALT over time, which showed more pronounced increase in both parameters at the beginning of treatment with gradual decrease over time in the proportion of patients with elevated ALT/AST. No such decrease was observed on placebo.

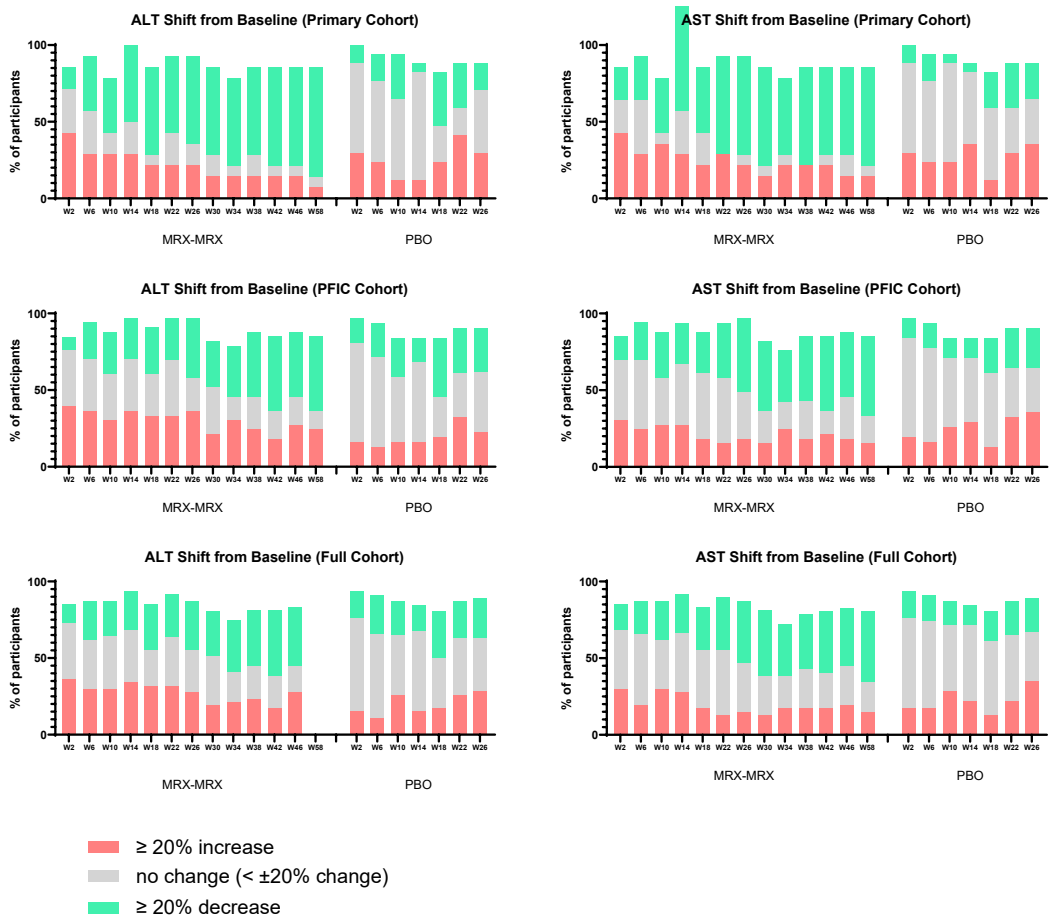


Figure 27 MRX-502 & MRX-503 – Shift from Baseline in ALT and AST levels

Hepatic synthetic function

The study participants in Study MRX-502 had preserved hepatic synthetic function at baseline and maintained normal function throughout the study and in LTE Study MRX-503, as judged by the levels of albumin.

Marker of end-stage liver disease severity and fibrosis markers

Study participants of the PFIC cohort of Study MRX-502 generally had low PELD scores, because patients with decompensated cirrhosis were excluded from the study. In the PFIC cohort, the mean (SD) PELD score at baseline was -1.6 (7.28) and ranged from -11 to 18. This score indicates the study population had a very low probability of death within the next 90 days and liver disease generally was not advanced.

In the placebo group, the PELD score increased significantly over the course of the study, indicating a small progression of disease. The LS mean (standard error [SE]) change from baseline to Week 18-26 in the placebo group was 1.981 (1.0760; p=0.0708). In contrast, a decrease from baseline was observed in the maralixibat group (LS mean [SE] of -1.805 [1.0377]; p=0.0879). The LS mean (SE) difference compared with placebo was -3.785 (1.4752; p=0.0131). The effect on PELD was maintained throughout long-term treatment as demonstrated in the open-label LTE Study MRX-503. A small trend for improvement from baseline in PELD score was also observed in study participants treated with maralixibat in Study MRX-503 who previously received placebo in Study MRX-502 (PBO-MRX) at all post-baseline study weeks except for Week 30 and Week 42 (Appendix 1 Q1a Table 5.5.2).

In Study MRX-502 (PFIC cohort), FIB-4 scores at baseline ranged from 0.01 to 1.12 with a mean (SD) score of 0.231 (0.2990; MRX-502 CSR Table 14.1.4). In the placebo group, a statistically significant increase in FIB-4 scores was observed with a LS mean (SE) change from baseline to Week 18-26 of 0.101 (0.0358, p=0.0062). In contrast, no significant change in FIB-4 was observed in the maralixibat group. The LS mean change from baseline did not reach statistical significance with an LS mean (SE) of -0.085 (0.11075, p=0.0838). FIB-4 scores also appear to be maintained over time in study participants treated with maralixibat in MRX-503 who previously received placebo in Study MRX-502 (PBO-MRX) at all post-baseline study weeks except for Week 30 and Week 42. FIB-4 scores tend to be maintained with continued treatment with maralixibat, with fluctuating mean changes from baseline.

APRI scores at baseline ranged from 0.17 to 4.40 with a mean (SD) score of 0.822 (0.9257). Overall, 11 of 45 participants (24.4%) in the PFIC cohort had a score of >0.99 at baseline, predictive of a severe fibrosis (F3-F4; Shiau et al. 2020). In Study MRX-502, APRI scores in the placebo group tended to increase over time with a LS mean (SE) change from baseline at Week 18-26 of 0.462 (0.2341; p=0.0570). In contrast, in the maralixibat treatment group, APRI scores tended to be maintained with a LS mean (SE) change from baseline of -0.039 (0.2189; p=0.8605). The difference between the treatment groups was not statistically significant (LS mean (SE) difference in the maralixibat group compared with placebo of -0.501 (0.3211; p=0.1287). Following 26 weeks of treatment, no meaningful changes in the number of participants with APRI scores >0.99 were observed in the maralixibat or placebo group. A similar trend for maintained APRI scores was observed in study participants treated with maralixibat in Study MRX-503 who previously received placebo in Study MRX-502 (PBO-MRX). In participants who continued maralixibat treatment in Study MRX-503, APRI average scores were further maintained.

Growth

In Study MRX-502, growth for the PFIC study population was stunted at baseline. Mean (SD) height z-scores at baseline were -2.073 (1.3752) and ranged from -4.92 to 0.88. Mean (SD) weight z-scores at baseline were -1.525 (1.3192) and ranged from -5.08 to 1.46. In Study MRX-502, there was a statistically significant increase in weight z-score in the maralixibat treatment group versus placebo (PFIC cohort) with an LS mean change from placebo of 0.227 (95% CI: 0.012, 0.442; p=0.0391). There was an increase in height z-score in the maralixibat group and a decrease in the placebo group (PFIC cohort; Table below); changes from baseline in height z-scores and the differences between groups were not statistically significant. The latest interim analysis of Study MRX-503 confirms that observed increases in weight z-scores were maintained throughout the continued treatment with maralixibat in Study MRX-503, whereas improvements in height z-scores further increased. The increase from baseline in height z-score reached statistical significance at Week 30 and was maintained until Week 118, after which the number of participants with assessments at the time point was <9 (MRX-MRX group in the PFIC cohort).

Table 28 Overview of Treatment Effects on Growth (SAP Predefined Analyses)

	Statistic	**MRX-502** Change from Baseline to Week 18-26 (MMRM) [a] (PFIC Cohort) Maralixibat (n=33)	Placebo (n=31)	Statistic	**MRX-503** Change from Baseline to Week 26 [b] (PFIC Cohort) PBO-MRX (n=27)	**MRX-801** Change from Baseline to Week 13 (PFIC Cohort) Maralixibat (n=10)
Height z-Score				n	25	9
	LS mean (SE)	0.078 (0.0851)	-0.131 (0.0909)	Mean	0.305	-0.058
	95% CI for LS mean	(-0.093, 0.248)	(-0.312, 0.051)	(95% CI for Mean)	(0.018, 0.591)	(-0.523, 0.406)
	p-value (CFB LS mean=0)	0.3652	0.1555	p-value [d]	0.0383	0.7793
	LS mean (SE) change from placebo	0.208 (0.1223)				
	95% CI for LS mean change from placebo	(-0.036, 0.453)				
	p-value (maralixibat LS mean=placebo LS mean)	0.0939				
Weight z-Score				n	25	9
	LS mean (SE)	0.347 (0.0738)	0.120 (0.0779)	Mean	0.079	0.372
	95% CI for LS mean	(0.199, 0.494)	(-0.036, 0.275)	(95% CI for Mean)	(-0.151, 0.309)	(0.091, 0.0652)
	p-value (CFB LS mean=0)	<0.0001	0.1301	p-value [c]	0.4855	0.0158
	LS mean (SE) change from placebo	0.227 (0.1075)				
	95% CI for LS mean change from placebo	(0.012, 0.442)				
	p-value (maralixibat LS mean=placebo LS mean)	0.0391				

CI=confidence interval; LS=least-squares; MMRM=mixed model for repeated measures; PBO-MRX= participants treated with maralixibat in MRX-503 who previously received placebo in MRX-502; PFIC=progressive familial intrahepatic cholestasis; SAP=statistical analysis plan; SE=standard error of the mean.

[a] Estimates are from an MMRM with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit, and treatment-by-visit interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-visit interaction. PFIC type is included in the model as an additional covariate. Average of Weeks 18, 22, and 26 are obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

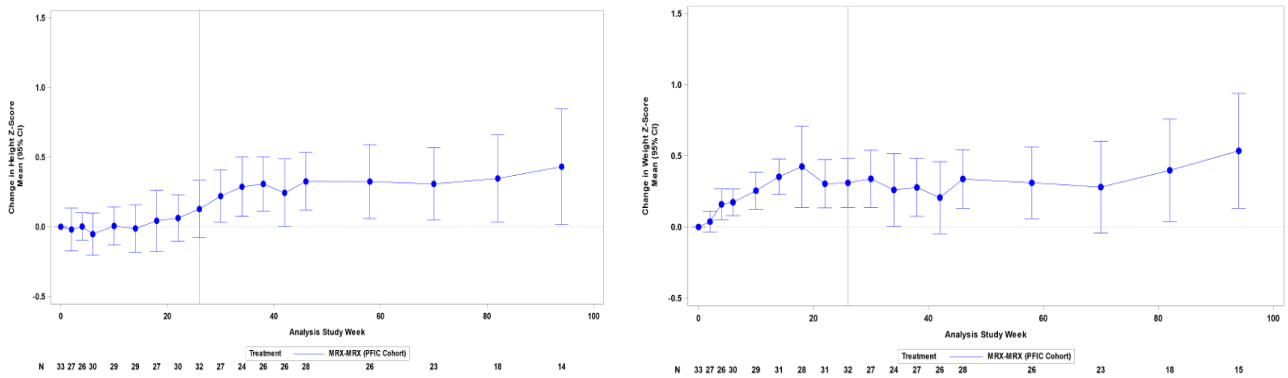
[b] Baseline for PBO-MRX is from MRX-503.

[c] Student's t-test used to test if mean change from baseline is statistically significant.

Sources: MRX-502 CSR Table 14.2.4.28.1, Table 14.2.4.29.1; Appendix 1 Q1a Table 5.9.2, Table 5.10.2; Q1b Table 6.8 and Table 6.9.

Sensitivity analyses for the change from baseline in participants treated with maralixibat for ≥2 years (MRX-MRX PFIC Cohort, N=28) up to Week 58 confirm that improvements in height and weight z-scores are observed with long-term treatment with maralixibat.

Figure 28 MRX-502 & 503 - Mean (95% CI) Change in Height Z-Score (left) and Weight Z-Score (right) Over Time (Safety Population – PFIC cohort)



MRX-MRX= participants treated with maralixibat in MRX-503 who previously received maralixibat in MRX-502; N=number of participants with applicable data at specified analysis visit; PFIC= progressive familial intrahepatic cholestasis.
Data extract date: 10-Jun-2023.
Data pooled from studies MRX-502 and MRX-503.
Vertical line denotes transition from study MRX-502 to MRX-503. Dashed horizontal line denotes no change.
Week 94 is used as a cutoff since the sample size drops below 10 after this point.

These results indicate an initial weight improvement with maralixibat treatment, followed by catch-up growth starting after 3–4 months of treatment. This temporal relation between weight gain and height gain of linear growth following replenishment of body weight is commonly described for children recovering from severe malnutrition (Walker and Golden 1988; Cliffer et al. 2022). Growth results after pharmacological biliary diversion with maralixibat are in line with data from a systematic review looking at the outcomes of nontransplant surgical interventions in PFIC (Davis et al 2009). This systematic review found that 4 out of 5 studies that mentioned growth reported improved growth velocity after SBD. The magnitude and dynamics of growth improvements after SBD remain to be established.

These consistent trends for catch-up growth in maralixibat-treated participants with PFIC across studies support a disease-modifying effect of maralixibat treatment in PFIC.

Liver-Associated Events (data cut-off 10 June 2023)

According to Study MRX-502 Statistical Analysis Plan, liver-associated events were defined as partial external biliary diversion (PEBD) surgery, listing for liver transplantation, liver decompensation (hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis) events, hepatocellular carcinoma, and death.

Four study participants of Study MRX-502 had been listed for liver transplantation prior to enrolling into the study. During the course of Study MRX-502, only one participant had a liver associated event (listing for liver transplantation followed by liver transplantation). In Study MRX-503 up to the data cut date of 10 June 2023, 13 participants had liver-associated events, of which listing for liver transplantation was the most common event type. The events comprised seven participants listed for liver transplant, three participants listed for liver transplant followed by liver transplantation, one participant had PEBD surgery, one participant had ascites followed by hepatic function abnormal and one participant had oesophageal varices bleeding followed by listing for liver transplantation and liver transplantation. ….

All participants except one that had a liver-associated event were sBA non-responders. And all participants except one were bilirubin non-responders. Maralixibat exposure duration up to the first event was between 97 to 1200 days.

The majority of these patients was very young at the time of study entry (1-2 years old).

Study MRX-801 – study in infants

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

The study comprises screening (up to 4 weeks), core study period with flexible dose escalation (Weeks 1 to 6) and stable dosing (Weeks 7 to 13) and long-term extension (LTE).

At the end of the core study period (Week 13), participants continue into an LTE until they are eligible to enter an expanded access program, the sponsor stops the program, or the drug is commercially

available. Participant below 12 months of age, attend visits every 4 weeks with a phone contact between the visits. Once the participant is ≥12 months of age, visits are scheduled every 16 weeks.

Initially, participants with PFIC are treated with 300 µg/kg maralixibat QD for at least 1 week, followed by 300 µg/kg maralixibat BID for at least 1 week, followed by the target dose of 600 µg/kg maralixibat BID. Dose escalation is to occur only in the absence of major safety (e.g., liver parameters) or tolerability (e.g., GI-related TEAEs) concerns related or possibly related to maralixibat. The investigator has up to Week 6 to escalate up to the target dose.

Aside of the routine assessments like demographics, ECG, assessment of development, blood tests (chemistry and blood count), etc., more specific data like, sBA, ItchRO (Obs) scores, clinicians scratch scale (CSS), 7αC4, fat soluble vitamins, lipid panel, coagulation, PK (pre-dose and 2.5 h ± 30 min post-dose) are being collected.

The primary objective of the study is assessment of MRX safety. A secondary objective of the study is to evaluate the treatment effect of maralixibat on sBA levels by assessing the change from baseline to Week 13.

By the data cut-off date 28 June 2023 a total of 10 participants (safety set) were enrolled in the study. Of these 10 patients, 9 completed the 13-week core study period and entered the LTE period, and 1 participant discontinued prior to entering the LTE period due to an adverse event (AE). All 9 participants who entered the LTE are ongoing in the study as of the cut-off date.

The mean (SD) age at study enrollment was 6.6 (3.89) months (range 1 to 11 months) Seven participants (70%) were male and 3 participants (30%) were female. The mean (SD) weight z-score and height z-score were -1.55 (1.134) and -1.49 (0.946), respectively. There were 7 participants (70%) with the ABCB11, 2 participants (20%) with the ATP8B1 and 1 participant (10%) with the TJP2 genotype. At baseline, the population had abnormal liver parameters, with increased ALT (mean (SD) 149.0 (110.11) U/L, AST (mean (SD) 159.1 (97.03) U/L, and total bilirubin (mean (SD) 41.02 (23.651) µmol/L). Overall, 9 out of 9 (100%) participants with available baseline sBA data had elevated levels, with baseline mean (SD) of 228.317 (107.5249) µmol/L that ranged from 60.91 to 391.65 µmol/L. Although pruritus was not an inclusion criterion at study entry, 7 out of 10 participants (70%) experienced pruritus, with severity on the CSS that ranged from 1 (rubbing or mild scratching when undistracted) to 3 (abrasion evident). Observer rated pruritus severity data using the Itch Reported Outcome (ItchRO) tool was collected for 6 participants, and 5 out of these had Weekly Average ItchRO(Observer [Obs]) Severity Score >0 at baseline. Average morning severity score ranged from 0.00 to 2.29 with median of 0.667. The average evening score ranged from 0.00 to 2.00 with a median of 1.071. The average daily worse score ranged from 0.00 to 2.29 with a median of 1.071.

Treatment duration ranged from 24.0 to 532.0 days with mean (SD) and median of 305.2 (173.23) and 257.5 days, respectively.

All participants were exposed to the target dose of 600 µg/kg BID. Of note, one participant received this dose for only 1 day prior to treatment discontinuation. One patient had temporary dose reduction to 300 µg/kg BID due to AEs (frequent bowel movements, abdominal discomfort, and diarrhea) with subsequent increase to 450 µg/kg BID and 600 µg/kg BID.

Three (3) participants had temporary drug interruptions (3 to 16 days) due to AEs (coagulopathy and gastroenteritis adenovirus; coagulopathy; appendicitis).

<u>Safety (Primary objective)</u>

All study participants with PFIC (100%) experienced at least 1 treatment-emergent adverse event (TEAE), including 3 participants (30%) related to study drug, and 1 (10%) with TEAE of Grade ≥3 (event of influenza and event of appendicitis, both considered not related to study drug). Three (3) participants (30%) experienced a serious adverse event (SAE) (influenza, adenovirus infection and appendicitis all in one Participant Grades 3 and 2; Grade 1 cough in one participant; Grade 2 gastroenteritis adenovirus in one participant), which all were considered not related to the study drug. One (1) TEAE led to study drug discontinuation. None led to death.

The most frequent TEAE (across MedDRA System Organ Class and by Preferred Term) was Vomiting (5 participants; 50%), followed by Nasopharyngitis (4 participants; 40%), Diarrhoea, Pyrexia, Cough, and Rhinorrhoea (3 participants each; 30%). Most TEAEs were Grade 1 in severity.

One (1) participant (10%) had a TEAE (Grade 2 ALT increased) that led to study drug discontinuation. The event was considered as related to study treatment at the data extract date of 28 June 2023. The participant discontinued the study for the reason of recurrent infections with significant transaminitis. After 12 August 2023, the site reclassified the event of Grade 2 ALT increased as not related to study drug. The participant later moved to the maralixibat Expanded Access Program (EAP) after discontinuing Study MRX-801.

Overall, there were no trends for clinically relevant changes from maralixibat baseline to postbaseline in key clinical chemistry and hematology laboratory parameters.

One participant had low hemoglobin and low hematocrit values at Week 13, and values normalized by Week 17.

One participant had low platelet counts at Week 6 and beyond, in addition to low leukocyte and lymphocyte counts from Week 29 and beyond.

One participant had low lymphocyte counts at Week 25, the last recorded visit at the time of the data extract.

sBA (Secondary Objective)

The baseline mean (SD) sBA was 228.317 (107.5249) µmol/L. The mean (SD) change in sBA from baseline at Week 13 was -107.965 (146.7659, p=0.0760) µmol/L and at ween 33 -37.521 (SD 158.8534) µmol/L. Median change from baseline at week 13 was -72.344 (Q1, Q3: -215.843, -18.490) µmol/L and at week 33 -6.484 (Q1; Q3: -146.783, 87.177) µmol/L. After ween 33 data are limited to 1 to 3 participants (Appendix 1, Q1b Table 6.1). Seven participants had decreases from baseline at Week 13 ranging from -332.11 to -14.5.53 µmol/L (7.0% to 206% decrease), but levels fluctuated at other time points in most of these participants. Two participants had an increase.

Liver chemistry (total bilirubin, direct bilirubin, ALT, AST) (secondary objective)

At baseline, most study participants had elevated total (8 of 10 participants) and direct bilirubin (10 of 10 participants) with the mean (SD) of 2.399 (1.3831) mg/dL and 1.811 (1.0905) mg/dL, respectively. All study participants, except for Participant 801-805, showed decreases in total and direct bilirubin over time. The mean (SD) change from baseline to Week 13 in total and direct bilirubin was -1.171 (1.0862, p=0.0120) and -1.064 (0.8852, p=0.0191), respectively.

At baseline, all study participants had elevated ALT and AST levels with the mean (SD) of 149.0 (110.11) U/L and 159.1 (97.03) U/L, respectively. All study participants, except for Participant 801-805, either showed stable or decreasing ALT and AST levels over time. The mean (SD) change from baseline to Week 13 in ALT and AST was -15.2 (42.39, p=0.3127) and -27.6 (30.91, p=0.0393), respectively.

Participant 801-805 had a large increase in ALT and AST from Week 3 until early discontinuation in response to the AE of elevated ALT.

Figure 29 MRX-801 - Change from Baseline in sBA (left) and Direct Bilirubin (mg/dL) (right) Over Time during Core Study Period (Safety Population – PFIC Cohort)

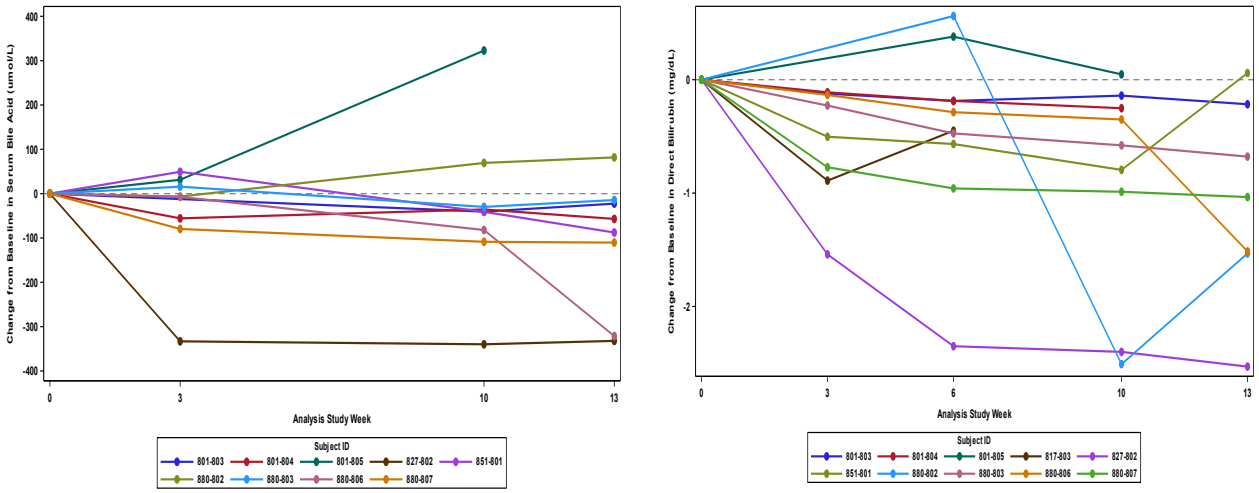
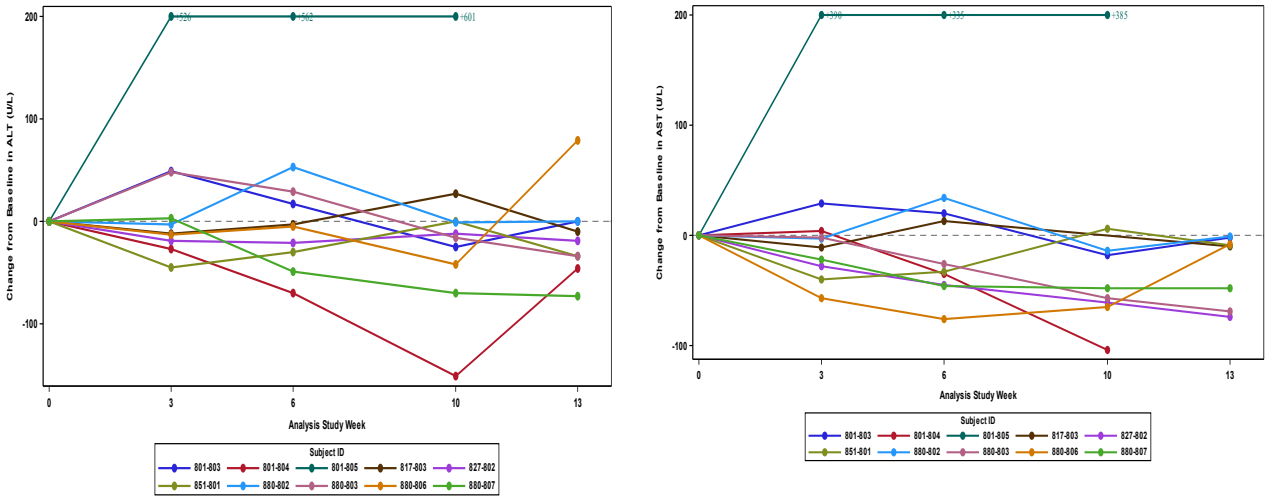


Figure 30 MRX-801 - Change from Baseline in ALT (U/L) (left) and AST (right) Over Time during Core Study Period (Safety Population – PFIC Cohort)



Fat Soluble Vitamins (Secondary Objective)

In Study MRX-801, FSV levels were maintained or increased during the study, reflecting the utilization of FSV supplementation that is standard of care for chronic cholestasis.

Two (2) participants had slightly elevated INR measurements at baseline. For both participants, the values normalized over the course of the study. Two (2) participants had small temporary INR increases up to 1.8 and 2.2 during the study.

Pharmacokinetics (Secondary Objective)

The mean (SD) concentration at 2.5 hours after maralixibat dosing was 0.5273 (1.21501) ng/mL. At doses of 600 µg/kg BID, 71.4% of samples were below the lower limit of detection. The highest plasma level detected was 5.78 ng/mL.

Pruritus (Exploratory Objective)

Seven of 10 patients had pruritus at the baseline (as per CSS and ItchRO). The youngest patient with pruritus was 3 months old. Two improved on MRX. This improvement was accompanied by reduction in sBA and bilirubin. Five remained unchanged. From those without pruritus at the baseline 2 developed pruritus during the study.

Growth (Exploratory Objective)

No clear trend in height z-scores over the course of the study were observed. The mean (SD) change from baseline to Week 13 in height z-score was -0.058 (0.6041, p=0.7793).

All study participants, except for one Participant, either showed stable or increasing weight z-scores over time. The mean (SD) change from baseline to Week 13 in weight z-score was 0.372 (0.3653, p=0.0158).

No significant changes or trends in head circumference z-scores and mid-upper-arm circumference z-scores over the course of the study were observed.

Justification for full extrapolation from children >12 months of age to infants 2 to 12 months of age as provided by the applicant

The full extrapolation of the benefit-risk profile of maralixibat from children ≥12 months of age to infants 3 to <12 months of age is based on the following:

- Data from the ongoing Study MRX-801 demonstrate that administration of maralixibat to infants with PFIC and Alagille syndrome (ALGS) who are 3–12 months of age have pharmacodynamic, PK, and safety profiles similar to those of children ≥12 months of age.

Clinical efficacy extrapolation is based on the following:

- Similar clinical manifestations of PFIC in patients <12 months of age and ≥12 months of age
- Similarity in pharmacology and mechanism of action of maralixibat in patients with PFIC <12 months of age (Study MRX-801) and ≥12 months of age
- Similarity in response to treatment with maralixibat across pediatric age groups

Similar to older patients, in infants with PFIC in Study MRX-801, sBA levels were elevated at baseline and were, on average, decreased after maralixibat treatment.

Safety profile in infants in Study MRX-801 is in line with the known safety profile of maralixibat from the pivotal Study MRX-502.

The most common TEAEs in participants treated with maralixibat in Study MRX-502 included diarrhea (57.4%), pyrexia (36.3%), and abdominal pain (21.3%). The most frequent TEAEs in Study MRX-801 were vomiting (50%), nasopharyngitis (40%), diarrhea, pyrexia, cough, and rhinorrhea (30% each). In Study MRX-502, the incidence of treatment emergent SAEs was similar between the maralixibat group (5 participants, 10.6%) versus the placebo group (3 participants, 6.5%). The most common SAE in the maralixibat-treated group of Study MRX-502 was urinary tract infection (2 participants [4.3%]). In the infants in Study MRX-801, the incidence of treatment emergent SAEs was 30% (3 participants) and were all considered not related to study drug. The reported SAEs were influenza, adenovirus infection, and appendicitis (all in one participant), and cough and gastroenteritis adenovirus. For all maralixibat-treated participants in Study MRX-502, only 1 treatment-related TEAE led to permanent discontinuation of the study (mild diarrhea). In Study MRX-801, there was 1 TEAE that led to study drug discontinuation (Grade 2 ALT increased).

There is a higher frequency of TEAEs in the infants <12 months of age that can be explained by the disproportion in sample size (the available data on infants with PFIC treated with maralixibat include

only 10 participants), as well as general differences in infant patients who, as a population, are susceptible to fevers and infections (Study MRX 801 enrolled during the COVID-19 pandemic).

Overall, there are no new safety signals seen in participants with PFIC who are <12 months of age.

Similar clinical manifestations of PFIC in patients <12 months of age and ≥12 months of age

In patients with PFIC, elevated sBA levels and liver chemistry abnormalities have been reported from an early age (Davit-Spraul et al. 2010). Symptoms including jaundice, discolored stools, and/or hepatomegaly appeared in the first month of life in 15% of patients with PFIC1 and 44% of patients with PFIC2 and by 3 months of age in 61% of patients with PFIC1 and 72% of patients with PFIC2. Pruritus is reported to occur in 11%–100% of patients at presentation and by 76%–100% of patients at follow-up and can occur as early as <1 month of age (Davit-Spraul et al. 2010; Baker et al. 2019).

In children 1 to 11 months of age in Study MRX-801, sBA levels at baseline were clinically significantly elevated in all 9 infants with available baseline sBA levels, ranging from 60.91 to 391.65 µmol/L. Also, other liver chemistry parameters were abnormal at study inclusion. Seventy percent of the patients had pruritus (assessed by the CSS) at baseline, the youngest being 3 months of age.

In summary, cholestatic manifestations of PFIC, including elevated sBA levels and pruritus, typically appear during the first months of life. Infants with PFIC between 2 and <12 months of age have physiopathology similar to those of children ≥12 months of age.

Similarity in pharmacology and mechanism of action of maralixibat in patients with PFIC <12 months of age (Study MRX-801) and ≥12 months of age

Absorption:

Maralixibat was designed to be minimally absorbed. The barrier to such molecules appears to be fully developed after the first few postnatal days (reviewed in Neal-Kluever et al. 2019). The intraluminal availability of maralixibat is therefore not expected to be affected by age. Clinical studies in participants with PFIC and ALGS confirmed that maralixibat is minimally absorbed both in children ≥12 months of age and in infants <12 months of age.

Mechanism of Action:

IBATs (target for MRX) are expressed and functional in human neonates starting from birth. Neonates exhibit clear postprandial increase in sBA, indicating intestinal bile acid absorption starting at birth (Suchy et al. 1981). Also, individuals with loss of IBAT function (a condition called primary bile acid malabsorption) have diarrhea starting from birth, indicating that IBATs are expressed and have a significant impact on bile acid recirculation starting at birth (Heubi et al. 1979, 1982; Qie et al. 2021). Active ileal absorption of bile acid has been directly demonstrated in tissue samples of infants, indicating maturation of intestinal bile acid transport during the first months of life (de Belle et al. 1979). Thus, the expectation is that newborns have intestinal bile acid reuptake via IBAT and would have response to maralixibat similar to that of children ≥12 months of age. This is further supported by the observed decrease in sBA, a pharmacodynamic marker of IBAT inhibition, in Study MRX-801 participants in response to maralixibat treatment.

Similarity in response to treatment with maralixibat across pediatric age groups

Serum bile acid response:

The LS mean (SE) change from baseline at Week 14 in the maralixibat group of Study MRX-502 (PFIC cohort) and the mean (SD) change from baseline at Week 13 in Study MRX-801 was -146.721 (23.8967) µmol/L and -107.965 (146.7659) µmol/L, respectively.

Serum bilirubin response:

The LS mean (SE) change in total bilirubin from baseline at Week 14 in the maralixibat group of Study MRX-502 (PFIC cohort) was -1.232 (0.5949) mg/dL (Module 2.7.3). In Study MRX-801, 9 out of 10 infants had a reduction in total bilirubin with maralixibat treatment. The mean (SD) change from baseline at Week 13 in total bilirubin was -1.171 (1.0862) mg/dL).

Pruritus response (CSS):

Study MRX-801 had no entry criterion related to pruritus and Study MRX-502 did require moderate-to-severe pruritus at study entry; therefore, CSS scores at baseline were higher in Study MRX-502 (PFIC cohort: mean [SD] 2.7 [0.87]) compared Study MRX-801 (mean [SD] 1.55 [1.212]).

The LS mean (SE) changes in CSS from baseline at Week 14 in the maralixibat group of Study MRX-502 and the mean (SD) change from baseline at Week 13 in Study MRX-801 were -1.469 (0.3462) and 0.15 (1.415), respectively. The interpretation of these results is limited by the small sample size (10 participants) in Study MRX-801. Also, participants of Study MRX-801 were in their first year of life, the age at which cholestatic pruritus first presents (in parallel with infant motor development), with no stability in its severity. Seven out of 10 participants had evidence of pruritus at baseline, with an improvement seen in 2 out of 7 participants. The 2 participants with improvement in pruritus also showed marked reductions in sBA and bilirubin.

LUM001-501

Study LUM001-501 is a completed Phase 2, open-label study of the efficacy and safety of maralixibat in 33 participants. It was the first study of maralixibat in patients with PFIC. Study LUM001-501 tested lower doses of maralixibat compared with the pivotal Study MRX 502 in participants with PFIC1 and PFIC2 (also referred to as FIC1 and BSEP deficiency) and demonstrated responses in a subset of participants. The study was initially designed as a 13 week study with a 59 week, long term exposure period. Participants who completed the 59 week long-term exposure period to Week 72 had the option to continue in a long-term extension of the study (for >6 years in total duration). Participants were initially treated with doses up to 280 µg/kg QD until implementation of Protocol Amendment 4 during the long-term extension (mean Week 118 [range 94–152]), which allowed partial responders or nonresponders (n=10) to be treated with doses up to 280 µg/kg BID. Twelve of 22 participants who completed the study continue to receive maralixibat in the ongoing rollover Study MRX 800. In Study MRX-800, participants were initially treated with a dose similar to the dose in Study LUM001-501 (280 µg/kg); subsequently, the investigator was allowed to increase the dosing up to 600 µg/kg BID.

The primary efficacy endpoint, which included all participants with PFIC1 and PFIC2 combined (n=33), was the change from baseline to Week 13 in fasting sBA level in the overall study population. The primary efficacy endpoint was not met. No sBA response was observed in participants with PFIC1 and participants with t-PFIC2. However, an sBA response to maralixibat treatment was observed in part of the participants with PFIC2. The most pronounced response occurred in participants with nt-PFIC2 who have residual BSEP function (described as mild or moderate mutational status).

No changes in the growth parameters were observed and no relevant change in the liver function tests were observed. Limitation of this study is absence of placebo control.

Extrapolation of efficacy from children and adolescents to the adult population as provided by the applicant

Maralixibat studies in patients with PFIC enrolled only participants ≤18 years of age to reduce age-related variability in study data. The maximum age at enrollment in Study MRX-502 was 17 years. During the course of Studies MRX 502, MRX 503, LUM001-501, and MRX-800, no participants with

PFIC turned 18 years of age. Thus, no data have been generated in the adult population with PFIC and extrapolation of the safety and efficacy data from children and adolescents is proposed based on the

- Similar pathophysiology of the disease
- Similar mechanism of action of MRX
- Similar/maintained efficacy in the patients after reaching adulthood (experience gained in the patients with ALGS (Initial MAA EMEA/H/C/005857/0000 Response to D120 question 71 of ALGS submission), that can be extrapolated to the population with PFIC
- Similar efficacy across various age subgroups (Study MRX-502)

2.4.3. Discussion on clinical efficacy

Key evidence of efficacy in this variation procedure is provided from the studies MRX-502, MRX-503 and MRX-801. LUM001-501 and MRX-800 studies evaluated lower doses of MRX in restricted population and in an open-label setting. These two studies are therefore not discussed in detail for efficacy.

MRX-502 is the pivotal study that provides evidence on efficacy and safety over a 6 month placebo-controlled period. Data on long-term safety and efficacy are derived from the ongoing MRX-503 study. Both studies were performed in patients 1 year of age and older with PFIC and using the maralixibat dose of 600 µg/kg BID. The MAH proposed extrapolation of efficacy and safety from this age group to infants with PFIC from 3 months of age. Supportive evidence of efficacy and safety and evaluation of PD markers and systemic exposure to MRX in patients below the age of 1 year on the recommended dose was collected in the ongoing MRX-801 study on maralixibat dose of 600 µg/kg BID.

Design and conduct of clinical studies

MRX-502 was a DB, randomised placebo-controlled 6-months study in the patients with PFIC (all types were to be included) from the age of 1 year and up-to 18 years. This is the pivotal study that aimed to evaluate short/mid-term efficacy of MRX in treatment of pruritus (primary, secondary and exploratory endpoints), as well as in reduction of sBA (key secondary and exploratory endpoints), other liver parameters, growth, quality of life, sleep, biomarkers of bile acid synthesis, liver fibrosis, pruritus, etc.

MRX-503 is the ongoing OL single-arm extension of the MRX-502 study and the aim of this study is to show similar effects in the patients switched from placebo (in MRX-502) to MRX treatment (in MRX-503), as were observed in the pivotal study, as well as, to demonstrate maintenance of effects over long-term treatment with MRX. Additionally, it was expected, that some of the long-term effects from MRX may be manifested in this study, as the MRX-502 was too short for this purpose.

MRX-801 is an ongoing OL study in the patients with PFIC younger than 12 months and is meant to provide sufficient evidence (effects on the PD biomarker – sBA and efficacy parameters) in a limited group of population and open-label setting, to support full extrapolation of the efficacy and safety data from older patients with PFIC to substantiate the broad age range from 3 months and older.

The study designs, durations, selected populations, objectives and endpoints are overall acceptable. The following key comments are being made:

MRX-502:

- The chosen primary endpoint concerns assessment of pruritus. The key secondary endpoint concerns assessment of sBA. Neither of these endpoints, or the short study duration, are adequate

to support the claimed indication "treatment of PFIC" as stand alone. However, exploratory endpoints on fibrosis biomarkers, liver-related events, liver function tests and utilisation of health care facilities are considered relevant as supportive parameters.

- Efficacy data were analysed in two patient cohorts: primary cohort (nt-PFIC2) and PFIC cohort (all PFIC types apart from t-PFIC2). Efficacy endpoints in the Full Cohort were analysed on request.
- The analysis in the PFIC cohort included PFIC type as covariate such that the stratified randomisation was taken into account. The hierarchical testing strategy ensures control of the family-wise type 1 error rate for the primary and secondary hypotheses. The primary analysis was specified in the primary cohort including all nt-PFIC2 participants; however, the hierarchical testing strategy allows also confirmatory conclusions for the PFIC population. The assessment in how far effects in the overall PFIC population are driven by effects in nt-PFIC2 participants is important such that the post-hoc analysis in non- nt-PFIC2 participants is relevant.
- The estimand was not consistently described. The applicant states in the CSR that, because the hypothetical strategy was adopted for all intercurrent events, a MMRM model was used. However, the statistical model alone does not determine the estimand that is targeted but what data is included in the analysis is also relevant. The Applicant has clarified that data collected after intercurrent events were not excluded from the analysis except for data after treatment discontinuation. The Applicant's clarification that efficacy assessments performed >7 days after the last dose of study drug were not included in any efficacy analyses is noted. This is usually not appropriate when targeting the effect irrespectively of treatment discontinuation which is usually of primary regulatory relevance, however, the number of patients who discontinued study was small (particularly in the active treatment group) such that this does not have a relevant impact on the conclusions from the study. For targeting the hypothetical effect 'if prohibited medication had not been taken', an analysis including data after rescue medication intake is not in alignment, however, it would anyway not be of primary regulatory interest and the number of patients with prohibited medication intake with potential influence on efficacy was very low such that a relevant influence on the conclusions can be excluded.
- In addition, missing data after treatment discontinuation needs to be handled in alignment with the targeted estimand. The MMRM model is not aligned to targeting the treatment effect irrespectively of treatment discontinuation (treatment policy) which is of primary relevance from a regulatory point of view, as the missing at random assumption is not plausible because loss of effect in the active group can be expected after discontinuation. However, as the number of patients who discontinued study was small (particularly in the active treatment group), this does not have a relevant impact on the conclusions from the study.
- Overall, the endpoints and the statistical analyses were planned so that data in the primary and in the PFIC cohort are considered confirmatory. As PFIC cohort is considered representative of the target indication, efficacy evidence in this cohort was the main focus of this assessment.
- Blinding and randomisation procedures are considered adequate. It must be noted that 4 amendments and 23 versions of the protocol (including local versions) were created and this large amount of changes raised concerns on data integrity. However, the majority of these amendments were local (country-level) amendments. Those which affected inclusion/exclusion criteria were introduced either prior to the first patient enrolled timepoint, or when few patients were in the study and those defining study analyses were introduced under blinded condition. Therefore, it can be assumed that data integrity likely was not affected.

<u>MRX-503</u>

This is an ongoing open-label extension (LTE) to the pivotal study MRX-502. Participants who completed the 6-month treatment in the MRX-502 study had the option to continue treatment in the open-label LTE Study MRX-503. All participants received maralixibat at the proposed commercial dose of 600 µg/kg BID. The study design of Study MRX-503 (the first 26 weeks) including dose escalation, study visit schedule, and schedule of assessments was designed to be comparable to Study MRX-502.

A planned interim analysis for Study MRX-503 with a data cut of 23 June 2022 was performed for the purpose of supporting this application. For the report, combined data from MRX-502 and MRX-503 were presented. Analyses were performed for the same cohorts as defined in Study MRX-502 and for the subgroups MRX MRX, PBO MRX, and All MRX, which is acceptable.

MRX-801

This is an ongoing open-label, multicenter, Phase 2 study to evaluate the safety and tolerability of maralixibat in the treatment of infants (<12 months of age) with cholestatic liver disease (Alagille syndrome [ALGS] or progressive familial intrahepatic cholestasis [PFIC]). The study comprises screening (up to 4 weeks), core study period with flexible dose escalation (Weeks 1 to 6) and stable dosing (Weeks 7 to 13) and long-term extension (LTE).

It is understood, that a confirmatory study with DB placebo-controlled design is not feasible in this population. The primary aim of the study is to provide further evidence on the systemic exposure to MRX, safety/tolerability and PD/efficacy in infants. This strategy is endorsed. Efficacy parameters (e.g., pruritus by means of CSS and sBA) are collected as secondary/exploratory parameters. Blood samples for evaluation of MRX concentrations are being collected. The study design and the collected parameters are endorsed.

Efficacy data and additional analyses

Recommended dosing regimen

The recommended dosing regimen is to start treatment with 300 µg/kg QD and to escalate the dose considering tolerability/safety up-to the target dose of 600 µg/kg BID (285 µg MRX base = 300 µg MRX chloride. The study reports and documentation present MRX chloride dosing. This was kept in the AR. The PI contains dosing in MRX base)

Duration of 1-2 weeks for titration steps is recommended. Administration 30 min prior to or together with meal is advised. Switch from weight-based to fixed dosing with maximum dose limitation is recommended after reaching 50 kg body.

Overall, comprehensive dose-finding in the target population was not done and the recommended maximum/target dose is approximately 3-fold higher than the approved maximum dose in the ALGS indication (starting dose - 1.5 times, target dose – 3 times and maximum total administered dose in the adult population (above 50 kg of weight in PFIC and above 70 kg in ALGS - 2 times) and the doses tested in the earlier PFIC studies with up-to 8 years of MRX exposure. However, similar dosing regimens were applied in the pivotal study MRX-502 and the infant study MRX-801 and data support the starting dose and the recommended minimum duration for each titration step. The maximum recommended dose/the target therapeutic dose of 600 µg/kg BID MRX is acceptable.

However, administration of Livmali containing 600 µg/kg MRX BID will lead to the expected exposure of up-to 50 mg/kg/day PG (excipient). This raises concerns in vulnerable populations who may have limited ability to metabolise and/or excrete PG quickly such as, <5 years old patients (due to physiological immaturity of liver/function of alcohol dehydrogenase), patients with impaired liver

function (which can become manifest and worsen already in early childhood; van Wessel et al., 2020) and patients with impaired renal function.

Safety data are available on PG exposure of up-to 26 mg/kg/day (that would correspond to the content of 300 µg/kg MRX in to be marketed Livmarli oral solution). Efficacy data show that an acceptable sBA response can be achieved already on 300 µg/kg BID dose of MRX in a relevant part of the treated patients. Further, differences in reduction of direct bilirubin and pruritus (as measured with Clinician Scratch Scale) were also observed on MRX compared to placebo at a reduced dose of 300 µg/kg BID (600 µg/kg/day). Post hoc analyses showed that 33% of the patients achieved relevant reduction in sBA on half the recommended dose of MRX (relevant reduction defined as sBA level <102 µmol/L, or decreased in sBA of at least 75%; NAPPED criteria). This level of response was achieved only in 45% of patients on full dose. Another post hoc analysis showed that 57% of patients achieved at least 80% of their individual change in sBA on half the MRX dose (i.e., 300 µg/kg BID), whereas only 63% of patients had the same effect reported on full dose. Overall, the presented evidence to support the use of reduced dose of Livmarli in part of the patients is limited, but considered sufficient. It may be that increase in dose of MRX in the same patients may lead to improvement in effects. Meaning, the patients on reduced dose may not achieve maximum benefit from the treatment. For such cases/in the case of lack of efficacy, switch to alternative treatment option is recommended in the SmPC. Thus, to summarise, the low dose of Livmarli can be recommended in all patients below the age of 5 years, and those with moderate renal or hepatic impairment.

It is unlikely that patients with severe hepatic impairment/cirrhosis may benefit from Livmarli, as the disease in these patients is progressed. Additionally, these patients and those with severe renal impairment are at increased risk of PG accumulation. Therefore, use of Livmarli is contraindicated for the patients with severe liver impairment/cirrhosis and severe renal impairment.

The dosing regimen is, thus, acceptable.

MRX-502

The study included 93 patients in total and the largest analysis set – ITT in the PFIC cohort included 64 patients with PFIC1, nt-PFIC2, PFIC3, PFIC4, and PFIC6, representing all types of PFIC apart from t-PFIC2 (which was excluded from the efficacy cohorts due to the expected lack of efficacy) and PFIC5 (no such patients came to the study). The size of the study is thus limited, but acceptable given the rarity of the disease.

The mean (SD) age was 4.6 (3.85) years and ranged from 1 to 15 years in the PFIC cohort and 1 to 17 in the Full Cohort. The mean body weight (min; max) at the time of study entry in the PFIC cohort was 16.31 kg (5.9; 44.3) and 16.7 kg (5.9; 53.0, 48.5 in the MRX treatment group) in the full cohort. Most participants (41 [64.1%]) were 1 to <6 years of age. Thus, the population was very young. No data were collected in the adults and even the number of adolescents was very limited (only 3 exposed to MRX in the PFIC cohort vs 1 on placebo).

Overall, the populations and treatment groups were fairly well balanced. Baseline values of pruritus, sBA, liver function parameters, and bile acid synthesis parameters showed various degrees of cholestasis, including moderate to severe cases. There were imbalances across the treatments in the FGF-19, FIB-4 and PELD. However, these are considered unlikely to have had major effects on the outcomes.

Overall, the populations in the PFIC cohort and Full cohort can be considered representative of the claimed indication in terms of disease characteristics. In terms of the age group the number of adolescents was very low and this group, as well as the adult population was under/not represented, respectively. The Applicant has provided justification for extrapolation of data from children to

adolescents/adults. Extrapolation is based on the similarity in the pathophysiology of the disease and in the mechanism of action of MRX. This is accepted.

Overall, rate of study discontinuation was low (6.3% in the PFIC and 7.5% in the Full Cohort), which is reassuring. Seven patients were considered to have major protocol violations related to use of forbidden medication. These patients were excluded from the PPS. This is agreed.

All but two patients reached the target dose, which suggests acceptable tolerability of the drug. Compliance was high (above 90%) which is also reassuring. The 2 patients not treated with maximum dose received 150 µg/kg BID and 450 µg/kg BID doses of MRX.

Primary and key secondary endpoints (improvement in pruritus evaluated by means of ItchRO(Obs) and reduction in sBA) showed significant improvement on MRX treatment compared to placebo and to baseline in the Primary and PFIC cohorts.

Multiple exploratory endpoints reflecting changes in pruritus and sBA (various scales used, responder definitions, calculation of days with mild or no pruritus, etc.) were consistent with the primary and secondary endpoints showing difference to placebo in the Primary and PFIC cohorts. These effects were seen soon after start of treatment reaching clinically relevant improvement at week 6 (which was end of the titration phase), that further improved till weeks 11-14 and remained stable during the 6 months treatment period.

Mean number of days with morning ItchRO(Obs) severity score $\leq$1, or the number of participants with morning ItchRO(Obs) severity score $\leq$1 for $\geq$50%, the number of responders, showed better efficacy on MRX compared to placebo.

In the maralixibat group of the PFIC cohort, 51.5% reached sBA thresholds found to be predictive of TFS beyond 15 years in patients with PFIC2 (average sBA level of <102 µmol/L OR at least a 75% average percent reduction, van Wessel et al. 2020).

Post hoc sensitivity analyses utilising various responder analyses for ItchRO(Obs) and sBA submitted with the responses to the first RSI showed consistently better responder rates on MRX compared to PLA.

All patient subgroups with various PFIC types showed either clinically and statistically significant, or only numerically relevant differences to placebo in reduction of pruritus measured with ItchRO(Obs) and of sBA. Difference to placebo did not reach significance levels in PFIC1 and PFIC3 for pruritus and PFIC3 and non-defined variant of PFIC for sBA. The Applicant explains this with small sample sizes which is accepted. A post hoc analysis conducted in the subpopulation with t-PFIC2 showed no relevant effects from the treatment with MRX. This was expected given the lack of BSEP function in this subpopulation. Respective warning is included in section 4.4 of the SmPC.

Sensitivity analyses for pruritus and sBA in various subgroups per age, sex, prior treatment with UDCA or rifampicin, etc., were conducted apparently in the primary cohort only and the numbers are too small and imbalanced e.g., (majority of subjects is in the age group of less than 6 years old), so that comparisons are difficult. However, no apparent differences can be spotted in the efficacy.

Reduction in bilirubin (total and direct) was observed on MRX. This reduction was significant when compared to placebo. The post hoc analyses of the biomarkers evaluating liver fibrosis, end-stage liver disease and synthesis of sBA are suggestive of stabilisation of the disease on MRX, while no such effect has been seen on PLA. Overall, these data suggest positive effects of MRX on liver and are supportive of the claimed indication. Notably, elevation of AST/ALT levels during the first months of treatment with MRX has been noted. However, it is agreed, that as it seems these parameters stabilise on prolonged treatment with MRX after 3-4 months as shown in post hoc analyses and with median

values. Based on individual patient listings some patients did not improve after the initial elevation in ALT/AST (and bilirubin). These patients also tended to achieve no, or insufficient reduction in sBA. Since such patients gain no benefit form MRX, but may be at increased risk of liver decompensation, continuous treatment with Livmarli is not recommended. Relevant recommendations and warnings that alternative treatment should be applied in the case of lack of efficacy of Livmarli (after 3 months of treatment) and that liver function should be monitored have been included in the PI (sections 4.2 and 4.4. of the SmPC).

Parameters evaluating quality of life, sleep, impression of severity showed improvement on treatment with MRX. Clinical relevance of these improvements (differences in the scores against placebo) is not fully clear. But consistency across the parameters is reassuring.

z-scores for weight and height improved on MRX, but not on placebo and may indeed suggest improved condition. The degree of improvement in the MRX-502 was small (about 0.5 scores change). However, the study duration was not long enough to allow the detection of true differences to placebo. These changes are reassuring.

Changes in C4 and autotaxin support the clinical effects resulted from treatment of MRX.

A post hoc analysis of efficacy in Full Cohort was submitted with the responses to the first RSI. The data are consistent with those from the PFIC cohort. Positive effects of MRX on pruritus, sBA, bilirubin (total and direct), growth, quality of life, fatigue, and sleep, whereas no effects, worsening or smaller improvements were observed on placebo. Fibrosis parameters show general trends towards improvement or stabilisation on MRX, whereas on placebo no such trends or worsening was observed. It is noted that the calculated mean values of fibrosis parameters are highly variable across visits. Increase in the levels of ALT on MRX was observed in the Full cohort as well and was similar to that in the PFIC cohort. Generally, these analyses support efficacy of MRX in reduction of pruritus and cholestasis in the broader PFIC population.

To summarise, overall, the presented data on efficacy are considered supportive of the claimed indication with regards to the patient population 1 year of age and older.

MRX-503

The study had 2 objectives: to show that the patients switched from placebo to MRX have similar effects from MRX as those in the previous study (MRX-502) and to demonstrate maintenance of effects over a prolonged treatment period. The first objective can be considered achieved, as patients that switched from placebo showed improvement in pruritus, sBA and bilirubin (to smaller extent) on short-term treatment with MRX. With respect to the long-term treatment effects (e.g., on growth parameters) and maintenance of effects (i.e., effects on pruritus, sBa, bilirubin, etc.), the conclusions made by the Applicant cannot be supported due to the quickly decreasing numbers of patients after the first 2-3 months in the study, mostly related to the early timing of the interim analysis. The same applies to the conclusions made regarding the growth and any other parameters. Further, a number of relevant efficacy parameters like, quality of life, impact on health care utilisation, caregiver burden, etc. were, obviously, not analysed.

To gain more clarity on the maintenance of effects and the long-term effects of MRX treatment, the Applicant has provided updated interim analyses. Generally, positive changes in the relevant parameters seem to be maintained on long-term treatment with MRX (i.e., up-to week 58, when the number of patients was relatively constant). However, it has been noted that the number of patients evaluated over long-term treatment period is lower than the full set in the cohorts. It seems that some patients were not included in these analyses. Also, possible confounders (e.g., concomitant medications) have not been adequately discussed. Therefore, the conclusion remains somewhat

tentative. At least no worsening was seen at the group level judging from the presented evidence, which is reassuring, as in this population worsening in various parameters would normally be expected to be seen.

Changes in the levels of FGF-19, C4, liver fibrosis parameters and PELD were consistent with the observations in the MRX-502 study.

Reduction in the level of Autotaxin is consistent with the changes in pruritus.

Liver function parameters, such as ALT, AST, etc. appear to improve after initial increase. However, the data may be confounded.

With the responses to the second RSI, updated data on liver-associated events was provided. Overall number of liver-associated events (14/47 patients, 30%) and of the cases of surgical treatments (6/47 – 13%) seems high for the age group tested (majority of patients was younger than 5 years of age at the time of event). However, these events seem to be roughly consistent with observations by van Wessel et al., 2020, who reported the median native liver survival in the patients with PFIC2, i.e., BSEP1, BSEP2 and BSEP3 of 10, 7 and 3.5 years, respectively, with 4% of BSEP1 (n = 3/72), 6% of BSEP2 (n = 8/136), and 9% of BSEP3 (n = 5/56) dying prior to LT at a mean age of 1.6 years (1.1–3.5 years). The Applicant has not provided analysis against an external data (e.g., NAPPED - the NAtural course and Prognosis of PFIC and Effect of biliary Diversion consortium, that represents the largest registry for PFIC1 and PFIC2 population). This analysis will be submitted post approval after completion of ongoing studies, including MRX-503.Notably, all but one patient with liver-related events was sBA non-responder and the reason for surgical treatment (undergoing or considering) was worsening of pruritus, increased levels of bilirubin, worsening of cirrhosis/decompensation, etc. The earliest event leading to the listing for liver transplant is at day 97 of treatment. The remaining events occurred >200 days on MRX treatment. Late time-to-event is not suggestive of PG-toxicity as possible cause/contributor. Negative effect through MRX (possible liver toxicity) is unlikely in almost all cases. In two patients causal relationship cannot be fully excluded. However, gaining of additional certainty through request of additional information does not seem realistic currently. A low-intervention clinical study with prospective collection of data on treatment with Livmarli and external and/or historical comparison (NAPPED) is planned in the post-approval phase (see the RMP and section 2.6). Also, pooled analysis with patients with PFIC from the completed studies is being requested. Both studies/analyses will evaluate long-term clinical outcomes against an external/historic comparator.

MRX-801

An updated data-set on treatment with MRX in 10 patients aged 1 month to 12 months (5 patients < 6 months and 5 patients 6-12 months old) at the study entry suffering from PFIC (7- PFIC2, 2- PFIC1 and 1 – PFIC3) has been provided with the responses to the RSI. The size of the studied population given the orphan status of the disease and the age group is acceptable.

The studied infants do not cover the whole range of PFIC types, but in regards of the characteristics of the disease (elevated levels of sBA, bilirubin, ALT, AST) are representative of the target population. The clinical picture, symptoms and signs of PFIC in the study population indicate that there is indeed a need in early start of treatment.

Median duration of exposure was around 8.5 months and is considered acceptable, but long-term safety and efficacy data need to be generated post-marketing.

Similarly low (<1%) bioavailability can be assumed in the patients from 3 months to 12 months of age as in >1 year olds. No relevant PK information is available in the patients below 3 months of age.

Serum BA and bilirubin reduction (mean values) was observed on MRX, that was roughly similar to the changes reported in older populations. No major changes in transaminases were seen in the study, apart from one case when increase in ALT and AST was reported in the 1-month patient. Inconsistent results in growth parameters with somewhat better outcomes for weight-z scores were reported, but this is not surprising, given the limited duration of the observation period (13 weeks).

Improvement in pruritus was observed in 2 (from baseline of 1 point in one case) out of 7 patients with pruritus at baseline, which is somewhat lower than the response rate observed in older children. However, it is agreed that assessment of pruritus in infants is difficult. Two patients developed pruritus during the study that indicates that pathophysiological processes of the disease are ongoing in this age group and full clinical picture manifests later in some infants. It is apparent that treatment with MRX did not prevent development of pruritus in these patients.

To summarise,

- The study population can be considered representative of the target indication (infants).
- Insufficient data are available in patients below the age of 3 months. Only one patient of 1 month of age was included, who was withdrawn due to an AE.
- Efficacy parameters do not show straightforward results and are difficult to interpret. However, effects on sBA and bilirubin are apparent in some patients and it is agreed that, together with the similarity in pathophysiology of the disease and mechanism of action of MRX, efficacy can be extrapolated from older patients.
- Safety information is limited and the safety profile not fully characterised. However, the PG-related concerns have been addressed by restricting the dose of Livmarli in infants and children below the age of 5 years, i.e., the patients at increased risk to have PG accumulation and to develop PG-related toxicity due to physiological immaturity of liver/alcohol dehydrogenase potentially combined with impaired liver function due to their disease. The dose reduction limits PG exposure to a maximum of 26 mg/kg/day for which safety data from clinical studies are available. Otherwise, extrapolation of safety from older population seems plausible. Although, data remain not comprehensive and post-approval collection of safety data to address the concerns related to possible risk of hepatotoxicity, chronic risks through PG exposure, etc. is planned (see the RMP)

Insufficient data were available in patients below the age of 3 months. Only one patient of 1 month of age was included who was withdrawn during titration due to an AE. Overall, data support the indication "treatment of PFIC in the patients 3 months of age and older". The applicant agreed to revise their claimed indication accordingly from 3 months. Post-approval measures to collect additional safety information and data on long-term clinical outcomes are required and have been agreed with the applicant.

Post-approval collection of data on long-term clinical outcomes

MRX-803 study was agreed by the MAH and added as Specific Obligation (category 2 study) to the RMP and to Annex II to meet the requirements for post-approval data collection and specific obligation (SOB) for both ALGS and PFIC populations. This study will replace the previously agreed SOBs MRX-311 and an open-ended SOB as soon as the protocol for MRX-803 is submitted and agreed.

MRX-311 study: In order to avoid further delay in start of the LEAP EU study (MRX-311), the Applicant agrees that adaptations related to inclusion of PFIC population will be introduced via a separate variation procedure/amendment

MRX-803 study (PFIC cohort):

- The study will be conducted as a low-intervention clinical study (as defined in the article 2 (2)(3) of the Clinical Trials Regulation and discussed in the EMA Q&A document - https://www.ema.europa.eu/en/documents/other/faqs-introduction-clinical-trials-regulation-eu-no-5362014-ctis-training-programme-module-01_en.pdf). Such study will allow to ensure compliance with GCP standards, including proper monitoring of data collection and of their quality.
- Use of natural history registry data for external/historical reference is agreed. In addition, retrospective data in the same sites from the patients not treated with MRX should will also be collected.
- The study does not have to be limited to European sites and recruitment can be extended to other regions. Further, the study will include new patients as well as be used to roll-over the patients with PFIC from the MRX-503, MRX-800 and MRX-801 to collect long-term data on clinical outcomes.
- Feasibility report, including the estimated recruitment rate and timelines will be submitted within 3 months from the end of this procedure, study protocol - within 6 months and statistical analysis plan – within 6 months from the study start.
- Interim report is to be submitted 5 years from the study start.

MRX-502 combined with MRX-503, LUM001-501, MRX-800, and MRX-801 studies (PFIC population) will be analysed for liver-related events and compared to historical reference. The analysis will be submitted in Q2 2025 together with the final reports of the ongoing MRX-503 and MRX-801 studies.

Please also refer to the adopted Risk Management Plan.

2.4.4. Conclusions on the clinical efficacy

The presented data are considered supportive of the claimed indication on "treatment of PFIC". Extrapolation of efficacy data to adolescent and adults is accepted. Extrapolation of efficacy data to infants from 3 months of age is acceptable. Further collection of efficacy data regarding long-term clinical outcomes such as hepatic transplantation, progression of the disease, liver decompensation, death, etc., is necessary in the post-marketing phase. Additional data on pruritus, growth, etc. will be collected. The Applicant agreed to provide a feasibility report, including the estimated recruitment rate and timelines, within 3 months and a comprehensive study protocol within 6 months of the end of this procedure.

2.5. Clinical safety

Introduction

This variation application for a new indication is based on results from studies MRX-502, LUM001-501, MRX-503, MRX-800 and MRX-801.

Safety assessment is based on data from participants with PFIC in the double-blind, placebo controlled pivotal study (MRX-502) and an open-label Phase 2 study (LUM001-501) and the extension Studies MRX-503 and MRX-800 providing long-term safety for maralixibat in participants with PFIC.

The ongoing study MRX-801 characterize the safety profile in infants <12 months of age with PFIC.

Safety information provided for this procedure focus primarily on data from pediatric participants with PFIC who received maralixibat in Study MRX-502, a completed Phase 3 multicenter study, and MRX-503,

an ongoing LTE study of participants who completed Study MRX-502. [Unless otherwise specified, discussion of safety data for Study MRX-502 within this document is focused on the full cohort (overall N=93).]

The applicant clarified that maralixibat safety data discussed for LTE Study MRX-503 are cumulative and include TEAEs reported in participants randomized to maralixibat during Study MRX-502 and TEAEs reported during the open-label Study MRX-503, through the data cutoff date of 23 June 2022.

- Participants who were assigned placebo during Study MRX-502 and received maralixibat in Study MRX-503 are grouped as PBO-MRX.
- Participants who were assigned maralixibat during Study MRX-502 (regardless of whether the participant continued in Study MRX-503) are grouped as MRX-MRX.

TEAEs for participants in MRX-MRX in Study MRX-503 could have started during Study MRX-502 or Study MRX-503.

The doses described in this document are of maralixibat chloride and are presented as "maralixibat." For example, 600 µg/kg maralixibat chloride is equivalent to 570 µg/kg maralixibat and will be referred to as 600 µg/kg maralixibat.

Patient exposure

Maralixibat is reported to have been studied in >1700 participants, including >280 pediatric or adult participants with cholestatic liver disease.

As of 23 June 2022, a total of 238 pediatric participants with cholestatic liver disease (ALGS [n=95], **PFIC [n=134]**, or biliary atresia [n=9]) have been exposed to maralixibat during the clinical development program. Duration of dosing has been over 7 years for participants with PFIC who have enrolled in long-term studies.

Exposure reported in the trials (as of 22 June 2022):

MRX-502: There were 93 participants enrolled in the study (47 participants in maralixibat arm and 46 participants in the placebo arm). This study was followed by an extension study (MRX-503), during which all participants who completed Study MRX-502 had the opportunity to be treated long term with maralixibat. In the full cohort, the mean (SD) maralixibat treatment duration was 177.1 (36.57) days (range: 12–256 days). A total of 45 of 47 (95.7%) study participants who received maralixibat dose escalated to the maximum maralixibat dose of 600 µg/kg BID.

In the PFIC cohort, the mean (SD) treatment duration was 184.4 (18.77) days (range: 108-256 days).

Table 29 Maralixibat Exposure (Safety Population) in the pivotal trial MRX-502

Variable Statistic	Primary Cohort (N=14)	PFIC Cohort (N=33)	Full Cohort (N=47)
Treatment duration, in days			
Mean	178.9	184.4	177.1
SD (SE)	20.69 (5.53)	18.77 (3.27)	36.57 (5.33)
Median	183.0	183.0	183.0
Q1, Q3	182.0, 185.0	183.0, 186.0	182.0, 187.0
Min, max	108, 193	108, 256	12, 256

Treatment exposure, in days			
Mean	177.1	180.8	174.1
SD (SE)	20.71 (5.53)	14.25 (2.48)	35.01 (5.11)
Median	182.5	183.0	183.0
Q1, Q3	181.0, 185.0	182.0, 186.0	181.0, 186.0
Min, max	108, 192	108, 192	10, 203

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

MRX-503: As of the data cutoff (23 June 2022) for Study MRX-503, 74 participants had transitioned from Study MRX-502 to Study MRX-503: 36 had received maralixibat in Study MRX-502, and 38 had received placebo in Study MRX-502.

In all maralixibat-treated participants, the mean (SD) average daily dose was 980.51 (182.494) µg/kg/day with mean (SD) maralixibat exposure of 340.2 (204.91) days; 68 of 74 participants (91.89%) dose-escalated to the maximum dose of 600 µg/kg BID.

Participants in the MRX-MRX group had mean (SD) maralixibat exposure of 385.5 (204.95) days, of which 177.1 (36.57) days occurred in the antecedent Study MRX-502.

MRX-801: As of the interim CSR (data cutoff of 23 June 2022), there were 4 participants with PFIC enrolled who received 600 µg/kg BID. In the 4 participants included in the interim CSR, the overall mean (SD) duration of treatment was 121.0 (34.03) days and ranged from 93 to 162 days. With the updated interim analysis (data cutoff of 28 June 2023) data in further 6 patients were provided. Median duration of exposure was around 8.5 months in the updated data-set.

LUM001-501: A total of 33 participants were enrolled in Study LUM001-501. During the study period, the mean (SE) daily dose for the overall study population was 292.6 (14.52) µg/kg/day, and the mean (SE) treatment duration was 1,019.0 (121.92) days. Nearly half of the participants (16 [48.5%]) had a treatment duration of at least 124 weeks.

MRX-800: As of the interim CSR (data cutoff of 01 January 2022), there were 12 participants with PFIC enrolled who received either 300 µg/kg/day (4 participants) or 600 µg/kg/day (8 participants). All participants with PFIC in Study MRX-800 had been treated with maralixibat in the earlier maralixibat Study LUM001-501; the average exposure to maralixibat prior to entering Study MRX-800 (MRX-800 baseline) was 5.059 years (maximum exposure 5.50 years). The average exposure to maralixibat in Study MRX-800 was 1.68 years (612.3 days), with a maximum exposure of 1.95 years (711 days). Participants with PFIC received maralixibat doses in Study MRX-800 with a range of 300 µg/kg QD to 600 µg/kg BID.

(For discussion of demographics in these trials please refer to the relevant section of the efficacy part in the AR.)

Exposure to propylene glycol:

All patients were exposed to similar amount of PG of up-to 26 mg/kg/day, those randomized to MRX and those receiving placebo. Of note, post-approval exposure of up-to 50 mg/kg/day is expected that

is consistent with the currently defined threshold of safety in the patients without hepatic and renal diseases and below 5 years of age (EMA/CHMP/704195/2013).

Adverse events

Table 30 Overall Summary of Treatment-Emergent Adverse Events (Safety Population) and TEAEs in at Least 5% of All Maralixibat-Treated Participants-by Preferred Term (Safety Population) in the pivotal trial MRX-502

	No. (%) of Participants with ≥1 Treatment Emergent					
	Primary Cohort		**PFIC Cohort**		**Full Cohort**	
	Maralixibat (N=14)	**Placebo (N=17)**	**Maralixibat (N=33)**	**Placebo (N=31)**	**Maralixibat (N=47)**	**Placebo (N=46)**
Adverse event	14(100.0)	16(94.1)	33(100.0)	30(96.8)	47(100.0)	43(93.5)
Adverse event categorized as severe	1 (7.1)	1 (5.9)	1 (3.0)	1 (3.2)	3 (6.4)	3 (6.5)
Adverse event related to study drug	5 (35.7)	2 (11.8)	12 (36.4)	2 (6.5)	18 (38.3)	2 (4.3)
Adverse event categorized as severe and related to study drug	0	0	0	0	0	0
Serious adverse event	3 (21.4)	1 (5.9)	3 (9.1)	3 (9.7)	5 (10.6)	3 (6.5)
Serious adverse event related to study drug	1 (7.1)	0	1 (3.0)	0	1 (2.1)	0
Adverse event that led to permanent study drug discontinuation	0	0	0	0	1 (2.1)	0
Adverse event resulting in death	0	0	0	0	0	0
TEAEs in at Least 5% of All Maralixibat-Treated Participants-by Preferred Term (Safety Population)						
With ≥1 TEAE	14 (100.0)	16 (94.1)	33 (100.0)	30 (96.8)	47 (100.0)	43 (93.5)
Abdominal pain	3 (21.4)	2 (11.8)	8 (24.2)	2 (6.5)	10 (21.3)	3 (6.5)
Alanine aminotransferase increased	2 (14.3)	3 (17.6)	4 (12.1)	3 (9.7)	6 (12.8)	3 (6.5)
Blood bilirubin increased	3 (21.4)	3 (17.6)	5 (15.2)	4 (12.9)	7 (14.9)	4 (8.7)
Constipation	2 (14.3)	1 (5.9)	4 (12.1)	2 (6.5)	4 (8.5)	2 (4.3)
Coronavirus infection	2 (14.3)	2 (11.8)	2 (6.1)	2 (6.5)	3 (6.4)	4 (8.7)
Cough	2 (14.3)	2 (11.8)	5 (15.2)	3 (9.7)	7 (14.9)	5 (10.9)
Diarrhoea	8 (57.1)	3 (17.6)	19 (57.6)	5 (16.1)	27 (57.4)	9 (19.6)
Gastroenteritis	1 (7.1)	1 (5.9)	2 (6.1)	2 (6.5)	3 (6.4)	2 (4.3)

Haematochezia	1 (7.1)	1 (5.9)	2 (6.1)	1 (3.2)	3 (6.4)	1 (2.2)
Headache	2 (14.3)		3 (9.1)		3 (6.4)	
Influenza	3 (21.4)		6 (18.2)	1 (3.2)	6 (12.8)	2 (4.3)
Nasopharyngitis	1 (7.1)	1 (5.9)	4 (12.1)	1 (3.2)	5 (10.6)	2 (4.3)
Pruritus	2 (14.3)	3 (17.6)	4 (12.1)	5 (16.1)	5 (10.6)	8 (17.4)
Pyrexia	7 (50.0)	1 (5.9)	15 (45.5)	9 (29.0)	17 (36.2)	13 (28.3)
Rhinorrhoea	2 (14.3)	2 (11.8)	7 (21.2)	4 (12.9)	8 (17.0)	5 (10.9)
Upper respiratory tract infection		2 (11.8)	1 (3.0)	2 (6.5)	3 (6.4)	6 (13.0)
Urinary tract infection	2 (14.3)		2 (6.1)	1 (3.2)	3 (6.4)	1 (2.2)
Viral upper respiratory tract infection			1 (3.0)		3 (6.4)	1 (2.2)
Vitamin D decreased		1 (5.9)	2 (6.1)	2 (6.5)	4 (8.5)	2 (4.3)
Vitamin D deficiency		1 (5.9)	2 (6.1)	3 (9.7)	4 (8.5)	4 (8.7)
Vitamin E decreased			2 (6.1)	2 (6.5)	4 (8.5)	3 (6.5)
Vitamin E deficiency		1 (5.9)	2 (6.1)	2 (6.5)	3 (6.4)	4 (8.7)
Vomiting	2 (14.3)	4 (23.5)	3 (9.1)	5 (16.1)	3 (6.4)	5 (10.9)

AE=adverse event; EOT=end of treatment; MedDRA=Medical Dictionary for Regulatory Activities; PFIC=progressive familial intrahepatic cholestasis; TEAE=treatment-emergent AE.
Notes: Percentages are 100*n/N. AEs were coded using MedDRA Version 22.1. Participants who reported >1 AE within each category were only counted once. A TEAE is defined as an AE that starts or deteriorates on or after the first dose of study drug and no later than 7 days following the last dose of study drug in Study MRX-502 (for participants who did not participate in the extension study) or reported through the Week 26/EOT visit (for participants who did not participate in the extension study). For participants with >7 days of study drug interruption/withdrawal, the definition of a TEAE considers both the date of the last dose prior to drug interruption and the actual last dose.

For the full cohort:

- The proportion of participants with TEAEs was slightly higher in the maralixibat arm (100%) compared with the placebo (93.5%) treatment group.
- For all maralixibat-treated participants, the most common TEAEs occurred in the SOC of Gastrointestinal disorders (74.5%). For all placebo-treated participants, the most common TEAEs occurred in the SOCs of Infections and infestations (54.3%).
- For all maralixibat-treated participants, the most common TEAEs by preferred term included diarrhoea (57.4%), pyrexia (36.2%), and abdominal pain (21.3%). For all placebo-treated participants, the most common TEAEs by preferred term included pyrexia (28.3%), diarrhoea (19.6%), and pruritus (17.4%).
- The proportion of participants with severe TEAEs was similar between maralixibat (6.4%) and placebo (6.5%) treatment groups.
- Although rates were similar, a slightly greater proportion of maralixibat (10.6%) than placebo (6.5%) participants had treatment-emergent SAEs.

- No participant had a TEAE categorized as severe and related to study drug or had a TEAE resulting in death.

Treatment-Related Treatment-Emergent Adverse Events

For all maralixibat-treated participants, the most common treatment-related TEAEs included diarrhoea (13 participants [27.7%]), abdominal pain and blood bilirubin increased (3 participants [6.4%] each; Table 29).

For all placebo-treated participants, no treatment-related TEAE occurred in >1 participant; treatment-related TEAEs included vomiting and diarrhoea (1 participant each).

Table 31 Summary of Treatment-Related Treatment-Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term	No. (%) of Participants with ≥1 Treatment-Emergent					
	Primary Cohort		PFIC Cohort		Full Cohort	
	Mara-lixibat (N=14)	Placebo (N=17)	Mara-lixibat (N=33)	Placebo (N=31)	Mara-lixibat (N=47)	Placebo (N=46)
With ≥1 TEAE	5 (35.7)	2 (11.8)	12 (36.4)	2 (6.5)	18 (38.3)	2 (4.3)
Gastrointestinal disorders	4 (28.6)	2 (11.8)	9 (27.3)	2 (6.5)	14 (29.8)	2 (4.3)
Diarrhoea	3 (21.4)	1 (5.9)	8 (24.2)	1 (3.2)	13 (27.7)	1 (2.2)
Abdominal pain	1 (7.1)		2 (6.1)		3 (6.4)	
Vomiting		1 (5.9)	1 (3.0)	1 (3.2)	1 (2.1)	1 (2.2)
Faeces soft	1 (7.1)		1 (3.0)		1 (2.1)	
Frequent bowel movements			1 (3.0)		1 (2.1)	
Haematochezia			1 (3.0)		1 (2.1)	
General disorders and administration site conditions			1 (3.0)		1 (2.1)	
Gait disturbance			1 (3.0)		1 (2.1)	
Investigations	2 (14.3)		4 (12.1)		5 (10.6)	
Blood bilirubin increased	2 (14.3)		2 (6.1)		3 (6.4)	
Alanine aminotransferase increased			1 (3.0)		1 (2.1)	
Gamma-glutamyltransferase increased			1 (3.0)		1 (2.1)	
Hepatic enzyme increased			1 (3.0)		1 (2.1)	
Transaminases increased					1 (2.1)	
Metabolism and nutrition disorders			1 (3.0)		1 (2.1)	
Vitamin E deficiency			1 (3.0)		1 (2.1)	
Respiratory, thoracic and mediastinal disorders					1 (2.1)	
Throat irritation					1 (2.1)	

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PFIC=progressive familial intrahepatic cholestasis; TEAE=treatment-emergent AE.
Notes: Percentages are 100*n/N. AEs were coded using MedDRA Version 22.1. At each level of summarization (System Organ Class and Preferred Term), participants who reported >1 AE were only counted once.

Adverse events of special interest

The applicant reports that no clinically relevant changes from baseline to postbaseline or differences between treatment groups for chemistry laboratory parameters were observed in this trial.

Based on this analysis of the pivotal safety population in Study MRX-502 (n=93), transaminase increases, FSV deficiencies, bleeding events, and fractures are unlikely to be risks associated with maralixibat.

Regarding a beneficial effect (i.e., improvement) in bilirubin levels, with normalization of bilirubin in responders, claimed for maralixibat please refer to the efficacy assessment of this AR.

Effects on Transaminases

In general, for patients with PFIC, abnormal liver enzymes vary by PFIC type; for PFIC1, approximately 70% have abnormal ALT at baseline, and for PFIC2, approximately 95% are abnormal at baseline (Sakita et al. 2018).

In the full cohort of Study MRX-502, 8 maralixibat participants (17%) and 3 placebo participants (6.5%) had elevated transaminases events. None of the events of elevated transaminases were considered serious, all were mild or moderate in severity (nonsevere), most events of elevated transaminases were not considered treatment related, and no events of elevated transaminases led to discontinuation of study drug. There were no trends noted in terms of latency or timing of event relative to the first dose of maralixibat. No dose-response relationship was detected.

Upon further review of the individual participant data, 6 of 8 participants with transaminase increased had no change in dose, and the majority of events (4 of 6) resolved with continued dosing in all participants except for two. These two participants had dose interruptions or reductions, with subsequent re-challenge to full dose of study drug without resolution or worsening of the event and without clinical sequalae, supporting a negative rechallenge. The remaining 6 out of 8 participants had confounders such as medical history (e.g., hepatitis A, CMV, etc.) or concurrent medications known to cause liver enzyme elevation (e.g., paracetamol, phenobarbital, montelukast, etc.) Importantly, there have been no DILI events observed to date in Study MRX-502 or Study MRX-503.

In summary, although subjective AE reporting of transaminase events was numerically higher in the maralixibat arm, for objective transaminase laboratory data, no clinically meaningful differences were observed between maralixibat and placebo for CFB at any time point in the overall study population. Furthermore, for the PFIC cohort, an MMRM analysis showed no clinically or statistically significant differences in ALT or AST between maralixibat and placebo. Elevations that occurred in the 8 individuals spontaneously resolved in the majority of participants. There were no discontinuations associated with elevated liver enzymes with maralixibat, and no DILI events were reported. The above observations and analyses suggest that maralixibat does not cause increased transaminases as such events are likely to be driven by underlying PFIC.

Post hoc analyses of ALT/AST show that ALT/AST increase in part of the MRX-treated population. Majority of the patients recover their baseline levels of ALT/AST after several weeks, but some retain elevated ALT/AST. In the recent PSUSA procedure (Procedure no.: EMEA/H/C/PSUSA/00011032/202309 from March 2024), the MAH provided a cumulative review regarding hepatotoxicity. Based on the gathered data the following adverse reactions were included into the SmPC: ALT increased, and AST increased under the SOC: Hepatobiliary disorders with a frequency common.

Effects on Bilirubin

In the analysis of pooled PTs related to bilirubin (Hyperbilirubinaemia, Blood bilirubin increased), the proportion of participants with events on maralixibat was lower than those on placebo (14.9% vs.19.6%; see Table 3).

MMRM-based analyses of total and direct bilirubin as prespecified exploratory efficacy endpoints demonstrated improvements in both parameters within the primary and PFIC cohorts between baseline and Weeks 18-26 (ITT Population) in Study MRX-502. For the PFIC cohort, the proportion of participants with elevated total bilirubin (i.e., >ULN at baseline) who normalized by Week 26 (≤ULN) was 40% (10/25) for maralixibat versus 0% (0/18) for placebo. For the All-Participants cohort (N=93), 21.3% of participants on maralixibat had a baseline bilirubin >ULN, which was normal at Week 26, versus 0% of such participants on placebo.

Effects on Fat-Soluble Vitamins

Clinically evident vitamin deficiencies, including coagulopathy, are common in PFIC and generally considered a core feature of the disease. At presentation in infancy, up to 20% of PFIC (depending on type) may have FSV deficiency; 8% may have coagulopathy at presentation (Alam and Lal 2022). In cholestatic disease, levels of bile acids in the intestinal lumen are lower than normal, and the systemic bile acid pool is increased (elevated serum bile acids) because bile flow is impaired. If intestinal bile acid levels fall below the critical micelle concentrations, their role in solubilization of fats to promote their absorption, and the subsequent absorption of FSVs can be reduced (Chiang 2013). With consideration of the role of intraluminal bile acids in FSV absorption, it is plausible that increased bile acid detergents in the small intestine with IBAT inhibition could help solubilize fats and potentially help their absorption.

In the analysis of pooled PTs for fat soluble vitamin deficiency (Vitamin A decreased, Vitamin A deficiency, Vitamin D decreased, Vitamin D deficiency, Vitamin E decreased, Vitamin E deficiency, Vitamin K deficiency, Activated partial thromboplastin time prolonged, Blood 25 hydroxycholecalciferol decreased, International normalized ratio increased, Prothrombin time abnormal, and Prothrombin time prolonged; the proportion of participants on maralixibat with events was lower than those on placebo (27.7% vs. 34.8%) indicating that maralixibat does not worsen FSV deficiencies. Additionally, review of laboratory data for all FSVs (vitamins A, D, E and PT/INR) revealed no clinically meaningful changes from baseline with one notable exception–the mean change from baseline for INR in maralixibat-treated participants was negative (i.e., decreased/improved) at every time-point assessed, with a mean change in INR of -0.301 at Week 26 for maralixibat (vs. -0.025 for placebo). Thus, there is no evidence to suggest that maralixibat contributes to FSV deficiency.

Bleeding Events

In the analysis of pooled PTs of Haematochezia and Rectal haemorrhage, the proportion of participants on maralixibat with lower GI bleeding events was higher than those on placebo (8.5% vs. 2.2%). The etiology of lower GI bleeding is multifactorial, and in each of the 4 maralixibat-treated participants with lower GI bleeding, a clear alternative etiology was identified upon a participant-level review, making it unlikely that maralixibat plays a causal role in such events. All events of hematochezia had other explanations for the GI bleeding and lasted for 1 day and resolved without intervention, which is not what would be expected if the hematochezia was attributable to maralixibat.

4 patients continued dosing with maralixibat in the long-term extension Study MRX-503 without recurrence of the GI bleeding. Importantly, INRs in all cases were stable from baseline.

Although the most likely potential mechanism for IBAT inhibition to cause bleeding events in general, including lower GI bleeding, would be through FSV deficiency (specifically, vitamin K deficiency leading to INR increases), all participants with hematochezia had normal or near-normal INR at the time of the bleeding event and did not demonstrate clinically meaningful increases in INR while on maralixibat; in fact, the mean change from baseline for INR in maralixibat-treated participants was negative (i.e., decreased/improved) at every timepoint assessed, with a mean change in INR of -0.301 at Week 26 for maralixibat (vs. -0.025 for placebo). Furthermore, INR levels just prior to the bleeding events for the 4 participants ranged from 0.98 to 1.23, which are not elevated enough to be associated with risk for bleeding events. Review of the incidence of vitamin K deficiency AEs also shows that these events are more prevalent in the placebo group (10.9%) than in the maralixibat group (4.3%). Additionally, placebo-controlled data from Study MRX-502 and epidemiological data suggest it is more likely that FSV deficiency in the PFIC population is due to the underlying disease instead of attributable to drug as there were more events observed in the placebo group.

Given the totality of evidence provided in this variation, it is unlikely that maralixibat causes bleeding events.

Fractures

The effect of cholestasis on bone metabolism has been studied previously in vitro and in vivo by Ruiz-Gaspa et al. (2011) who treated human primary osteoblasts with bilirubin or serum from jaundiced patients. The study showed decreased osteoblast viability and differentiation and reduced expression of osteogenic transcription factors and up-regulation of factors inducing osteoclastogenesis (Loomes et al. 2019). These results support the deleterious consequences of increased bilirubin in advanced chronic cholestasis and in end-stage liver diseases, resulting in disturbed bone formation related to osteoblast dysfunction. (Ruiz-Gaspa et al. 2011).

In the analysis of PTs of Femur fracture, Lower limb fracture, Radius fracture, and Ulna fracture, the proportion of participants on maralixibat with fracture events was higher than those on placebo (6.4% vs. 0%). However, the etiology of fractures is multifactorial, and in each of the 3 maralixibat-treated participants with fractures, a clear alternative etiology such as trauma was identified upon a participant-level review, making it unlikely that maralixibat plays a causal role in such events. All 3 fractures were deemed not related to maralixibat by the treating physicians, and none required changes to maralixibat dosing.

Additionally, all 3 participants with fractures had low vitamin D levels at baseline (i.e., prior to initiation of maralixibat) ranging between 11–15 ng/ml (standard reference range: 20–100 ng/ml) consistent with epidemiological data demonstrating that clinically evident vitamin deficiencies, including fractures, are common in PFIC and considered a core feature of the disease. At presentation in infancy, up to 20% of patients with PFIC (depending on type) may have FSV deficiency, and 3%–22% may have rickets at presentation. In one article looking at osteopenia/rickets in chronic liver disease (including PFIC), it was noted that that 42% of PFIC cases had osteopenia (Samra et al. 2018).

A hypothetical mechanism for IBAT inhibition to cause fractures could be through FSV deficiency (specifically, exacerbation of Vitamin D deficiency). However, review of vitamin D levels over time (including around the time of the fracture events) for each participant demonstrated stable or improved levels relative to baseline, with supplementation of vitamin D increased in only 1 participant who had a medical history of pre-existing malnutrition. Overall, there was no clinically meaningful difference in mean or median change from baseline in vitamin D levels over time, between maralixibat and placebo participants. These placebo-controlled data from Study MRX-502 and epidemiological data suggest it is more likely that FSV deficiency in the PFIC population is due to the underlying disease instead of attributable to drug, and therefore, unlikely that maralixibat is related to events of fractures.

Serious adverse event/deaths/other significant events

Serious Adverse Events by Study

Pivotal Study MRX-502

For the full cohort, 5 maralixibat participants (10.6%) and 3 placebo participants (6.5%) had treatment-emergent SAEs (Table). For maralixibat participants, the most common treatment-emergent SAE was urinary tract infection (2 participants [4.3%]), while no treatment-emergent SAE occurred in >1 placebo participant.

Most treatment-emergent SAEs were considered not treatment related; only 1 treatment-emergent SAE was considered treatment related (blood bilirubin increased, mild in severity, primary cohort

maralixibat participant). Most treatment-emergent SAEs were moderate in severity. Most SAEs had study drug action taken of dose not changed, and all SAEs resolved.

Treatment-emergent SAEs in the primary and PFIC cohorts in the pivotal trial MRX-502 are summarized in Table below.

Table 32 Summary of Treatment-Emergent Serious Adverse Events (Safety Population; Study MRX-502 Full Cohort)

System Organ Class Preferred Term	No. (%) of Participants	
	Maralixibat (N=47)	**Placebo (N=46)**
With ≥1 treatment-emergent SAE	5 (10.6)	3 (6.5)
Blood and lymphatic system disorders		
Coagulopathy	0	1 (2.2)
Gastrointestinal disorders		
Constipation	1 (2.1)	0
Hepatobiliary disorders		
Cholestasis	1 (2.1)	0
Infections and infestations		
Urinary tract infection	2 (4.3)	0
Gastroenteritis viral	0	1 (2.2)
Injury, poisoning, and procedural complications		
Accidental exposure to product	0	1 (2.2)
Investigations		
Blood bilirubin increased	1 (2.1)	0
Metabolism and nutrition disorders		
Vitamin K deficiency	0	1 (2.2)
Nervous system disorders		
Seizure	0	1 (2.2)
Respiratory, thoracic, and mediastinal disorders		
Idiopathic pneumonia syndrome	1 (2.1)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PFIC=progressive familial intrahepatic cholestasis; SAE=serious adverse event.
Notes: Percentages are 100*n/N. AEs were coded using MedDRA Version 22.1. At each level of summarization (System Organ Class and Preferred Term), participants who reported >1 AE were counted only once. Source: Table 14.3.3.1.

Study MRX-503

Unless otherwise specified, the safety data discussed for Study MRX-503 are cumulative (i.e., includes all SAEs reported while receiving maralixibat treatment during Study MRX-502, regardless of whether the participant continued on Study MRX-503, and SAEs reported during Study MRX-503 that started on or before the data cutoff of 23 June 2022).

Overall, 14 participants (16.5%) had treatment-emergent SAEs, inclusive of SAEs which occurred during MRX-502. For all participants, the most common treatment-emergent SAE was gastroenteritis (3 participants [3.5%]).

For participants in the MRX-MRX group, with longer mean exposure to maralixibat, the most common treatment-emergent SAE was urinary tract infection (2 participants [4.3%]).

For participants in the PBO-MRX group, with first exposure to maralixibat in Study MRX-503, the most common treatment-emergent SAE was gastroenteritis (2 participants [5.3%]).

Overall, 1 participant had an SAE that was considered treatment related (increased blood bilirubin; MRX-503); the event occurred while the participant was enrolled in Study MRX-502. The participant did not continue in Study MRX-503.

Study LUM001-501

Serious AEs were experienced by 15 participants (45.5%) during this Phase 2 study. The only SAEs reported for >1 participant were abdominal pain, diarrhea, and gastroenteritis, each experienced by 2 participants (6.1%). Treatment-related SAEs were experienced by 5 participants (15.2%). The treatment-related SAEs were reported for 1 participant each and included abdominal pain, abdominal pain upper, diarrhea, pancreatitis, blood bilirubin increased, and INR increased.

Study MRX-800

One participant in the 600-µg/kg/day maralixibat treatment group experienced treatment-emergent SAEs: Anal fissure (1 event) and Condition aggravated (2 events; worsening of PFIC and exacerbation of primary disease). All SAEs were considered not related to study drug.

Deaths

Two deaths, regarded not related to maralixibat by investigators, were reported in participants who had previously been enrolled in Study MRX-503: one (following an event of PT Respiratory tract infection) occurred 19 days after study drug discontinuation, and the other (following an event of PT Hepatic function abnormal) occurred 3 months after maralixibat discontinuation and 2 months after study discontinuation. The second case was related to liver decompensation: The participant had a medical history of very high values for liver transaminases up to 1800 U/L), and had further disease progression during study MRX-502 and study MRX-503.

No deaths were reported in participants with PFIC in Studies MRX-502, MRX-800, MRX-801, and LUM001-501.

Safety in the patients of 3 months to 12 months of age - Study MRX-801 (n=10)

Overall frequency of the AEs was higher than in older patients, with infections representing a large portion of the AEs. This may be due to the higher susceptibility to infections in younger population.

Majority of the AEs (e.g., diarrhoea, abdominal pain) reported are in line with the known safety profile of MRX (ALGS and PFIC populations, older patients). Vomiting (not related) was reported more frequently. Whether this was due to reduced tolerability of study medication or related to other factors such as the background disease cannot be finally concluded due to the absence of placebo control and small sample size in the MRX-801 study.

One patient (1 month old) was withdrawn due to the Grade 2 AE of ALT increase. Detailed narrative on this patient has been submitted and shows that the event was likely related to recurring infections in this patient.

No deaths were reported.

Laboratory findings

Haematology

The applicant reports that no clinically relevant changes from baseline to post-baseline or differences between treatment groups for haematology laboratory parameters were observed in Studies MRX-502, MRX-503 and LUM001-501, while these parameters were not analysed in the MRX-800 PFIC iCSR or

the MRX-801 PFIC iCSR. In addition, mean changes from baseline in haematology parameters were minor during long term treatment Study MRX-503.

Clinical Chemistry

Pivotal Study MRX-502

The applicant reports that no clinically relevant changes from baseline to post-baseline or differences between treatment groups for chemistry laboratory parameters were observed in this trial, with the exception of bilirubin that was reported improved with maralixibat versus placebo. Please refer to efficacy part of this report for further details.

Study MRX-503

The applicant reports that no clinically relevant changes from baseline to post-baseline or differences between treatment groups for chemistry laboratory parameters were observed in this trial.

Study LUM001-501

The applicant reports that no clinically relevant changes from baseline to post-baseline or differences between treatment groups for chemistry laboratory parameters were observed in this trial, with the exception of numerical reductions (improvement) in mean serum transaminases (ALT/AST) concentrations from baseline in the overall study population.

Safety in special populations

Intrinsic Factors

Safety-Events by **Age** Group- Pivotal Study MRX-502

In Study MRX-502, all age groups that were dosed with maralixibat experienced at least 1 AE compared with placebo wherein 96.6%, 93.3%, and 50% reported adverse events in the 1 to <6 years of age, 6 to <13 years of age, and 13 to 18 years of age, respectively. Severe AEs occurred in the two lower age groups (<13 years old). There were 3 SAEs reported in the 1 to <6 years old age group in maralixibat arm and 1 each for the two older age groups (>6 years old). There were no deaths, and no AEs that led to treatment discontinuation in all age groups except for 1 participant on maralixibat from the 13 to 18 years age group that discontinued treatment due to an AE.

Safety-Events by **Sex**–Pivotal Study MRX-502

In Study MRX-502, in both males and females dosed with maralixibat, 100% had at least 1 TEAE. Male and female participants in the placebo arm reported at least 1 TEAE at 90.9% and 95.8%, respectively. There were no adverse events categorized as severe and related in either males or females for both maralixibat and placebo arms. SAEs occurred more frequently in the males (3[15%] maralixibat vs 2 [9.1%] placebo) than in the females (2 [7.4%] maralixibat vs 1 [4.2%] placebo) for both treatment arms. One female participant in the maralixibat group discontinued treatment due to an AE. There were no deaths due to an AE in males or females in either treatment groups.

Safety related to drug-drug interactions and other interactions

There are no safety concerns regarding drug interactions with maralixibat as detailed and discussed already during the initial MAA procedure. The 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.

Discontinuation due to adverse events

In general, the rate of AEs that led to discontinuation was low for studies in the PFIC development program with the exception of Study LUM001-501, in which the most common AE that led to discontinuation was disease progression.

Study LUM001-501 had a study duration of 6 years, which could explain the higher rates of disease progression in this study compared with the other studies of shorter duration, which allowed less time for disease to progress.

Adverse Events That Led to Discontinuation–Pivotal Study MRX-502

For all maralixibat-treated participants, only 1 participant permanently discontinued study drug for a treatment-related TEAE (mild diarrhea). No placebo-treated participant had a treatment-related TEAEs that led to permanent discontinuation.

Adverse Events That Led to Discontinuation–Study MRX-503

For all participants, TEAEs that led to permanent discontinuation of study drug occurred in 3 participants; of these, one occurred during MRX-502 (diarrhea).

During Study MRX-503, increased ALT and increased blood bilirubin in one Participant led to treatment discontinuation, and hepatic/decompensated cirrhosis in another Participant led to treatment discontinuation; both participants were in the MRX-MRX group. The second event led to fatal outcome 90 days after discontinuation of maralixibat treatment.

Adverse Events That Led to Discontinuation–Study MRX-801

One participant had a Grade 2 increase in ALT that led to study drug discontinuation.

Adverse Events That Led to Discontinuation–Study LUM001-501

A total of 10 participants (30.3%) experienced TEAEs that led to permanent treatment discontinuation. Treatment-emergent AEs that led to permanent treatment discontinuation in >1 participant were reported as blood bilirubin increased (2 participants) and disease progression (4 participants). Study LUM001-501 had a study duration of 6 years, which could explain the higher rates of discontinuation in this study compared with the other studies.

Adverse Events That Led to Discontinuation–Study MRX-800

No participants had a TEAE that led to study drug discontinuation.

Post marketing experience

On 09 December 2022, Livmarli was approved in the European Union for the treatment of cholestatic pruritus in patients with Alagille Syndrome 2 months of age and older. The Livmarli international birth date (29 September 2021) was used as the European Union Reference Date (EURD).

Cumulative post-marketing experience for Livmarli is presented within the PSUR report; during the reporting period covered by this aggregate safety report, no signals were newly identified, closed, under monitoring, or awaiting evaluation.

2.5.1. Discussion on clinical safety

Safety assessment for patients from one year of age is mainly based on data from 47 participants with PFIC receiving maralixibat in the double-blind, placebo controlled (n=43) pivotal study (MRX-502) compared with 43 participants who received placebo, an open-label Phase 2 study (LUM001-501) and the extension Studies MRX-503 and MRX-800 providing long-term safety for maralixibat in participants with PFIC. While study MRX-801 characterizes the safety profile in infants <12 months of age with PFIC.

Unless otherwise specified, discussion of safety data for Study MRX-502 within this document is focused on the full PFIC cohort (overall N=93). Please note that maralixibat safety data discussed for the LTE Study MRX-503 are cumulative and include TEAEs reported in participants randomized to maralixibat during Study MRX-502 and TEAEs reported during the open-label extension Study MRX-503, through the data cutoff date of 23 June 2022.

In general, the safety profile of maralixibat was already characterised during the initial approval procedure on Alagille Syndrome and from the new data no new safety signal was detected in the PFIC population. Systemic exposure to maralixibat is absent or minimal in both conditions making systemic adverse drug effects unlikely.

The indication in Alagille Syndrome, an orphan disease, is currently authorized under exceptional circumstances and also the now applied for indication in PFIC concerns a very rare orphan disease in which only a small population was exposed for a relative short period of time with maralixibat. Thus, uncertainties regarding the safety characterisation are evident but expected considering the rarity of the disease.

Maralixibat is an oral agent that is only minimally absorbed and was specifically designed to maximize local exposure of the molecule in the gut and to minimize systemic exposure. Insofar, systemic toxicity from MRX can be presumed to be low. The product contains propylene glycol as an excipient, which is generally considered to be safe and well tolerated. The threshold accepted as safe in patients 1 month to 5 years old without renal/hepatic diseases is 50 mg/kg/day (EMA guidance EMA/CHMP/334655/2013 and Appendix to the excipients guideline EMA/CHMP/302620/2017 Rev. 2*). Notably, exposure to propylene glycol was restricted to a maximum dose of 26 mg/kg/day in the clinical trials in PFIC. However, with the formulation and dose strength applied for, the expected exposure of PG with the maximum recommended dose of Livmarli will reach 50 mg/kg/day. The expected exposure of up to 50 mg/kg/day PG raises concerns in vulnerable populations such as patients with an age below 5 years (due to physiological immaturity of liver/function of alcohol dehydrogenase and related limited ability to metabolise PG quickly), in patients with impairment of liver function, which can become manifest and worsen already in early childhood (van Wessel et al., 2020) and in patients with impaired renal function.

To address this concern, a restricted dose of 300 µg/kg BID Livmarli limiting daily PG exposure to a maximum of 26 mg/kg/day is recommended. Additionally, Livmarli is contraindicated in patients with severe renal or hepatic impairment.

Exposure

As of 23 June 2022, a total of 238 pediatric participants with cholestatic liver disease (ALGS [n=95], PFIC [n=134], or biliary atresia [n=9]) have been exposed to maralixibat during the clinical development program.

Duration of dosing has been over 7 years for participants with PFIC who have enrolled in long-term studies. In trial MRX-502 pivotal for the applied PFIC target population 93 participants were enrolled. In the PFIC cohort, the mean (SD) treatment duration was 184.4 (18.77) days (range: 108-256 days)

A total of 45 of 47 (95.7%) study participants who received maralixibat dose escalated to the maximum maralixibat dose of 600 µg/kg BID.

Adverse events

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

In the PFIC Cohort of the placebo-controlled pivotal trial MRX-502 all patients (100%) under maralixibat treatment reported TEAEs, while the number of participants who had TEAEs was slightly lower in the placebo arm (93.5%).

However, the proportion of participants with severe TEAEs was similar between maralixibat (6.4%) and placebo (6.5%) treatment groups, while in the full cohort a slightly greater proportion of maralixibat (10.6%) than placebo (6.5%) participants had treatment-emergent SAEs. The majority of Drug related TEAEs were mild to moderate in severity, transient in nature, and resolved while treatment.

Only one participant in maralixibat arm with PFIC had a treatment-emergent SAE assessed as related to study drug by the investigators. The only subjects who discontinued permanently the trial was a maralixibat treated patient. No participant had a TEAE resulting in death during the study period.

For all maralixibat-treated participants, the most common TEAEs by preferred term included diarrhoea (57.4%), pyrexia (36.2%), and abdominal pain (21.3%). For all placebo-treated participants, the most common TEAEs by preferred term included pyrexia (28.3%), diarrhoea (19.6%), and pruritus (17.4%).

With respect to treatment related TEAEs for all maralixibat-treated participants, the most common treatment-related TEAEs were diarrhoea (13 participants [27.7%]), abdominal pain and blood bilirubin increased (3 participants [6.4%]) while no treatment-related TEAE occurred in >1 participant in the placebo arm; treatment-related TEAEs included vomiting and diarrhoea (1 participant each).

No relevant difference between the PFIC and the ALGS population in terms of the type of the TEAEs reported could be identified. Due to the low number of subjects no meaningful further conclusions can be derived from this data.

Symptoms of upper respiratory tract infection as nasopharyngitis, cough and pyrexia were observed more frequently in younger compared to older children but occurred at roughly similar frequency as in the general paediatric population of comparable age (Vissing et al. 2018). Also, there is no scientific rationale that would explain potential causal relationship to maralixibat. Thus these TEAEs are not considered treatment related.

A more permeable intestinal barrier may occur in situations where the gastrointestinal system is acutely or chronically disturbed and could lead to higher exposure of maralixibat and potentially induce systemic adverse events. However, non-clinical data on higher exposure are without safety findings (the NOAEL is 100 mg/kg/day for maralixibat). Nevertheless, considering the small population investigated with PFIC, additional data from a post-approval study is deemed essential to further characterise safety.

Adverse events of special interest

Adverse events of special interest are ALT and Bili increase in order to exclude DILI due to maralixibat exposure, fat soluble vitamin deficiencies (FSV), including coagulopathy as well as fractures. These adverse events are common in PFIC and generally considered a core feature of the disease.

In order to prevent complications of FSV (fat-soluble vitamins) deficiencies (up to 20% of PFIC population) prophylactic substitution is recommended in the product information and was practiced in the trial.

Effects on Transaminases

Elevations in transaminases were observed more frequently in the laboratory evaluations than reported as AE by investigators. Analyses of changes in ALT/AST, bilirubin are presented and discussed in the efficacy part of the report in more detail.

Elevations that occurred and were reported as AEs in 8 individuals, spontaneously resolved in the majority of participants, no discontinuations associated with elevated liver enzymes with maralixibat, and no DILI events were reported in the MRX-502 and MRX-503 studies by the time of the presented data cut-off (23 June 2022). However, for the recent PSUSA procedure (Procedure no.: EMEA/H/C/PSUSA/00011032/202309 from March 2024), the MAH provided a cumulative review regarding hepatotoxicity. Based on the gathered data, including 15 cases with increased transaminases and a close temporal relationship to maralixibat intake, positive de-challenge, and re-challenge, it was concluded that a causal relationship between maralixibat and ALT increased and AST increased is at least a reasonable possibility. Accordingly, it was agreed to add the adverse reactions - ALT increased and AST increased under the SOC: Hepatobiliary disorders with a frequency common – to the PI. With the responses to the RSI of this variation procedure, the company showed that the levels of transaminases, as well as bilirubin seem to stabilize on continuous treatment with MRX in patients with PFIC (see the efficacy section), which is reassuring. A warning, that liver function tests should be monitored prior to and on treatment with Livmarli has been included in the PI.

Fat soluble Vitamin deficiency

In cholestatic disease, levels of bile acids in the intestinal lumen are lower than normal, and the systemic bile acid pool is increased (elevated serum bile acids) because bile flow is impaired. If intestinal bile acid levels fall below the critical micelle concentrations, their role in solubilization of fats to promote their absorption, and the subsequent absorption of FSVs can be reduced. With consideration of the role of intraluminal bile acids in FSV absorption, it is plausible that increased bile acid detergents in the small intestine with IBAT inhibition could help solubilize fats and potentially help their absorption. In the analysis of pooled PTs for fat soluble vitamin deficiency the proportion of participants on maralixibat with events was lower than those on placebo (27.7% vs. 34.8%) and thereby indicate that maralixibat does not worsen FSV deficiencies or contribute to FSV deficiency.

Bleeding Events

The proportion of participants on maralixibat with lower GI bleeding events was higher than those on placebo (8.5% vs. 2.2%). However, it is acknowledged that the etiology of lower GI bleeding is multifactorial, and in each of the 4 maralixibat-treated participants with lower GI bleeding, a clear alternative etiology was identified upon a participant-level review and the VIt.K dependent INRs in all cases were stable from baseline. Thus, it is agreed that maralixibat did not appear to play a causal role in the bleeding events observed considering the limited data submitted.

Fractures

The effect of cholestasis on bone metabolism and deleterious consequences of increased bilirubin in advanced chronic cholestasis and in end-stage liver diseases, resulting in disturbed bone formation related to osteoblast dysfunction is well documented in the literature. The proportion of participants on maralixibat with fracture events was higher than those on placebo (6.4% vs. 0%). However, since the etiology of fractures is multifactorial, and in each of the 3 maralixibat-treated participants (020003, 023001, and 031005) with fractures, a clear alternative etiology such as trauma was identified upon a

participant-level review, making it unlikely that maralixibat plays a causal role in such events. All 3 fractures were deemed not related to maralixibat by the treating physicians, and none required changes to maralixibat dosing. Additionally, all 3 participants with fractures had low vitamin D levels at baseline. However, there was no clinically meaningful difference in mean or median change from baseline in vitamin D levels over time, between maralixibat and placebo participants.

Insofar, it seems rather unlikely that maralixibat has significantly contributed to the fracture events observed, although it remains evident that all fractures occurred in the maralixibat treated patients.

SAEs and deaths

For the full cohort, 5 maralixibat participants (10.6%) and 3 placebo participants (6.5%) had treatment-emergent SAEs. For maralixibat participants, the most common treatment-emergent SAE was urinary tract infection (2 participants [4.3%]), while no treatment-emergent SAE occurred in >1 placebo participant. Only 1 treatment-emergent SAE was considered treatment related (blood bilirubin increased, mild in severity, primary cohort maralixibat participant). Most treatment-emergent SAEs were moderate in severity. Most SAEs had study drug action taken of dose not changed, and all SAEs resolved.

Two deaths, not related to maralixibat, were reported in participants who had previously been enrolled in Study MRX-503: one (following an event of PT Respiratory tract infection) occurred 19 days after study drug discontinuation, and the other (following an event of PT Hepatic function abnormal) occurred 3 months after maralixibat discontinuation and 2 months after study discontinuation in trial MRX-503. Causal relationship of fatal event related to respiratory tract infection does not meet criteria for being treatment-emergent or treatment related. As to the death due to abnormal hepatic function, the patient had very high levels of ALT reported before start of treatment and developed moderate cirrhosis (and liver decompensation) after >200 days on maralixibat. The fatal event occurred about 3 months after stop of treatment with maralixibat. Thus, death in this patient is unlikely related to use of maralixibat. Possible contribution of MRX to decompensation of liver function cannot be fully excluded, but seems also unlikely given the late occurrence of the event. The events of cirrhosis and liver decompensation, as well as the event of death were assumed to be connected with the disease progression by the Applicant and the investigator.

In summary, the AE profile in PFIC subjects treated with maralixibat appears to be similar to that observed in the ALGS population despite the considerably higher daily dose. No new safety issues have been identified, apart from reported AEs of elevated ALT and AST (in the ALGS studies, ALT elevations were observed in some patients but not reported as AE).

Effects of Livmarli on survival and time to liver related events will be further investigated in post-approval phase. (see the efficacy part of this report, RMP and Annex II).

Laboratory findings:

No clinically relevant changes from baseline to post-baseline or differences between treatment groups for the investigated haematology or chemistry laboratory parameters were reported from Studies MRX-502, MRX-503 and LUM001-501.

With respect to the hepatic safety, mostly transitory elevations in ALT and AST in some of the PFIC patients on MRX have been observed (post hoc analyses). These increases were partly associated with increases in bilirubin and the applicant's conclusion that these events can be seen as part of the natural history of the underlying disease is not fully agreed. (please refer to above paragraph *"Effects on Transaminases"* and section 2.4 *"Clinical Efficacy")*

Based on the totality of the available data (including those from 1700 adults) and its minimal absorption it seems unlikely that maralixibat treatment is associated with a high risk for drug induced liver injury. However, higher doses are proposed in the PFIC population than in the ALGS indication, including in infants, and data are limited on this high doses in the target population. Also, patients with hepatic impairment were excluded from the studies and safety of chronic use of PG in this vulnerable population is unknown. Therefore, further evaluation of the safety profile is needed post-marketing.

Hepatotoxicity is already included in the RMP as an important potential risk and will be further evaluated in the post-approval phase.

The current recommendation included in section 4.4 of the SmPC, to monitor liver function in all patients prior to and during treatment with Livmarli, is considered acceptable. Additionally, risk minimization and monitoring measures, such as restricted dosing regimen in the patients at increased risk of PG accumulation have been put in place in order to limit potential PG-toxicity.

Dosing errors:

A considerable number of cases (reference is made to the efficacy part of this document) of erroneous dosing of MRX was reported in the clinical studies in PFIC, which suggests that in a less standardized and monitored environment, daily practice, errors in the medication dosing may occur, potentially leading to increased PG exposure. Therefore, the Applicant included the risk of erroneous dosing of Livmarli in the list of important potential risks and agreed to additional risk minimization measures (patient booklet, dosing guide).

Subgroup analyses:

The applicant stated that in general a comparison of the safety profile of maralixibat for PFIC in children ≥12 months of age and infants <12 months of age indicates that the safety profile in infants in Study MRX-801 is in line with the known safety profile of maralixibat from the pivotal Study MRX-502. Additionally, PK analysis showed that systemic exposure to MRX remains very low also in infants (sparse sampling). This allows assumed that safety profile of Livmarli in regards to systemic exposure to MRX in infants should be similar to older population.

However, the data suggested a higher frequency of TEAEs in infants <12 months of age (25%). This might be explained by the disproportion in sample size (the available data on infants with PFIC treated with maralixibat include only 10 participants in the updated data-set), as well as general differences in infant patients who, as a population, are susceptible to fevers and infections (Study MRX-801 enrolled during the COVID-19 pandemic). It seems reassuring that none of the SAEs reported in Study MRX-801 was considered to be drug-related. Moreover, 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 Study MRX-502, all age groups that were dosed with maralixibat experienced at least 1 AE compared with placebo wherein 96.6%, 93.3%, and 50% reported adverse events in the 1 to <6 years of age, 6 to <13 years of age, and 13 to 18 years of age, respectively. Severe AEs occurred in the two lower age groups (<13 years old). There were 3 SAEs reported in the 1 to <6 years old age group in maralixibat arm and 1 each for the two older age groups (>6 years old). There were no deaths (while on treatment), and no AEs that led to treatment discontinuation in all age groups except for 1 participant on maralixibat from the 13 to 18 years age group that discontinued treatment due to an AE.

In general, the small number of subjects in the cohorts and the associated imbalances in age distribution preclude any firm conclusions regarding potential differences in safety according to age. Post-approval data collection is planned, also in the youngest affected population.

Immunological events:

No new or additional information need to be discussed during this procedure for the PFIC population. Animal data seems to 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

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 feces as intact parent drug, it seems plausible that the drug has only a low potential for drug-drug interactions in general.

No new or additional information need to be discussed during this procedure for the PFIC population.

Discontinuation due to AEs

In general, the rate of AEs that led to discontinuation was low during the paediatric trial program in general and for studies in the PFIC development program (with the exception of Study LUM001-501, in which the most common AE that led to discontinuation was disease progression).

For all maralixibat-treated PFIC participants, 1 participant permanently discontinued the study drug for a treatment-related TEAE (mild diarrhea, probably drug related) in MRX-502, and two additional subjects in extension trial MRX-503 (increased ALT and Bili due to disease progression, assessed as not drug related). No placebo-treated participant had a treatment-related TEAEs that led to permanent discontinuation.

In LUM001-501, a total of 10 participants (30.3%) experienced TEAEs that led to permanent treatment discontinuation. Treatment-emergent AEs that led to permanent treatment discontinuation in >1 participant were reported as blood bilirubin increased (2 participants) and disease progression (4 participants). Since study LUM001-501 had a study duration of 6 years, this could explain the higher rates of discontinuation in this study compared with the other studies of shorter duration, which allowed less time for the disease to progress.

2.5.2. In the infants' study MRX-801 one out of 10 patients was withdrawn due to elevated ALT.Conclusions on clinical safety

Safety data from the pivotal trial MRX-502 and the long term extension study MRX-503 in the PFIC Safety data from the pivotal trial MRX-502 and the long term extension study MRX-503 in the PFIC population show a similar profile as for the authorised ALGS population.

Similar to the observations in ALGS, the risk profile in the significantly younger PFIC population appears to be dominated by gastrointestinal adverse events as diarrhoea, abdominal pain and vomiting. They are reported to be the most common adverse events. Diarrhoea and abdominal pain are known ADRs and evidence is not convincing to support inclusion of vomiting to the list of ADRs. Elevations of ALT/AST and partly of bilirubin have been reported on MRX in part of the patients and in the majority of the cases these parameters stabilized or even improved on prolonged treatment. ALT elevated and AST elevated are included as new ADRs in the PI following the recommendations of the recent PSUSA. Hepatotoxicity remains an important potential risk.

SAE rates were low and events that occurred were considered not drug-related and almost all of the TEAEs observed were mild to moderate and resolved with no action taken with maralixibat.

The submitted data do not suggest PG-related toxicity on the PG exposure tested (26 mg/kg/day). Safety data on the exposure >26 mg/kg/day propylene glycol in the target population are missing. The proposed target dose of Livmarli for PFIC is higher than the dose of Livmarli approved for Alagille

Syndrome and, with the formulation and dose strength applied for, will lead to an exposure of up to 50 mg/kg/day PG. PG intake of up to 50 mg/kg/day is considered safe in infants > 4 weeks and in children < 5 years of age. However, the risk of developing PG-related toxicity in the targeted vulnerable population, including those at very young age and those with hepatic or renal dysfunction may be increased. Therefore, upon request by the CHMP and to minimise the PG exposure risks, a reduction of the recommended therapeutic dose of Livmarli (to 300 µg/kg BID maralixibat chloride equivalent to 285 mcg/kg BID maralixibat base) in the PFIC patients at increased risk of PG toxicity (below the age of 5 years and patients with moderate renal or hepatic impairment) was introduced in the SmPC. In addition, use of maralixibat has been contraindicated in patients with severe liver or renal impairment. The overall safety profile of maralixibat can be considered favourable. However, due to very limited safety database in this rare disease collection of long-term, post-approval data is needed to further characterise safety of MRX in PFIC (including long-term exposure to PG).

Additionally, impact on liver-related events and overall survival will be evaluated in the post-approval phase (primarily as efficacy parameter, but with relevance to safety). Based on cases of erroneous dosing due to unclear communication between investigators and care-givers and concerns regarding miscalculation of the dose that may increase the exposure to PG "Medication error resulting from erroneous dosing (PFIC population)" was included as an important potential risk in the RMP and several risk minimisation measures were agreed and included in the SmPC and RMP (e.g., warnings in section 4.2 of the SmPC and in PL; physician dosing guide and a patient booklet included as measures in the RMP.

Overall, since the size of the safety data base in PFIC, especially in the patients below the age of 1 year and over long-term treatment is limited and there is no experience of chronic exposure to PG in the target population. Therefore, post-approval data collection is warranted and has been agreed (see section 2.6 and Annex II). Data such as, hepatotoxicity and erroneous dosing, long-term safety of chronic exposure to PG, long-term clinical outcomes/survival, etc. as potential will be monitored (MRX-803 study and pooled analysis of MRX-502, MRX-503, MRX-800, MRX-801).

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 4.1 with this application.

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

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	None

Important potential risks	Hepatotoxicity Medication error resulting from erroneous dosing (PFIC patients)
Missing information	Long-term safety Long-term safety of chronic exposure to propylene glycol in PFIC patients

PFIC=progressive familial intrahepatic cholestasis

Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Date**
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
MRX-803 (former MRX-311): "Long-Term Safety and Clinical Outcomes of Livmarli in Patients with Alagille Syndrome and Progressive Familial Hepatic Cholestasis" Low-interventional clinical study Planned	The objectives are to: • evaluate the long term safety • evaluate the long-term efficacy (impact on liver related events/clinical outcomes, growth and development)	Hepatotoxicity Medication error resulting from erroneous dosing (PFIC patients) Long-term safety Long-term safety of chronic exposure to propylene glycol in PFIC patients	Submission of feasibility assessment (PFIC cohort)	Within 3 months of EC decision
			Protocol submission	Within 6 months of EC decision
			SAP submission	Within 6 months of study start
			Interim report	Within 5 years from study start
			Interim results	Yearly reporting with annual reassessment
Category 3 – Required additional pharmacovigilance activities				
MRX-800: "A Long-Term Safety Study of Maralixibat, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Subjects Who Previously	To evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS and PFIC.	Hepatotoxicity Long-term safety	End date of collection (LPO):	Q3 2024
			Final report of study results (final CSR):	Q1 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
Participated in a Maralixibat Study (MERGE)" 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 (RISE)" Ongoing	To assess the safety and tolerability of maralixibat in infants <12 months of age with cholestatic liver disease due to ALGS or PFIC	Hepatotoxicity Long-term safety	End date of collection (LPO):	Q4 2024
			Final report of study results (final CSR):	Q2 2025
MRX-503: "An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)" Ongoing	Primary objective: To evaluate the long-term safety and tolerability of maralixibat. Secondary objective: To evaluate the long-term efficacy of maralixibat, including the maintenance of severity and frequency of pruritus as well as serum bile acids (over time and growth in the primary cohort	Hepatotoxicity Long-term safety	End date of collection (LPO)	Q4 2024
			Final report of study results (final CSR):	Q2 2025
MRX-502, MRX-503, MRX-800, MRX-801: "A retrospective study to compare	Primary objective: To evaluate the long-term effects on	Hepatotoxicity Long-term safety	Final report of study results (final CSR):	Q2 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date
impact of maralixibat treatment on long-term clinical outcomes against historical control in the patients with PFIC"	liver related events and clinical outcomes			

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

Risk minimisation measures

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

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

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC have been updated. Package Leaflet has been updated accordingly. Please refer to the full PI as attachment.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed extension of the indication includes "treatment of PFIC in patients 3 months of age and older". The initially proposed indication was for treatment of patients 2 months of age and older. Since relevant data were only available in patients aged 3 months and above, the indication was amended accordingly (insufficient data were available in patients below the age of 3 months. Only one patient of 1 month of age was included, who was withdrawn during titration due to an AE.).

PFIC is a group of rare inherited diseases considered as PFIC types and affects one in every 50,000 to 100,000 children born worldwide. Each PFIC type is based on mutations in different genes that disrupt normal bile formation. This results in an accumulation of hepatotoxic levels of BAs, leading to severe pruritus, growth retardation, and ultimately cirrhosis. Many patients with PFIC progress to end-stage liver disease and require liver transplantation; 70%–80% of patients ultimately require liver transplantation.

In patients with PFIC, 76%–100% suffer from significant, persistent, and debilitating cholestatic pruritus. Patients with PFIC consider pruritus the most devastating symptom, leading to cutaneous mutilation and excoriations, loss of sleep, fatigue, irritability, poor attention, and impaired school performance, all of which results in a poor quality of life. Treatment-resistant pruritus is the leading indication for surgical biliary diversion procedures (SBD), particularly in patients with PFIC2, where it is listed as an indication for surgery in 89% of patients (van Wessel et al. 2019). Caregiver burden is significant in this setting along with depression, family impact on daily living, and associated economic burden.

3.1.2. Available therapies and unmet medical need

Odevixibat was approved (EMEA/H/C/004691) "for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older" in 2021.

A number of pharmacologic therapies (rifampicin, UDCA, cholestyramine, etc.) are commonly employed off-label but are often only transiently or partially effective, do not address the underlying cholestasis, and may have undesirable adverse effects in patients with underlying liver disease.

The only other proven treatment options to treat the pruritus and progressive liver disease associated with PFIC are surgical interventions including surgery for biliary diversion and liver transplant.

Given the limitation of approved pharmacotherapy, (currently there is no approved treatment in patients <6 months of age) the invasive nature of surgical treatment options, and patients' short- and long-term morbidity and mortality, there is an unmet medical need for an additional pharmacological treatment.

3.1.3. Main clinical studies

This variation application is based on the data of one completed randomised, double-blind, placebo-controlled, multi-centre 6-month study MRX-502 in patients 1-17 years of age with PFIC and interim results of 2 supportive studies: one open-label single arm study in infants of 1-12 months of age with

PFIC (study MRX-801) and an ongoing open-label single-arm extension study MRX-503 to the pivotal study MRX-502. Data of > 13-weeks treatment (Median duration of exposure of around 8.5 months in the updated data-set as of 28 June 2023) in 10 infants with PFIC and 93 patients of 1-17 of age over mean/median treatment duration of about 1 year (data cut-off 23 June 2022) have been presented.

The key objective of the pivotal MRX-502 study was to demonstrate short-term effects of MRX (titrated to maximum dose of 600 µg/kg BID) in the PFIC population including various PFIC subtypes. The primary endpoint was pruritus (measured by means of ItchRO(Obs)). The key secondary endpoint was sBA.

In study 502, efficacy data were analysed in two patient cohorts: the primary cohort (nt-PFIC2, n=31) and the PFIC cohort (all PFIC types apart from t-PFIC2, n=64). The primary analysis was specified in the primary cohort including all nt-PFIC2 participants, however, the hierarchical testing strategy also allows confirmatory conclusions for the PFIC population. Since the wider PFIC cohort is more relevant for the target population of the indication, the focus of the B/R assessment is on this population.

The key objectives of the ongoing MRX-503 study is to replicate the short-term effects of MRX observed in the MRX-502 study in the patients switched from placebo treatment in the MRX-502 and to demonstrate maintenance of effects during long-term treatment. Similar efficacy parameters as in the pivotal study have been assessed, but parameters, requiring long-term treatment to show effects (e.g., growth) are more relevant in this study. Results on 86 patients from study MRX-503 have been presented for this application.

Study MRX-801 is an ongoing open-label Phase 2 study to evaluate the safety and tolerability of maralixibat in the treatment of infants (<12 months of age) with ALGS or PFIC that aims to evaluate safety and tolerability of MRX in infants, test systemic exposure and provide exploratory information on efficacy/PD parameters to support data extrapolation from older population. Results on ten infants with PFIC have been presented for this application.

3.2. Favourable effects

Study MRX-502 (DB phase)

Primary cohort: There was a statistically significant difference between the maralixibat and placebo treatment groups for the average change in morning ItchRO(Obs) severity score between baseline and Weeks 15–26, with a LS mean difference vs. placebo of 1.039 [95% CI: -1.807, -0.272], p=0.0098) in the primary cohort.

PFIC cohort:

Similar results were seen in the PFIC cohort, with a LS mean difference vs. placebo of 1.173 (95% CI: 1.705, 0.642; p<0.0001).

The difference in mean change in total serum bile acid levels from baseline to average of weeks 18, 22, and 26 between the maralixibat and placebo treatment groups was statistically significant (160 µmol/L (95% CI: 220.8, 100.0), p<0.0001).

The percentage of serum bile acid responders was 51.5% for maralixibat and 6.5% for placebo participants, p <0.0001. Serum bile acid responders were defined as a participant having an average sBA level of <102 µmol/L (applies only if baseline sBA level was ≥102 µmol/L) OR ≥75% average reduction from baseline. For the purpose of determining response, the average sBA value from weeks 18, 22, and 26 values was compared to baseline.

Maralixibat showed a statistically significant difference to placebo for the average change from baseline in morning ItchRO(Obs) score at weeks 15–26, with a LS mean change from placebo of 1.173 (95% CI: 1.705, 0.642; p<0.0001).The percentage of ItchRO(Obs) responders was 63.6% for maralixibat and 25.8% for placebo participants, p=0.0023 (Table 4). An ItchRO(Obs) responder was defined as a participant having a 4-week average morning ItchRO(Obs) severity score decrease from baseline of at least 1.0 OR an average severity score of ≤1.0.

Improvements in bilirubin were observed; the difference between maralixibat and placebo for total bilirubin (µmol/L) was -34.3 (-68.06, -0.05); p=0.0471 and for direct bilirubin was -26.4 (-52.46, -0.26); p=0.0480. Abnormal total bilirubin levels at baseline normalised by week 26 in 40% (10/25) of patients on maralixibat vs. 0% (0/18) on placebo.

There was a statistically significant reduction (improvement) in the mean sleep disturbance scores in the maralixibat treatment group compared with placebo.

There was a statistically significant increase (improvement) in weight z-score between baseline and average of weeks 18, 22, and 26 in the maralixibat treatment group compared with placebo (LS mean change from placebo of 0.227 (0.012, 0.442), p=0.0391).

In the placebo group, a statistically significant increase in FIB-4 scores was observed with a LS mean (SE) change from baseline to Week 18-26 of 0.101 (0.0358, p=0.0062). In contrast, no significant change in FIB-4 was observed in the maralixibat group (LS mean (SE) of -0.085 (0.11075), p=0.0838).

In Study MRX-502, APRI scores in the placebo group tended to increase over time with a LS mean (SE) change from baseline at Week 18-26 of 0.462 (0.2341; p=0.0570). In contrast, in the maralixibat treatment group, APRI scores tended to be maintained with a LS mean (SE) change from baseline of -0.039 (0.2189; p=0.8605). The difference between the treatment groups was not statistically significant (LS mean (SE) difference in the maralixibat group compared with placebo of -0.501 (0.3211; p=0.1287).

Study MRX-503 (OL extension phase)

The effects observed in study MRX-502 could be largely replicated in patients switching from placebo to maralixibat in study MRX-503.

Maralixibat showed maintenance of treatment effect with sustained reductions in serum bile acid and bilirubin levels as well as continuous pruritus improvement. Growth acceleration as measured by height and weight z-scores were further improved throughout the follow-up indicating catch-up growth in children with PFIC. The APRI and FIB-4 scores were also maintained and are indicative of stabilization of disease progression and fibrosis staging on maralixibat.

Pruritus severity (assessed with CSS) decreased showing LS mean (SE)(95% CI) change from baseline on maralixibat of -0.942 points (0.1548) (-1.251, -0.632)(-0.697, -0.058) and difference from placebo of -0.564 points (0.2108)(-0.987, -0.142).

MRX-801 study: Age group 1 to <12 months at enrolment (n=10)

The mean (SD) change in sBA from baseline at Week 13 on MRX was -107.965 (146.7659) µmol/L.

Nine out of 10 infants had a reduction in total bilirubin with maralixibat treatment. The mean (SD) change from baseline at Week 13 in total bilirubin was -1.171 (1.0862) mg/dL).

The mean (SD) change from baseline at Week 13 was 0.15 (1.415). Seven out of 10 participants had evidence of pruritus at baseline, with an improvement seen in 2 out of 7 participants. The 2 participants with improvement in pruritus also showed marked reductions in sBA and bilirubin.

The mean (SD) change from baseline to Week 13 in ALT and AST was -15.2 (42.39, p=0.3127) and -27.6 (30.91, p=0.0393), respectively.

Restricted dose (150 µg/kg BID followed by 300 µg/kg BID for one week each)

In Study MRX-502, differentiation from placebo in the key biomarkers of cholestasis, sBA and direct bilirubin, manifested as early as the first post-baseline assessment time point at study Week 2 (PFIC cohort).

LS Mean change (SE) (95% CI) showed significant difference from placebo for sBA of -123.024 mmol/L (25.7726)(-174.634, -71.414) and for direct bilirubin of -0.945 mg/dL (0.4684)(-1.883, -0.006). 33% of patients on MRX 300 µg/kg BID vs 3% on placebo had clinically relevant sBA response (defined as sBA <102 umol/L, OR a ≥-75% average percent change from baseline). Additional 12% of patients (45% in total) gained response on MRX on the doubled dose, i.e., the recommended 1200 µg/kg/day at week 6 (0% on placebo).

A post hoc analysis showed that 57% of patients achieved at least 80% of their individual change in sBA on half the MRX dose (i.e., 300 µg/kg BID), whereas only 63% of patients had the same effect reported on full dose.

Pruritus severity (assessed with CSS) also decreased significantly at Week 2 showing LS mean (SE)(95% CI) difference from placebo of -0.564 points (0.2108)(-0.987, -0.142)

3.3. Uncertainties and limitations about favourable effects

Uncertainties and limitations of favourable effects are related to the following:

- The presented data set is limited by size (PFIC cohort - n=64 in the 1-15 year olds; n=10 in 1-12 month olds) and by age group. Treatment duration is relatively short (especially in infants).
- Duration of placebo-controlled phase is too short to assess full effects on growth, fibrosis parameters, liver-related outcomes cannot manifest. Therefore, long-term efficacy data on clinical outcomes will need to be provided post-approval.
- Data in adolescent patients with PFIC are limited and virtually absent in adult patients. Data are also very limited in infants but it is acknowledged that studies in infants are very difficult to perform. The Applicant has provided justification for extrapolation of data from children to adolescents/adults and to infants. Extrapolation is based on the similarity in the pathophysiology of the disease and the mechanism of action of MRX. This is accepted.

3.4. Unfavourable effects

Safety data in the applied paediatric target population is limited to 47 children with Progressive Familial Intrahepatic Cholestasis (PFIC) in patients 1 months of age and older in one pivotal trial (MRX-502) and the open label extension trial MRX-503. Additional information from open label trials LUM001-501, MRX-800 and MRX-801 is rather of limited relevance for the safety assessment due to the small number of patients included.

In accordance with the known safety profile of the pharmacological class of ASBT inhibitors, GI events including diarrhoea (57.4%) and abdominal pain (21.3%) were the most frequently reported adverse drug reactions for maralixibat in the pivotal study. This is overall similar to that known from the ALGS population considering the overall heterogeneous 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 placebo-controlled pivotal study MRX-502 may allow to assess some differences regarding the SOCs of TEAEs. However, it remains open, whether differences observed are chance findings reasoned due to heterogeneity in the small paediatric population or real.

The most frequent TEAEs in the PFIC population are reported as abdominal pain (21.3%), cough (14.9%), diarrhoea (57.4%), headache (6.4%), nasopharyngitis (10.6%), pyrexia (36.2), upper respiratory tract infections (6.4%) and vomiting (6.4%). (e.g. from MRX-502). Median time to first onset for events of diarrhoea and abdominal pain was in most cases during the first months of treatment and event duration is described as short (several days).

As in the ALGS population the laboratory data showed several mostly isolated and seemingly asymptomatic, but significant elevations in ALT also in some PFIC subjects during treatment, which are reflected in the SmPC. The data available are too limited to draw firm conclusions regarding potential hepatotoxicity of maralixibat. Hepatotoxicity has been defined already as important potential risk in the RMP for the ALGS population and will need to be monitored post-approval also for PFIC subjects. ALT/AST elevations, sometimes accompanied with elevation in bilirubin and mostly of transitory nature have been reported also in PFIC. ALT/AST elevations are identified as ADRs (frequency common) and are included in the PI of Livmarli.

Unfavourable effects in infants: The most frequent TEAE (across MedDRA System Organ Class and by Preferred Term) was Vomiting (5 participants; 50%), followed by Nasopharyngitis (4 participants; 40%), Diarrhoea, Pyrexia, Cough, and Rhinorrhoea (3 participants each; 30%). Most TEAEs were Grade 1 in severity.

Three (3) participants (30%) experienced a serious adverse event (SAE) (influenza, adenovirus infection and appendicitis all in one participant; cough in one participant and gastroenteritis adenovirus in one participant) and one patient was withdrawn due to elevated ALT. All were considered not related to the study drug.

Long terms safety of MRX and PG remains unknown at present and will be followed up in a long-term safety and clinical outcomes study as describe in the RMP and Annex II of this marketing authorisation under exceptional circumstances.

3.5. Uncertainties and limitations about unfavourable effects

Although safety risks in PFIC subjects seemed to be rather similar to that known from the ALGS subjects, both safety populations are 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.

Laboratory data showed mostly transitory increase in liver function tests on MRX in part of the treated patients. It seems that in some patients (e.g., those with baseline high level ALT/AST) this elevation remains. Monitoring of liver function tests is recommended in the SmPC, as well as switch to an alternative treatment in case the individual benefit-risk ratio becomes unfavourable.

Maralixibat was designed to be minimally absorbed following oral administration because the site of action is within the lumen of the GI tract. Current data in infants from the age of 3 months suggest similarly low systemic exposure to MRX (<1%) as older patients.

The potential impact of maralixibat on the microbial biome has not been investigated and remains unknown.

The proposed target dose in the PFIC population is approximately 3-fold higher than the dose of MRX approved for the ALGS indication. While the higher MRX dose appears to be similarly well tolerated as the already approved lower dose, there are concerns with the increased exposure to propylene glycol, which could be up to 50 mg/kg/day, when using the recommended highest dose of the to be marketed formulation of Livmarli. Safety data on the exposure to >26 mg/kg/day propylene glycol in the target population is missing. Generally, PG intake of up-to 50 mg/kg/day is considered safe. However, the risk of developing PG-related toxicity may be increased in vulnerable populations such as patients below age 5 years and those with hepatic or renal dysfunction. Use of a lower maximum dose of 600 µg/kg/day of Livmarli (equivalent to 25 mg/kg/day PG) is, therefore, recommended in the SmPC for such patients. In addition, Livmarli is contraindicated in patients with severe hepatic or renal impairment.

Several cases of dosing errors were reported in the PFIC studies and CHMP expressed concerns that dosing errors, potentially leading to increased exposure to PG, may occur more frequently in clinical practice. Therefore, the Applicant included the risk of erroneous dosing of Livmarli in the list of important potential risks and agreed to additional risk minimization measures (patient booklet, dosing guide).

Unfavourable effects seem similar across the evaluated age groups (3-12 months olds vs. >1 – 17 years olds), but small size of especially infant population (n=10) and relatively short treatment duration, especially in infants create uncertainty. Therefore, post-approval collection of safety data is planned and agreed.

3.6. Effects Table

Table 33 Effects table for Livmarli in the indication of treatment of PFIC (data cut-off: 23 June 2022 for MRX-502 and June 2023 for MRX-801)

Effect	Short description	Unit	Treatment - MRX	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Morning ItchRO(Obs) (primary cohort; ITT)	Average change in morning ItchRO(Obs) severity score between baseline and Weeks 15–26	LS mean (SE) 95% CI for LS mean p-value (CFB LS mean=0) LS mean (SE) change from placebo 95% CI for LS mean change from placebo p-value (maralixibat LS mean=placebo LS mean)	-1.718 (0.2708) -2.272, -1.163 <0.0001 -1.089 (0.3691) -1.845, -0.334 0.0063	-0.628 (0.2479) -1.136, -0.121 0.0171	Small sample, restricted population, not representative for the claimed indication. Confirmatory evidence	MRX-502
Morning ItchRO(Obs)	Average change in morning	LS mean (SE)	-1.811 (0.1834)	-0.610 (0.1947)	Small sample, but	MRX-502

Effect	Short description	Unit	Treatment - MRX	Placebo	Uncertainties / Strength of evidence	References
(PFIC cohort; ITT)	ItchRO(Obs) severity score between baseline and Weeks 15–26	LS mean (SE) change from PBO 95% CI for LS mean change from PBO p-value (maralixibat LS mean=PBO LS mean)	-1.200 (0.2630) -1.727, -0.674 <0.0001		representative for the target indication. Confirmatory evidence	
sBA (PFIC cohort; ITT)	Mean Change in Total sBA Level between Baseline and Average of Weeks 18, 22, and 26 (ITT Population – PFIC Cohort)	LS mean (SE) LS mean (SE) change from PBO 95% CI for LS mean change from PBO p-value (maralixibat LS mean=PBO LS mean)	-157.489 (21.3609) -160.403 (30.1827) -220.836, -99.970 <0.0001	2.913 (22.6264)	Small sample, but representative for the target indication. Confirmatory evidence	MRX-502
ItchRO(Obs) responder (PFIC cohort; ITT)	Defined as a participant with a 4-week average morning ItchRO(Obs) score decrease from baseline of at least 1.0 OR an average severity score of ⩽1.0.	n (%) p value vs PBO	21 (63.6) 0.0023	8 (25.8)	As any change from baseline was partly considered a response these data are considered potentially confounded. Comparison vs. placebo. Moderately strong evidence.	MRX-502
sBA Responder (PFIC cohort; ITT)	A participant having an average sBA level of <102 µmol/L (applied only if baseline sBA level was ⩾102 µmol/L) OR at least a 75% average percent reduction from baseline. The average sBA from Weeks 18, 22, and 26 was used.	n (%) p value vs PBO	15 (45.5) 0.0004	2 (6.5)		
Number of days with mild/no pruritus	Number of days the morning ItchRO(Obs) severity score	Number of days p value vs.	53.0 0.0008	25.5	Depending on the baseline scores, the data may be	MRX-502

Effect	Short description	Unit	Treatment - MRX	Placebo	Uncertainties / Strength of evidence	References
(PFIC cohort; ITT)	was ⩽1 over the last 84 study days	placebo			confounded. Exploratory analysis.	
Number of patients with at least 50% treatment days with mild/no pruritus (PFIC cohort; ITT)	Number of participants with morning ItchRO(Obs) severity score ⩽1 for ⩾50% of the time period (Weeks 15 – 26)	% p value vs. placebo	72.7% 0.0037	35.5%	Depending on the baseline scores, the data may be confounded. Exploratory analysis.	MRX-502
z-score for Weight (PFIC cohort; ITT)	Change in weight z-score between baseline and average of Weeks 18, 22, and 26 vs PBO	LS mean (95% CI) change from placebo p value vs PBO	0.227 (0.012, 0.442) 0.0391		Slightly improved scores on MRX compared to PBO Exploratory evidence	MRX-502
z-score for Height (PFIC cohort; ITT)	Change in height z-score between baseline and average of Weeks 18, 22, and 26 vs baseline	LS mean (95% CI) change from baseline p value vs baseline	0.078 (-0.093, 0.248) 0.3652	decrease (worsening) in height z-score	No apparent improvements on MRX and no difference to PBO shown, may be due to short treatment duration. Exploratory evidence	MRX-502
Change in EDQ(Obs) morning severity score (PFIC cohort; ITT)	Change in average EDQ(Obs) morning severity score at Weeks 15–26	LS mean (95% CI) difference to PBO p value vs. PBO	-1.098 (-1.721, -0.475) 0.0009		Exploratory analysis.	MRX-502
Sleep disturbance (PFIC cohort; ITT)	Morning EDQ(Obs) sleep disturbance score between baseline and average of Weeks 18, 22, and 26	LS mean (95% CI) change from placebo p value vs PBO	-1.190 (-1.783, -0.597) 0.0002		Exploratory analysis.	MRX-502
FIB-4 (PFIC cohort; ITT)	Change from baseline to Week 18-26	LS mean (SE) change from baseline p value LS mean (95% CI) change from placebo	0.016 (0.0328) 0.6242 -0.085 (-0.182, 0.012) 0.0838	0.101 (0.0358) 0.0062	Exploratory analysis.	MRX-502

Effect	Short description	Unit	Treatment - MRX	Placebo	Uncertainties / Strength of evidence	References
		p value vs PBO				
APRI (PFIC cohort; ITT)	Change from baseline to Week 18-26	LS mean (SE) change from baseline p value	-0.039 (0.2189) 0.8605	0.462 (0.2341) 0.0570	Exploratory analysis.	MRX-502
Change in sBA (PFIC cohort; ITT)	The mean change (SD) from baseline in sBA values at the end of the core study period at Week 13	Mean change (SD) µmol/L	-107.965 (146.7659, p=0.0760) µmol/L	NA	Exploratory analysis. Limited evidence.	MRX-801
Unfavourable Effects						
			MRX PFIC cohort (N=33)	**Placebo PFIC cohort (N=31)**	**MRX Full Cohort(N=47)**	
Diarrhoea		n/N %	19/33 57.6%	5/31 16.1%	27/47 57.4%	MRX-502
Abdominal pain	PT= Abdominal+ upper abdominal pain	n/N %	10/33 30.3%	3/31 9.7%	12/47 25.5%	MRX-502
Vomiting		n/N %	3/33 9.1%	5/31 16.1%	3/47 6.4%	MRX-502
Pyrexia		n/N %	15/33 45.5%	9/31 29.0%	17/47 36.2%	MRX-502

Safety-Source: Tbl. 38 Overall Summary of Treatment-Emergent Adverse Events (Safety Population) and TEAEs in at Least 5% of All Maralixibat-Treated Participants-by Preferred Term (Safety Population)in the pivotal trial MRX-502

CI=confidence interval; ITT=intent to treat; LS=least-squares; PFIC=progressive familial intrahepatic cholestasis; SE=standard error of the mean; sBA = serum bile acids; ItchRO (Obs) = pruritus assessment tool; PBO = placebo.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy:

The totality of the presented evidence shows that MRX exerts positive effects on cholestasis biomarkers (sBA, bilirubin (total and direct)), improves symptoms of the disease (pruritus, growth retardation, fatigue, poor quality of life) and suggests slowing the process of progressive liver damage (PELD, liver fibrosis parameters) in > 1 years old children with PFIC. Changes in autotaxin and C4 are consistent with the observed effects.

Based on similarity of pathomechanisms of the disease and the mechanism of action of MRX in the patients with PFIC across all age groups, and considering the available data on efficacy/PD parameters extrapolation of efficacy to

- adult population is supported with the caveat that efficacy data in the patients with body weight of >50 kg are missing and some decrease in efficacy due to the cap of the maximum dose in these patients cannot be excluded. However, respective recommendation that treatment should be stopped if not effective has been included in the SmPC.
- infants from the age of 3 months is supported.

Long-term efficacy data on clinical outcomes will be additionally collected post-approval.

The Applicant has submitted the justification for approval under exceptional circumstances including the proposal of SOBs. This has been adequately justified and is agreed (please refer to 3.7.3 below).

Safety: Maralixibat appears to have an acceptable safety profile in the applied for PFIC patients that is rather similar to that observed in subjects with ALGS. As in the ALGS population gastrointestinal adverse events as diarrhoea, abdominal pain and vomiting were reported to be the most common adverse drug reactions also in the PFIC population. Differences observed between both populations are not further interpretable due the small number of subjects and may be chance findings. Similar to the ALGS population SAEs were rare and assessed as not drug related and mostly mild to moderate and resolved with no action taken with maralixibat. Notably, two new ADRs have been identified during the recent PSUSA, ALT and AST elevated.

With respect to safety across age groups, some small differences were noted in younger children, but no clear relationship between adverse events and maralixabat could be concluded. Due to the small sample size in each age group, a meaningful interpretation is not possible.

No new safety signals were identified from the currently available post marketing data base, which is reassuring.

As the proposed dosage in the PFIC indication is much higher than the one approved for patients with ALGS and those tested in previous developments and the safety database, the degree of uncertainty regarding its safety and tolerability (especially long-term and in infants) is naturally high. This particularly concerns the higher exposure to PG, especially in more vulnerable populations/populations at risk (children <5 years of age; patients with renal or hepatic impairment). The data submitted by the Applicant do not provide evidence for PG-related toxicity at the PG exposure tested, i.e., up to 25 mg/kg/day. However, the data were collected in PFIC patients with intact hepatic and renal function. Therefore, a reduced dose of Livmarli is recommended in all patients below the age of 5 years and those with moderate liver or renal impairment. Additionally, Livmarli is contraindicated in patients with severe hepatic or renal impairment. Also, further risk minimisation measures have been agreed to reduce the risks of medication errors potentially leading to PG toxicity.

The applicant has provided evidence that the reduced dose recommended for patients at increased risk of PG toxicity will also be sufficiently effective. Overall, efficacy of Livmarli with the proposed posology has been demonstrated and the safety profile of appears acceptable.

3.7.2. Balance of benefits and risks

The small size of the efficacy and safety database is acknowledged in this rare condition. This refers in particular to the relatively short treatment duration (especially in infants) and short placebo control in the pivotal trial, potential Hepatotoxicity and the missing information on chronic exposure to propylene glycol. Further information will be provided post authorisation with a low-interventional clinical study that is made specific obligation to this Marketing authorisation under exceptional circumstances.

Considering the demonstrated efficacy in the treatment of PFIC in patients from 3 months of age and older and the acceptable safety profile, similar to that observed in subjects with the approved

indication ALGS, the Benefit / Risk in the indication "treatment of Progressive familial cholestasis (PFIC) in patients 3 months and older" is positive.

3.7.3. Additional considerations on the benefit-risk balance

Livmarli was approved as a Marketing Authorisation Under Exceptional Circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004. As comprehensive data on the new indication "Treatment of Progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older" are not available, the Applicant claims that the extension of indication comply with the requirements for a marketing authorisation under exceptional circumstances.

The following arguments were presented by the MAH to support the approval of the extension of indication:

- **The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence**

The exact prevalence of PFIC is unknown, but incidence is estimated to affect 1 in every 50,000 to 100,000 births worldwide (Davit-Spraul et al. 2009). Based on a recent literature review of PFIC conducted by Baker and colleagues (2019), the prevalence of PFIC in Europe was estimated at 0.07/10,000 persons.

In the overall maralixibat program for PFIC, clinically relevant and statistically significant improvements in multiple cholestasis parameters and disease burden were observed in a study population that is representative of the overall cholestasis PFIC population. Significant improvement effects were maintained throughout the long-term treatment period.

There is no potential for the Applicant to conduct future clinical studies in PFIC that would generate further efficacy and safety data beyond what has previously been shown in the current clinical program, due to the rarity of the disease and further limitations to identify patients with PFIC who are available to participate in clinical studies.

- **Proposal for detailed information on the specific obligation to be conducted**

In addition to the planned ongoing pharmacovigilance activities (e.g., collecting long-term data from clinical studies MRX-503, MRX-801, and MRX-800) as per the revised EU Risk Management Plan, the Applicant initially proposed to conduct a prospective 5-year registry-based study (MRX-504) on patients with PFIC by collecting clinical outcomes (according to an agreed protocol) to support the approval of the "PFIC indication" under exceptional circumstances. This proposal was changed with the responses to the second RSI and the Applicant proposes to collect post-approval efficacy and safety information in PFIC population as part of the post-approval low-interventional PASS LEAP EU study. Yearly reports will be provided.

The comprehensiveness assessment in the currently targeted indication is provided below:

1. Quality of evidence: The key evidence of efficacy is limited to a relatively small, double-blind, placebo-controlled, parallel-group, 6-months study in a 1 to 15 years old patient population with various sub-types of PFIC (PFIC 1, PFIC2, PFIC3, PFIOC4 and PFIC6). To allow for proper assessment of the effects of MXT on clinical outcomes, a study with the duration of several years would be required. It is however acknowledged by the CHMP that use of placebo in this rare disease over years would not be ethical and is not feasible. Consistency is seen across various parameters suggestive of improved/stabilised liver function on MRX (e.g., sBA levels, ItchRO, growth parameters, liver fibrosis markers, PELD, fatigue scores), which also suggest potential

positive effects on clinical outcomes. Evidence of efficacy in infants is limited to a small, single-arm, open-label trial, with efficacy parameters restricted to sBA and CSS assessments mostly over the time period of around 13 weeks.

2. The precision of effect size: Treatment effect was demonstrated in a relatively small sample and its precision is therefore naturally low. However, effects on sBA, bilirubin and pruritus are sufficiently large to conclude on a relevant potential benefit.

3. The endpoints are considered to be clinically meaningful, as these capture various aspects of the burden of the target indication. However, the most relevant endpoints, such as effects on long-term clinical outcomes (e.g., progression of liver dysfunction, improvement in NLS, delay in surgical treatment) have not been studied and will need to be provided post-approval.

4. The maintenance of effect has been shown for up-to week 54 (24 weeks against placebo control), which can be considered sufficient to evaluate the maintenance of effect on the early/mid-term changes in the relevant efficacy parameters (e.g., sBA, bilirubin, pruritus, growth, liver fibrosis parameters, PELD), which may be suggestive of potential benefits in the long-term (e.g., improved native liver survival – NLS). Absence of data on long-term clinical outcomes is acknowledged as limitation. These will need to be provided post-approval.

5. Safety exposure: Safety database is limited, especially in infants (n=10). It is not possible to draw robust conclusions, especially on long-term safety, given the much higher doses recommended compared to the treatment with Alagille Syndrome and limited exposure. Moreover, expected high level of exposure to PG under the conditions of chronic use, especially in the patients younger than 5 and 1 years of age, as well as, in those with hepatic/renal dysfunction raises concerns. Risks of potential overdose/erroneous dosing will also need to be evaluated in the post authorisation PASS.

6. The safety follow up duration is considered acceptable to grant the approval in the patients above the age of 1 year, but is limited. In younger population data are even more limited. Post-approval collection of safety information is, therefore, necessary.

In conclusion, the CHMP considers the data provided not fully comprehensive.

Moreover, 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, requirements set out in Article 14 (8) of the Regulation (EC) No 726/2004 are considered fulfilled.

In addition, the CHMP considers necessary the amendment of the existing specific obligation as follows:

The Marketing Authorisation holder will collect further data on safety and efficacy via the low-interventional LEAP EU study which is expected to run open-ended.

The MAH committed to adapt the LEAP EU (MRX-803 (formerly MRX-311) study, accordingly and to include patients with PFIC to gather the relevant data by means of a low-interventional clinical study (as defined in the article 2 (2)(3) of the Clinical Trials Regulation. Such study will allow to ensure compliance with GCP standards, including proper monitoring of data collection and of their quality.

3.8. Conclusions

The overall B/R of Livmarli is positive for the indication treatment of progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and III
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	Type IA	None

Grouped variation consisting of:
1) Extension of indication to include treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in patients 3 months of age and older for LIVMARLI, based on results from studies MRX-502, LUM001-501, MRX-503, MRX-800 and MRX-801; MRX-502 is an international, multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 3 study that evaluated the efficacy and safety of maralixibat in PFIC participants aged >12 months to <18 years on a proposed dosage of up to 600 µg/kg BID over 6 months. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Annex II are updated in accordance. Version 4.1 of the RMP is agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the labelling.

2) B.I.b.1.b - type IA - To tighten the active substance maralixibat specification limits for genotoxic impurities. In addition, further editorial changes are made in module 3 which are consequential to the extension of indication and the higher maximum daily dose.

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

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II and III and to the Risk Management Plan are recommended.

This recommendation is subject to the following amended conditions:

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.

In addition, 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.

Additional risk minimisation measures

Due to the propylene glycol content in order to minimise the important potential risks "Medication error resulting from erroneous dosing (PFIC patients)" the MAH should make available in each Member State (MS) where Livmarli is marketed:

- A dosing guide developed to help physicians to guide patients for the dosing schedule, volume and required syringe size to be used
- A patient booklet where the physician will enter the date, patient's weight, calculated dose and volume and required syringe size to be used

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) and in the treatment of patients with PFIC, the MAH shall conduct and submit the results of study LEAP (MRX-803) 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 reassessment)

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0436/2022and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Livmarli-EMEA/H/C/005857/II/0003/G'.