22 May 2025
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Livmarli

Maralixibat

Procedure no: **EMA/PAM/0000267764** (previously EMEA/H/C/005857/P46/006)

Note

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

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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	16.09.2024	16.09.2024	☐
☐	CHMP Rapporteur Assessment Report	21.10.2024	28.10.2024	☐
☐	CHMP members comments	04.11.2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07.11.2024	n/a	☐
☐	RSI	14.11.2024	14.11.2024	☐
☐	Submission	25.02.2025	12.02.2025	☐
☐	Re-start	26.02.2025	26.02.2025	☐
☐	CHMP Rapporteur Assessment Report	12.03.2025	12.03.2025	☐
☐	CHMP members comments	17.03.2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20.03.2025	n/a	☐
☐	2nd RSI	27.03.2025	27.03.2025	☐
☐	Submission	22.04.2025	17.04.2025	☐
☐	Re-start	23.04.2025	23.04.2025	☐
☐	CHMP Rapporteur Assessment Report	07.05.2025	25.04.2025	☐
☐	CHMP members comments	12.05.2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	15.05.2025	n/a	☐
☒	CHMP adoption of conclusions:	22.05.2025	22.05.2025	☐

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1. Introduction

On 03 September 2024, the MAH submitted a completed paediatric study for LIVMARLI 9.5 mg/ml oral solution, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

LIVMARLI (maralixibat) has been authorised in the EU on 9 December 2022 for the treatment of cholestatic pruritus in patients with ALGS aged 2 months and older and on 28 June 2024 for the treatment of PFIC in patients 3 months of age and older (MA number EU/1/22/1704/001).

The MAH is also pursuing the development of maralixibat in the "treatment of biliary atresia" and has agreed to a relevant PIP within May 2021 (EMEA-001475-PIP04-20). This PIP includes two clinical trials:

- Study 1:
  "Multicentre, double-blind, placebo-controlled, randomised parallel-group, followed by an open-label extension (OLE) in participants from 21 days of age to less than 90 days of age with biliary atresia (BA) after hepatoportoenterostomy (HPE)" (MRX-701).
- Study 2:
  "Multicentre, double-blind, placebo-controlled, randomised parallel group study, in participants from birth to less than 18 years of age with biliary atresia (BA) after hepatoportoenterostomy (HPE)" (MRX-702).

Study 1 (MRX-701) has been completed and there is no upcoming regulatory procedure foreseen by the MAH relying on the results of this study.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study "Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Biliary Atresia after Hepatoportoenterostomy" (MRX-701) is a standalone study.

This submission refers to an Article 46 submission; it includes the final clinical study report of the study MRX-701. This paediatric study in patients with biliary atresia has been conducted in accordance with the relevant paediatric investigational plan (EMEA-001475-PIP04-20) for maralixibat in the "treatment of biliary atresia". No further regulatory procedures are foreseen by the MAH based on the results of this study at this point.

2.2. Information on the pharmaceutical formulation used in the study

In Study MRX-701, maralixibat was provided as ready-to-use oral solution in multiple dosage strengths (5, 10, 15, and 20 mg/mL; strengths are reported as maralixibat chloride; 10 mg/mL maralixibat chloride is equivalent to 9.5 mg/mL maralixibat). The drug product contained maralixibat drug substance (maralixibat chloride), and the same excipients as included in Livmarli® 9.5 mg/mL oral solution (propylene glycol, sucralose, grape flavour, disodium edetate dihydrate, purified water). To accurately dose patients <5.0 kg, caregivers were instructed to dilute the ready-to-use maralixibat formulation with water immediately prior to administration. That included a 5-fold dilution of assigned study drug with a predefined quantity of water. The diluted formulation has been demonstrated to be stable for up to 24 hours at ambient conditions.

Maralixibat was provided in 30-mL volumes packaged in amber-coloured polyethylene bottle and was administered per participant's weight at each study visit (Table 1 and 2). For participants <5 kg for whom at-home dilution was required, the information in parentheses indicates the diluted formulation that was given to the participant.

***Table 1** Study Dosing Plan (for patients ≥1 Month of Age)*

Body Weight (kg)	Strength* and Dose			
	5 mg/mL	**10 mg/mL**	**15 mg/mL**	**20 mg/mL**
	150 µg/kg/dose	**300 µg/kg/dose**	**450 µg/kg/dose**	**600 µg/kg/dose**
2.5–3.0	0.4 (diluted formulation)	0.4 (diluted formulation)	0.4 (diluted formulation)	0.4 (diluted formulation)
3.1–3.5	0.5 (diluted formulation)	0.5 (diluted formulation)	0.5 (diluted formulation)	0.5 (diluted formulation)
3.6–4.0	0.6 (diluted formulation)	0.6 (diluted formulation)	0.6 (diluted formulation)	0.6 (diluted formulation)
4.1–4.5	0.7 (diluted formulation)	0.7 (diluted formulation)	0.7 (diluted formulation)	0.7 (diluted formulation)
4.6–4.9	0.8 (diluted formulation)	0.8 (diluted formulation)	0.8 (diluted formulation)	0.8 (diluted formulation)
5–6	0.15	0.15	0.15	0.15
7–9	0.25	0.25	0.25	0.25
10–12	0.30	0.30	0.30	0.30
13–15	0.40	0.40	0.40	0.40
16–19	0.50	0.50	0.50	0.50
20–24	0.60	0.60	0.60	0.60
25–29	0.80	0.80	0.80	0.80
30–34	0.90	0.90	0.90	0.90
35–39	1.00	1.00	1.00	1.00
40–49	1.25	1.25	1.25	1.25
50–59	1.50	1.50	1.50	1.50
60–69	1.75	1.75	1.75	1.75
70–79	2.00	2.00	2.00	2.00
80+	2.50	2.50	2.50	2.50

*Strengths are reported as maralixibat salt.

***Table 2** Study Dosing Plan (for patients <1 Month of Age)*

Body weight (kg)	Dose volume (mL)
2.5–3.0	0.20 (diluted 5 mg/mL formulation)
3.1–3.5	0.25 (diluted 5 mg/mL formulation)
3.6–4.0	0.30 (diluted 5 mg/mL formulation)
4.1–4.5	0.35 (diluted 5 mg/mL formulation)
4.6–4.9	0.40 (diluted 5 mg/mL formulation)
5–8	0.10
9–12	0.15

Note: Dose taken once daily.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Biliary Atresia after Hepatoportoenterostomy, MRX-701

2.3.2. Clinical study

MRX-701

Description

Phase 2 study MRX-701 (EudraCT 2020-000974-22) was a 26-week, multicentre, double-blind, placebo-controlled, randomised parallel-group study, followed by an open-label extension (OLE) including analyses up to Week 104, in participants with biliary atresia (BA).

It was conducted between 08 July 2021 (first participant enrolled) and 07 February 2024 (study completion date); the report is dated 18 July 2024.

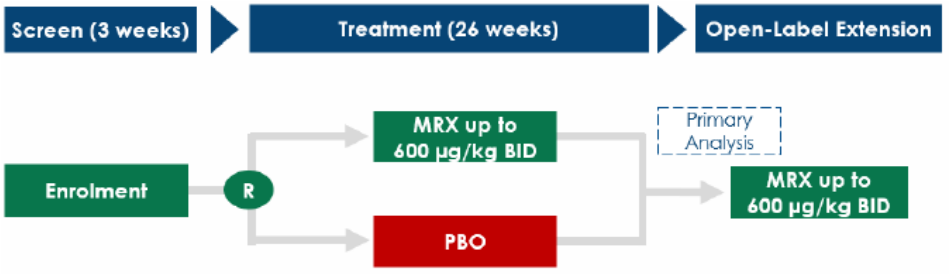
Methods

In the double-blind period of the study, participants were randomised 1:1 to receive either placebo or maralixibat, up to 600 µg/kg BID (as maralixibat chloride, equivalent to 570 µg/kg maralixibat, the currently recommended dose of Livmarli to treat patients with PFIC). Study periods were as follows:

1. Screening (1 week up to 3 weeks)
2. Double-blind period
   a. Dose escalation (4–8 weeks)
   b. Stable dosing (18–22 weeks)
3. OLE period (78 weeks)
   a. Dose escalation (4–8 weeks)
   b. Stable dosing (70–74 weeks)
4. Follow-up (2 weeks)

During the treatment period, participants received standard-of-care treatment in line with investigator and caregiver preference and in addition to study medication.

Figure 1 Study Schema



BID=twice daily; MRX=maralixibat; PBO=placebo; R=randomization.

Protocol MRX-701 was amended five times. The most relevant changes are summarised below by amendment.

Version 2 (dated 24 August 2020) implemented the following changes:

- Revised length of the planned study period
- Added Bayley neurocognitive assessment to baseline visit
- Revised the enhanced liver injury monitoring criteria, treatment interruption criteria, cholangitis diagnostic criteria, and study medication discontinuation rules for Grade 4 AE to reflect feedback from the US Food and Drug Administration

Version 3 (dated 03 February 2021) implemented the following changes:

- Updated exploratory objectives and endpoints to better capture clinically meaningful measures and updated hierarchical testing accordingly
- Revised to include participants <1 month of age
- Revised to clarify participant continuation into the OLE, to extend the OLE period, and to provide the dose for participants <1 month of age
- Added prohibited medications for participants <1 month of age
- Added information and guidance about maralixibat risks and benefits in line with recommendations from regulatory authorities
- Added pruritus and spleen size assessments in line with recommendations from regulatory authorities
- Added propylene glycol toxicity as an AESI and provided information for safety monitoring for propylene glycol toxicity
- Provided additional guidance for management of diarrhoea in line with recommendations from regulatory authorities
- Removed testing of the treatment group-by-interaction to avoid performing model selection and inferential testing on the same dataset at the recommendation of a health authority because this could lead to biased estimates and alter the interpretation of the treatment effect

Version 4 (dated 06 May 2021) implemented the following changes:

- Reduced the number of clinic visits to decrease burden on study participants and their caregivers
- Added a secondary and open-label extension objectives regarding rate of liver-related clinical events and corresponding endpoints per request by regulatory authority
- Added Asia as a region of study conduct
- Revised criterion for participant inclusion to include participants with gestational age <36 weeks, with approval by the medical monitor
- Revised dose escalation to a prespecified 2-step dose-escalation schedule, when prespecified criteria are met, upon recommendation by the DMC
- Added sensitivity analysis for the DMC-approved dose escalation

Version 5 (dated 25 March 2022) implemented the following changes:

- Removed fibrosis-4 from the exploratory endpoints and protocol assessments

Study participants

The inclusion criteria were:

1. Informed consent (by the legally authorized representative) per the Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Male or female participants with a body weight ≥2500 g (before or during the screening period) who are ≥21 days old and ≤90 days old at the time of HPE or Kasai procedure
3. Gestational age ≥36 weeks at birth (Those with gestational age <36 weeks with no present clinical or developmental preterm complications that could impact participation in the study may be included after evaluation and approval by the medical monitor.)
4. HPE or Kasai Procedure within 3 weeks prior to randomization

5. Clinical diagnosis of BA at laparotomy (with subsequent confirmation on histology of the biliary remnant)
6. Caregiver willingness to comply with all study visits and requirements, including ability to read and understand the questionnaires and, if applicable, capable of diluting study medication per investigator training and written instructions
7. Caregiver access to email or phone for remote participant contacts

The exclusion criteria were:

1. Chronic diarrhoea requiring ongoing IV fluid or nutritional intervention at screening, during the screening period, or during the 30 days prior to screening
2. History of surgical disruption of the enterohepatic circulation other than HPE
3. Has had any of the following: HPE performed by laparoscopy, undergone a second HPE, or has undergone an exploratory bile duct procedure
4. Participant not tolerating enteral feeds at screening or during the screening period
5. Evidence of another pathology involving the intrahepatic bile ducts (e.g., paucity, sclerosing cholangitis)
6. Diagnosis of polysplenia syndrome, including evidence of BA splenic malformation syndrome, or major malformation of another organ system
7. Diagnosis of cystic BA (based on clinician judgment, including but not limited to ultrasonography and cholangiography results)
8. Decompensated cirrhosis (international normalized ration [INR] >1.5 after correction of possible vitamin K deficiency, history or presence of clinically significant ascites, known varices, variceal haemorrhage, and/or encephalopathy)
9. Previous or imminent need for liver transplantation
10. Known hypersensitivity to maralixibat or any of its excipients
11. Previous use of an IBAT inhibitor, N-acetyl cysteine, immunoglobulins, or traditional or herbal medicine remedies that are used to treat liver diseases or with a safety profile known to impact liver parameters
12. Receipt of investigational drug, biologic, or medical device within 30 days or 5 half-lives (whichever is longer) prior to screening
13. Treatment with other medications containing propylene glycol (PG) or alcohol or any substrate for alcohol dehydrogenase (e.g., ethanol). For participants <1 month of age only
14. Known caregiver history of unreliability, mental instability, or cognitive impairment that, in the opinion of the investigator or sponsor medical monitor, could compromise the validity of informed consent, compromise the safety of the participant, or lead to nonadherence with the study protocol or inability to conduct the study procedures
15. Presence of other significant liver disease or any other conditions or abnormalities which, in the opinion of the investigator or sponsor medical monitor, may compromise the safety of the participant or interfere with participation in or completion of the study (prior or current cytomegalovirus infection is allowed)
16. History or presence of any other disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, including bile salt metabolism in the intestine (e.g., inflammatory bowel disease), per investigator discretion

Treatments

Study treatments: See above.

Concomitant use of standard-of care medications was allowed if recorded within concomitant medication records. Standard of care includes but is not limited to the use of steroids, antibiotics,

aldactone, furosemide, albumin, rifampicin, and UDCA. Standard of care excludes the use of N-acetylcysteine and immunoglobulins.

Objectives

The Primary Objective of the placebo-controlled portion of this study was:

- to evaluate the efficacy of maralixibat on biliary drainage after HPE in participants with BA.

The Secondary Objectives of the placebo-controlled portion of this study were:

- to evaluate the rate of clinically relevant reductions in cholestatic biomarkers with maralixibat treatment
- to evaluate the rate of liver-related clinical events
- to evaluate the safety, tolerability, and pharmacokinetics of maralixibat.

The OLE objectives included the same primary and secondary objectives analysed over the full study duration, including the OLE period (through Week 104).

Outcomes/endpoints

The primary efficacy endpoint was defined as the mean change in total serum bilirubin levels from baseline through Week 26.

Secondary Efficacy Endpoints were proportion of participants with total serum bilirubin levels <2 mg/dL at Week 26, mean change in total sBA levels from baseline through Week 26, proportion of participants with sBA levels ≤40 mmol/L at Week 26, proportion of participants with total serum bilirubin levels ≤1.2 mg/dL at Week 26, proportion of participants observed to have a liver-related clinical event, including liver transplantation, liver decompensation (hepatic encephalopathy, variceal bleeding, new persistent ascites) or death through Week 26, proportion of participants undergoing liver transplantation or death through Week 26, proportion of participants observed to develop clinically evident portal hypertension defined as splenomegaly (spleen size >2 cm below the costal margin palpated on physical examination) and thrombocytopenia (platelet count <150 x 109/L) or clinically evident ascites or endoscopic evidence of oesophageal or gastric varices through Week 26, incidence of treatment-emergent adverse events (TEAEs), including serious, related to study medication, leading to withdrawal, special interest TEAEs, along with TEAEs by severity and by relationship to study medication, change from baseline in safety laboratory, physical examination findings, vital signs, neurodevelopmental assessment, and maralixibat PK profile.

Endpoints of the OLE were analogue to above primary and secondary endpoints, but for study data through Week 104.

Sample size

Estimates for placebo response and variance are drawn from Bezerra et al. (Bezerra JA, Spino C, Magee J, et al. Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia. The START randomized clinical trial. JAMA 2014;311:1850–9). Under the assumption of no change over time in total bilirubin levels in the placebo group provides 80% power to detect an expected reduction in total bilirubin compared with placebo of approximately [redacted] by Week 26 of treatment, at the 2-sided alpha-level of 0.05, with use of a 1:1 randomization scheme, and with allowance for a 10% attrition rate, 72 participants (36 per group) were planned for enrolment into the study.

Randomisation and blinding (masking)

Treatment assignment used a block randomization process scheme by study site (i.e., stratified by study site).

Statistical Methods

The primary analysis on the primary efficacy endpoint was conducted in the ITT population; a restricted maximum likelihood (REML)-based mixed-effects model for repeated measures (MMRM) was used. The repeated measures include post-baseline visits during the double-blind phase through Week 26, with the change from baseline in total bilirubin as the dependent variable. The MMRM model included [redacted]. 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 least squares [LS] means) between treatment groups using [redacted]. Significance tests will be based on LS means using a 2-sided significance level (2-sided 95% CIs).

Sensitivity analyses were performed on the primary efficacy endpoint to quantify the possible impact of missing data and to demonstrate the robustness of the conclusions; both an MNAR- and MAR-based analyses were used.

Summary statistics on total bilirubin and a figure with the LS mean ± SE of change from baseline in total bilirubin by treatment group and visit were also presented.

For continuous secondary efficacy endpoints, an analysis similar to that described for the primary efficacy endpoint, including the sensitivity analyses, was performed for each of the secondary efficacy endpoints.
For the binary outcomes looking at proportions of participants (e.g., proportion of participants with total bilirubin levels <2 mg/dL at Week 26), the number and proportion of participants were summarised by treatment group. Barnard's exact test was used to calculate the p-value for the difference between treatment groups.

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

In order to maintain study-wide Type I error control, a hierarchical testing procedure was used in the comparisons between maralixibat and placebo on the primary and secondary efficacy endpoints on the primary cohort in the ITT population using the primary analysis method (as described for the primary endpoint).

Exploratory efficacy endpoints were summarised descriptively. The treatment effect was estimated using a Cox's Proportional Hazard model stratified by the randomisation strata to calculate the hazard ratio. Kaplan-Meier (i.e., product-limit) estimates of median OS time were presented by treatment arm together with two-sided 95% CIs calculated according to Brookmeyer and Crowley (Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29–41.). The number of participants at risk versus failed along with Kaplan-Meier estimates of [redacted] were estimated with corresponding two-sided 95% CIs derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data, New York: John Wiley & Sons 1980.). The estimate of the standard error was computed using Greenwood's formula.

OLE endpoints were summarised descriptively.

As regards pharmacokinetic analyses, plasma maralixibat concentrations at each nominal time point and sampling time were summarised using descriptive statistics.

Results

Participant flow

A total of 75 participants were enrolled; in the double-blind period of the study, 40 participants were randomised to maralixibat and 35 to placebo. Of these, 52 (69.3%) completed the double-blind period of the study (28 maralixibat, 24 placebo). These 52 participants received maralixibat in the OLE period of the study.

The majority of participants were able to dose escalate to the maximum dose of 600 µg/kg BID in both the double-blind and OLE periods.

A total of 74 participants (98.7%) discontinued from the study due to various reasons: study terminated by sponsor [45 participants], AE [11 participants], liver transplant or imminent need for liver transplant [12 participants], withdrawal by parent/guardian [3 participants], and other [3 participants]. The remaining participant has been recorded as having completed study treatment due to irreconcilable data entry issues; this participant discontinued during the OLE period due to the study being terminated by sponsor.

A summary of participant disposition is provided in the table below.

Table 3 **Participant Disposition (Screened)**

	No. of Participants (%)		
Status or Category	Maralixibat	Placebo	Overall
Screened for eligibility			77
Screen failure			2
Randomized	40	35	75
Safety Population [a]	40	35	75
ITT Population [b]	40 (100)	35 (100)	75 (100)
Per-Protocol Population [c]	40 (100)	35 (100)	75 (100)
Completed double-blind period	28 (70.0)	24 (68.6)	52 (69.3)
Completed study treatment	0	1 (2.9) [d]	1 (1.3) [d]
Discontinued during double-blind period	12 (30.0)	11 (31.4)	23 (30.7)
Reason for discontinuation			
Adverse event	5 (12.5)	3 (8.6)	8 (10.7)
Liver transplant or imminent need for liver transplantation	5 (12.5)	6 (17.1)	11 (14.7)
Withdrawal by parent/guardian	2 (5.0)	1 (2.9)	3 (4.0)
Other [e]	0	1 (2.9)	1 (1.3)

	No. of Participants (%)		
Status or Category	Maralixibat	Placebo	Overall
Discontinued during the OLE period	28 (70.0)	23 (65.7)	51 (68.0)
Reason for discontinuation			
Adverse event	3 (7.5)	0	3 (4.0)
Liver transplant or imminent need for liver transplantation	0	1 (2.9)	1 (1.3)
Study terminated by sponsor	23 (57.5)	22 (62.9)	45 (60.0)
Other [e]	2 (5.0)	0	2 (2.7)

ITT=intent-to-treat; OLE=open-label extension.
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 have a potential impact on the efficacy analysis.
d Reported as completed due to irreconcilable data issue. Participant [redacted] discontinued during the OLE period due to the study being terminated by the sponsor.
e One disease progression and one drug interruption criteria met.
Source: Table 14.1.1.1.

Recruitment

The study was conducted between 08 July 2021 (first participant enrolled) and 07 February 2024 (last participant completed).

Baseline data

At baseline, the mean (standard deviation [SD]) age was 76.1 (17.63) days and ranged from 41 to 109 days. Participants were between the ages of 21 and 87 days (mean age [SD] 59.0 [17.11] days) at the time of hepatoportoenterostomy (HPE).

Mean total serum bilirubin (TSB) was 7.40 mg/dL (median: 6.88 mg/dL; range: 0.99 – 21.7 mg/dL) and mean serum bile acid (sBA) was 149.20 µmol/L (median: 140.0 µmol/L; range: 24.31 – 353.35 µmol/L) at baseline. More than 90% of patients used ursodeoxycholic acid at the baseline. Liver function tests were increased, but relatively balanced across treatment groups, apart from GGT, that was particularly elevated and imbalanced across the groups with placebo patients having higher values (e.g., mean/median GGT were 791 U/L and 712 U/L in MRX group and 1086 U/L and 1015 U/L in placebo population).

Median AST to platelet ratio index (APRI) was 0.461 and 0.419 and median paediatric end-stage liver disease (PELD) scores were 0.779 and 2.725 in MRX and placebo groups, respectively.

Medical history at the baseline was collected (judging from the CRFs) but not summarised in a table.

Number analysed

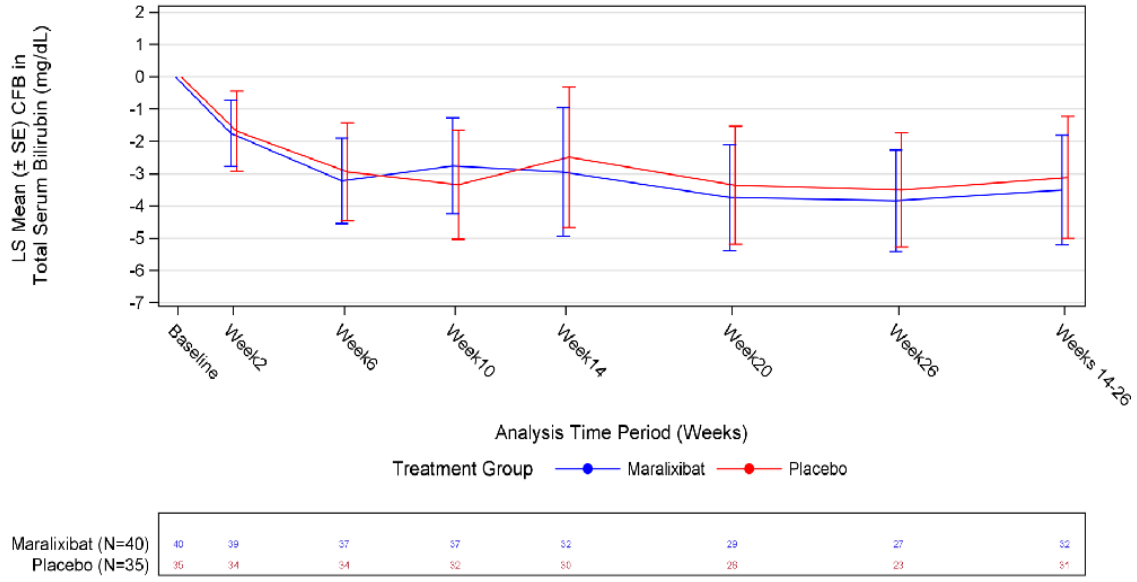
See above.

Efficacy results

The Week 26 analysis was performed on 15 December 2023; at that time, the study was unblinded and the primary and secondary endpoints were reviewed. The study did not meet its primary and

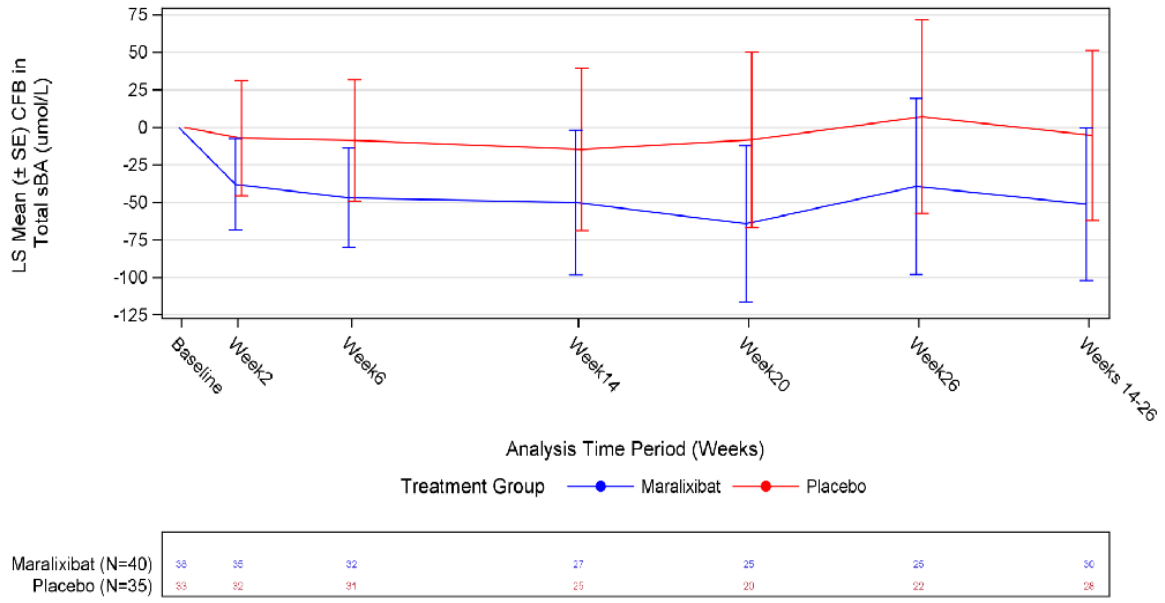
secondary endpoints. Maralixibat and placebo groups had reductions in TSB from the first post-baseline point of measurement (week 2) and over the whole treatment period. During the second half of the DB period (weeks 14-26) LS mean change from baseline in TSB in the maralixibat and placebo arms was -3.50 mg/dL and -3.11 mg/dL, respectively.

Figure 2 Plot of MMRM LS Mean (±SE) Change from Baseline in Total Serum Bilirubin (mg/dL) over Time (Intent-to-Treat Population)



Mean sBA (MMRM analysis) showed decrease which was numerically larger in the maralixibat arm compared with placebo, -51.19 µmol/L and -5.29 µmol/L, respectively. Comparative analysis of sBA by means of MMRM has not been done for median values.

***Figure 3** Plot of MMRM LS Mean (±SE) Change from Baseline in Total sBA (umol/L) Over Time (Intent-to-Treat Population)*



The proportion of participants who experienced liver-related events, liver transplantation, normalisation of TSB, and clinically lowering of TSB and sBA below pre-defined thresholds were similar in both groups. No deaths occurred in the study.

***Table 4** Primary and Secondary Efficacy Endpoints (Intent-to-Treat Population)*

	MRX (n=40)	PBO (n=35)	Difference
Primary Endpoint			
Mean change (95% CI) in TSB levels from baseline through Weeks 14-26	-3.50 (-5.21, -1.80) p=0.0001	-3.11 (-5.00, -1.23) p=0.0016	-0.39 (-2.76, 1.97) p=0.7419
Secondary Endpoints			
Mean change (95% CI) in total sBA levels from baseline through Weeks 14-26	-51.19 (-102.04, -0.34) p=0.0485	-5.29 (-62.03, 51.46) p=0.8531	-45.90 (-116.86, 25.05) p=0.2002
Proportion of participants with mean TSB levels <2 mg/dL through Weeks 14-26	24 (60.0%)	20 (57.1%)	p=0.8412
Proportion of participants observed to have a liver-related clinical event or death[a] through Week 26	8 (20.0%)	7 (20.0%)	p>0.9999
Proportion of participants undergoing liver transplantation or death[a] through Week 26	5 (12.5%)	3 (8.6%)	p=0.6658
Proportion of participants observed to develop clinically evident portal hypertension through Week 26	3 (7.5%)	4 (11.4%)	p=0.6236
Proportion of participants with mean TSB levels ≤1.2 mg/dL through Weeks 14-26	23 (57.5%)	18 (51.4%)	p=0.6658
Proportion of participants with mean sBA levels ≤40 mmol/L through Weeks 14-26	10 (25.0%)	7 (20.0%)	p=0.6659

MRX=maralixibat; PBO=placebo; sBA=serum bile acid; TSB=total serum bilirubin.
a No deaths occurred in the study.
Notes: Liver-related clinical event includes imminent need for liver transplantation, liver transplantation, liver decompensation, development of portal hypertension, or death.
Clinically Evident Portal Hypertension is defined as splenomegaly (spleen size >2 cm below the costal margin palpated on physical examination) and thrombocytopenia (platelet count <150 x 109/L) on the same assessment date.
Statistics for the mean change from baseline are from a mixed model for repeated measures with change from baseline as the dependent variable.
p-values for proportions comparing maralixibat with placebo treatment groups are calculated using a Barnard's exact test.
Sources: Tables 14.2.1, 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4, 14.2.2.5, 14.2.2.6, 14.2.2.7.

None of the liver function tests showed relevant difference to placebo. Clinician's scratch scale did not show relevant difference to baseline, or to placebo.

7αC4 (ng/mL) increased gradually from the baseline level of 8.8 ng/mL and reached significant change at weeks 14, 20, and 26 on MRX (LS Mean change from baseline at Weeks 14-26 was 28 ng/mL; p=0.0013; fitted summary statistics from MMRM, Intent-to-treat population), but showed no relevant

change in the placebo arm (7.7 ng/mL at baseline). Absolute values for this parameter during treatment could not be located.

Safety results

Exposure

Safety data are presented by double-blind period, by OLE period, and by overall participants who received maralixibat. Data are presented in the following groups:

- MRX: Study participants who received maralixibat in the double-blind period
- PBO: Study participants who received placebo in the double-blind period
- MRX-MRX: Study participants who received maralixibat in the double-blind period and received maralixibat in the OLE
- PBO-MRX: Study participants who received placebo in the double-blind period and received maralixibat in the OLE
- Overall: Study participants who received maralixibat at any time during the study

A summary of maralixibat exposure is provided in the table below. In the double-blind period, participants had mean (SD) maralixibat exposure of 147.6 (50.33) days. A total of 35 of 40 participants (87.5%) dose-escalated to the maximum dose of 600 µg/kg BID in the double-blind period. In the OLE, participants had mean (SD) maralixibat exposure of 152.2 (106.20) days. A total of 46 of 52 participants (88.5%) dose-escalated to the maximum dose of 600 µg/kg BID in the OLE. In all participants exposed to maralixibat during the study, the mean (SD) average daily dose was 995.90 (178.86) µg/kg/day with mean (SD) maralixibat exposure of 215.9 (135.11) days, with a range of 19–524 days.

Table 5 Maralixibat Exposure (Safety Population)

Variable Statistic	Double-Blind Period (n=40)	OLE (n=52)	Overall (n=64)
Treatment duration, in days			
Mean	151.5	153.1	219.1
SD (SE)	49.48 (7.82)	107.32 (14.88)	137.12 (17.14)
Median	179.0	137.5	201.5
Q1, Q3	121.5, 183.0	75.5, 202.0	98.5, 331.5
Min, max	19, 189	7, 524	19, 532
Treatment exposure, in days			
Mean	147.6	152.2	215.9
SD (SE)	50.33 (7.96)	106.20 (14.73)	135.11 (16.89)
Median	173.5	137.5	198.0
Q1, Q3	117.5, 182.0	74.0, 202.0	96.0, 329.0
Min, max	19, 189	7, 524	19, 524
Average daily dose, in µg/kg/day			
Mean	987.63	990.08	995.90
SD (SE)	182.774 (28.899)	218.862 (30.351)	178.862 (22.358)
Median	1051.50	1089.56	1067.85
Q1, Q3	944.48, 1102.61	934.54, 1142.95	953.34, 1120.11
Min, max	325.5, 1151.0	300.0, 1178.4	325.5, 1171.2

max=maximum; min=minimum; OLE=open-label extension; 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. Treatment exposure (days) = treatment duration in days – number of days both morning and evening doses were missed.
Source: Table 14.1.6.

Observed plasma concentrations were overall low.

Table 6 **Systemic exposure to maralixibat (Week 26; pre- and post-dose values; ng/ml; Safety population)**

Analysis Visit Sample Time Point Statistic	Maralixibat (N=40)	Placebo (N=35)
Week 26		
Pre-Dose		
No.	26	24
Mean	0.2030	0.0000
(95% CI for Mean)	(0.0921, 0.3138)	(NE, NE)
SD (SE)	0.27444 (0.05382)	0.00000 (0.00000)
CV (%)	135.2	NE
Median	0.0000	0.0000
Q1, Q3	0.0000, 0.3960	0.0000, 0.0000
Min, Max	0.000, 0.936	0.000, 0.000
Geometric Mean	0.4445	NE
Post-Dose		
No.	23	22
Mean	0.6567	0.1269
(95% CI for Mean)	(0.4175, 0.8958)	(0.0082, 0.2456)
SD (SE)	0.55314 (0.11534)	0.26771 (0.05708)
CV (%)	84.2	211.0
Median	0.5610	0.0000
Q1, Q3	0.2610, 0.9110	0.0000, 0.0000
Min, Max	0.000, 2.410	0.000, 0.982
Geometric Mean	0.6250	0.5084

Adverse events

An overall summary of TEAEs is provided in the table below.

For participants in the double-blind period:

- The percentage of participants with TEAEs was similar between the treatment groups, with the majority of participants (97.5% on maralixibat and 97.1% on placebo) experiencing a TEAE.
- The percentage of participants with a TEAE categorized as Grade ≥3 was similar between maralixibat (62.5%) and placebo (68.6%) treatment groups.
- The percentage of participants with a TEAE categorized as Grade ≥3 and related to study drug was similar between maralixibat (7.5%) and placebo (5.7%) treatment groups.
- A similar percentage of maralixibat (65.0%) and placebo (71.4%) participants had a treatment-emergent SAE.
- The percentage of participants with a treatment-emergent SAE related to study drug was similar between maralixibat (7.5%) and placebo (5.7%) treatment groups.
- The percentage of participants with a TEAE that led to permanent discontinuation of study drug was similar between maralixibat (12.5%) and placebo (8.6%) treatment groups.

During the OLE, participants in the MRX-MRX group had a longer mean exposure to maralixibat than participants in the PBO-MRX group because of being exposed to maralixibat during the 26-week double-blind period. For participants in the OLE:

- The percentage of participants with TEAEs was similar between the treatment groups, with the majority of participants (96.4% of MRX-MRX and 91.7% of PBO-MRX) experiencing a TEAE.
- The percentage of participants with a TEAE categorized as Grade ≥3 was slightly higher in MRX-MRX (50.0%) than PBO-MRX (41.7%) treatment groups.
- There was 1 participant (3.6%) with a TEAE categorized as Grade ≥3 and related to study drug in the MRX-MRX treatment group.
- The percentage of participants with a treatment-emergent SAE was similar between MRX-MRX (39.3%) and PBO-MRX (41.7%) treatment groups.

- There were no participants in either group with a treatment-emergent SAE related to study drug during the OLE.
- Three participants (10.7%) in the MRX-MRX treatment group had a TEAE that led to permanent discontinuation of study drug.

For all participants exposed to maralixibat over time in Study MRX-701 (cumulative data):

- A total of 3 participants (4.7%) had an SAE related to study drug.
- A total of 8 participants (12.5%) had a TEAE that led to permanent discontinuation of study drug.
- A total of 4 participants (6.3%) had a TEAE categorized as Grade ≥3 and related to study drug.

No participant had a TEAE that resulted in death. Two patients died after early cessation of treatment and withdrawal from the study, but both cases were considered related to progression of the background disease (see below).

Table 7 Overall Summary of Treatment-Emergent Adverse Events – Safety Population

	No. (%) of Participants with ≥1 TEAE				
	Double-Blind Study Period		OLE Study Period [a]		Overall
Variable Statistic	MRX (n=40)	PBO (n=35)	MRX-MRX (n=28)	PBO-MRX (n=24)	MRX[b] (n=64)
AE	39 (97.5)	34 (97.1)	27 (96.4)	22 (91.7)	61 (95.3)
AE related to study drug	9 (22.5)	9 (25.7)	5 (17.9)	5 (20.8)	17 (26.6)
AE categorized as Grade ≥3	25 (62.5)	24 (68.6)	14 (50.0)	10 (41.7)	39 (60.9)
AE categorized as Grade ≥3 and related to study drug	3 (7.5)	2 (5.7)	1 (3.6)	0	4 (6.3)
SAE	26 (65.0)	25 (71.4)	11 (39.3)	10 (41.7)	39 (60.9)
SAE related to study drug	3 (7.5)	2 (5.7)	0	0	3 (4.7)
AE that led to permanent study drug discontinuation	5 (12.5)	3 (8.6)	3 (10.7)	0	8 (12.5)
AE that led to death	0	0	0	0	0
AE of special interest	16 (40.0)	12 (34.3)	7 (25.0)	6 (25.0)	27 (42.2)

AE=adverse event; MRX=maralixibat; MRX-MRX=participants who received maralixibat in the double-blind portion of the study and received maralixibat in the OLE; OLE=open-label extension; PBO=placebo; PBO-MRX=participants who received placebo in the double-blind portion of the study and received maralixibat in the OLE; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
a Events that occurred during the OLE period
b Events that occurred while receiving maralixibat during the double-blind and OLE study periods.
Notes: Percentages are 100*n/N. AEs are coded using MedDRA Version 26.1. Participants with more than one reported AE within each category were counted only once.
Source: Table 14.3.1.1.1.

During the double-blind period, the most common Treatment-Emergent Adverse Events (TEAEs) were pyrexia and cholangitis (37.5% each) and diarrhoea (32.5%) in maralixibat participants and cholangitis (54.3%), vitamin D deficiency (28.6%), and pyrexia (25.7%) in placebo participants.

During the OLE, for participants in the MRX-MRX group, the most common TEAEs were pyrexia and upper respiratory tract infection (28.6% each) and diarrhoea (21.4%). For participants in the PBO-MRX group, the most common TEAEs were diarrhoea (25.0%) and upper respiratory tract infection, vitamin D deficiency, and cough (20.8% each).

For all participants exposed to maralixibat during the study, the most common TEAEs were diarrhoea (37.5%), pyrexia (34.4%), and cholangitis (32.8%). The most common TEAEs in participants exposed to maralixibat during the study occurred in the SOC of Infections and infestations (76.6%), followed by Gastrointestinal disorders (59.4%; Table 14.3.1.2.1).

Table 8 TEAEs in ≥20% of Participants in Any Treatment by System Organ Class and Preferred Term – Safety Population

	No. (%) of Participants				
	Double-Blind Study Period		OLE Study Period [a]		Overall
SOC PT	MRX (n=40)	PBO (n=35)	MRX-MRX (n=28)	PBO-MRX (n=24)	MRX[b] (n=64)
Participants with ≥1 TEAE	39 (97.5)	34 (97.1)	27 (96.4)	22 (91.7)	61 (95.3)
Gastrointestinal disorders					
Diarrhoea	13 (32.5)	8 (22.9)	6 (21.4)	6 (25.0)	24 (37.5)
General disorders and administration site conditions					
Pyrexia	15 (37.5)	9 (25.7)	8 (28.6)	4 (16.7)	22 (34.4)
Hepatobiliary disorders					
Cholangitis	15 (37.5)	19 (54.3)	4 (14.3)	4 (16.7)	21 (32.8)
Infections and infestations					
Pneumonia	10 (25.0)	6 (17.1)	1 (3.6)	4 (16.7)	15 (23.4)
Upper respiratory tract infection	7 (17.5)	4 (11.4)	8 (28.6)	5 (20.8)	15 (23.4)
Metabolism and nutrition disorders					
Vitamin A deficiency	4 (10.0)	8 (22.9)	2 (7.1)	1 (4.2)	7 (10.9)
Vitamin D deficiency	7 (17.5)	10 (28.6)	3 (10.7)	5 (20.8)	15 (23.4)
Respiratory, thoracic and mediastinal disorders					
Cough	8 (20.0)	5 (14.3)	3 (10.7)	5 (20.8)	14 (21.9)

AE=adverse event; MRX=maralixibat; MRX-MRX=participants who received maralixibat in the double-blind portion of the study and received maralixibat in the OLE;
OLE=open-label extension; PBO=placebo; PBO-MRX=participants who received placebo in the double-blind portion of the study and received maralixibat in the OLE; PT=preferred
term; SOC=system organ class; TEAE=treatment-emergent adverse event.
a Events that occurred during the OLE period.
b Events that occurred while receiving maralixibat during the double-blind and OLE study periods.
Notes: Percentages are 100*n/N. AEs are coded using MedDRA Version 26.1. Multiple TEAEs were counted only once per participant for each SOC and PT.
Source: Table 14.3.1.2.1.

During the double-blind period, Grade ≥3 TEAEs that occurred in ≥2 participants included cholangitis, pneumonia, bronchiolitis, diarrhoea, and increased hepatic enzyme in maralixibat and cholangitis, pneumonia, COVID-19, and sepsis in placebo participants.
During the OLE, Grade ≥3 TEAEs that occurred in ≥2 participants included cholangitis and adenovirus infection in MRX-MRX participants and cholangitis and pneumonia in PBO-MRX participants.
During the double-blind period, there were 2 participants with life-threatening (Grade 4) events (ascites and hepatic cirrhosis in 1 participant each). The event of ascites was initially recorded as a Grade 2; 20 days after the discontinuation of maralixibat, the event was updated to Grade 4. According to guidelines provided to the site, the highest grade of the event was to be recorded; therefore, whereas the database notes the event as Grade 4, the severity was Grade 2 while the participant was on study drug. The events were considered by the investigator as not related to study drug.
Most TEAEs were categorized as severity Grade ≥3.

During the double-blind period, the most common treatment-related TEAE in the maralixibat group was diarrhoea (17.5%) and in the placebo group was diarrhoea and increased ALT (11.4% each).
During the OLE, for participants in the MRX-MRX group the most common treatment-related TEAE was diarrhoea (7.1%). For participants in the PBO-MRX group, with first exposure to maralixibat in the OLE, the most common treatment-related TEAE was also diarrhoea (16.7%).
For all participants exposed to maralixibat during the study, the most common treatment-related TEAE was diarrhoea (20.3%).

Table 9 Summary of Treatment-Related TEAEs by System Organ Class and Preferred Term – Safety Population

	No. (%) of Participants				
	Double-Blind Study Period		OLE Study Period [a]		
SOC PT	MRX (n=40)	PBO (n=35)	MRX-MRX (n=28)	PBO-MRX (n=24)	All MRX [b] (n=64)
Participants with ≥1 treatment-related TEAE	9 (22.5)	9 (25.7)	5 (17.9)	5 (20.8)	17 (26.6)
Blood and lymphatic system disorders					
Coagulopathy	0	1 (2.9)	0	0	0
Gastrointestinal disorders					
Abnormal faeces	0	0	0	1 (4.2)	1 (1.6)
Constipation	0	1 (2.9)	0	0	0
Diarrhoea	7 (17.5)	4 (11.4)	2 (7.1)	4 (16.7)	13 (20.3)
Hepatobiliary disorders					
Cholangitis	1 (2.5)	0	0	0	1 (1.6)
Investigations					
Alanine aminotransferase increased	2 (5.0)	4 (11.4)	1 (3.6)	0	2 (3.1)
Hepatic enzyme increased	1 (2.5)	0	0	0	1 (1.6)
Metabolism and nutrition disorders					
Vitamin A deficiency	1 (2.5)	0	1 (3.6)	0	2 (3.1)
Vitamin E deficiency	1 (2.5)	0	1 (3.6)	0	2 (3.1)
Skin and subcutaneous tissue disorders					
Dermatitis diaper	0	0	1 (3.6)	0	1 (1.6)
Pruritus	0	1 (2.9)	0	0	0

AE=adverse event; MRX=maralixibat; MRX-MRX=participants who received maralixibat in the double-blind portion of the study and received maralixibat in the OLE;
OLE=open-label extension; PBO=placebo; PBO-MRX=participants who received placebo in the double-blind portion of the study and received maralixibat in the OLE; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
a Events that occurred during the OLE period.
b Events that occurred while receiving maralixibat during the double-blind and OLE study periods.
Notes: Percentages are 100*n/N. AEs are coded using MedDRA Version 26.1. Multiple TEAEs were counted only once per participant for each SOC and PT.
Source: Table 14.3.2.2.

During the double-blind and OLE periods, the most frequent and common treatment-emergent SAE was cholangitis (15 participants [37.5%] in maralixibat and 18 participants [51.4%] in placebo treatment groups; 4 participants [14.3%] in MRX-MRX and 4 participants [16.7%] in PBO-MRX treatment groups).

For all participants exposed to maralixibat 39 participants (60.9%) had treatment-emergent SAEs, with the most common being cholangitis (21 participants [32.8%]).

Most treatment-emergent SAEs were considered not treatment-related; 6 treatment-emergent SAEs were considered treatment related (increased ALT, cholangitis, coagulopathy, diarrhoea [2 events], and increased hepatic enzyme). Most treatment-emergent SAEs were Grade 3 in severity. Most treatment-emergent SAEs had study drug action taken of dose not changed or study drug interrupted, and most resolved (3 events were reported as not recovered/not resolved).

See the table below for a summary of treatment-emergent SAEs.

***Table 10** Summary of Treatment-Emergent Serious Adverse Events Occurring in ≥2 Participants – Safety Population*

	No. (%) of Participants				
	Double-Blind Study Period		OLE Study Period [a]		
SOC PT	MRX (n=40)	PBO (n=35)	MRX-MRX (n=28)	PBO-MRX (n=24)	All MRX [b] (n=64)
Gastrointestinal disorders					
Diarrhoea	2 (5.0)	0	0	0	2 (3.1)
Hepatobiliary disorders					
Cholangitis	15 (37.5)	18 (51.4)	4 (14.3)	4 (16.7)	21 (32.8)
Infections and infestations					
Adenovirus infection	0	0	2 (7.1)	0	2 (3.1)
Bronchiolitis	2 (5.0)	1 (2.9)	1 (3.6)	0	2 (3.1)
COVID-19	1 (2.5)	3 (8.6)	0	0	1 (1.6)
Gastroenteritis	0	0	1 (3.6)	1 (4.2)	2 (3.1)
Parainfluenzae virus infection	2 (5.0)	0	0	0	2 (3.1)
Pneumonia	8 (20.0)	4 (11.4)	0	2 (8.3)	10 (15.6)
Rotavirus infection	1 (2.5)	0	0	1 (4.2)	2 (3.1)
Sepsis	0	2 (5.7)	0	0	0
Investigations					
Hepatic enzyme increased	2 (5.0)	0	0	1 (4.2)	3 (4.7)

AE=adverse event; MRX=maralixibat; MRX-MRX=participants who received maralixibat in the double-blind portion of the study and received maralixibat in the OLE; OLE=open-label extension; PBO=placebo; PBO-MRX=participants who received placebo in the double-blind portion of the study and received maralixibat in the OLE; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
a Events that occurred during the OLE period.
b Events that occurred while receiving maralixibat during the double-blind and OLE study periods.
Notes: Percentages are 100*n/N. AEs are coded using MedDRA Version 26.1. Multiple TEAEs were counted only once per participant for each SOC and PT.
Source: Table 14.3.2.1.

During the double-blind period, the percentage of participants with a TEAE that led to permanent discontinuation of study drug was similar between maralixibat (5 participants [12.5%]) and placebo (3 participants [8.6%]) treatment groups. The TEAEs that led to permanent discontinuation of study drug in participants in the maralixibat treatment group were cholangitis, cytomegalovirus infection, increased ALT, rotavirus infection, and hepatic cirrhosis (1 participant each). TEAEs that led to permanent discontinuation of study drug in participants in the placebo treatment group were cholangitis (2 participants) and haematochezia (1 participant).
During the OLE, there were 3 participants (10.7%) with a TEAE that led to permanent discontinuation of study drug; the events were gastrointestinal haemorrhage, increased blood bilirubin, and ileus (all in participants in the MRX-MRX treatment group).
No participant had a treatment-related TEAE that led to premature discontinuation of study drug.

Adverse events of special interest (AESIs) identified for Study MRX-701 were LSV deficiency requiring study drug discontinuation, liver parameter disruption requiring study drug interruption and/or dose modification (see Protocol MRX-701), and any event suspected and/or confirmed to be due to propylene glycol toxicity, which includes but is not limited to neurological complications, haemolysis, and cardiac arrhythmias. There were no reported AESIs due to LSV deficiency or propylene glycol toxicity. There were 27 participants who had AESIs due to liver parameter disruption, as summarized below.
During the double-blind period, AESIs occurred in similar percentages between treatment groups: 16 participants (40.0%) in maralixibat and 12 participants (34.3%) in placebo treatment groups.

During the OLE, AESIs occurred in 7 participants (25.0%) in MRX-MRX and in 6 participants (25.0%) in PBO-MRX treatment groups.
For all participants exposed to maralixibat during the study, AESIs occurred in 27 participants (42.2%). A summary of AESIs by SOC and PT is provided in the table below.

Table 11 Summary of Treatment-Emergent Adverse Events of Special Interest – Safety Population

	No. (%) of Participants				
	Double-Blind Study Period		OLE Study Period [a]		
SOC PT	MRX (n=40)	PBO (n=35)	MRX-MRX (n=28)	PBO-MRX (n=24)	All MRX [b] (n=64)
Participants with ≥1 TEAE	16 (40.0)	12 (34.3)	7 (25.0)	6 (25.0)	27 (42.2)
Blood and lymphatic system disorders					
Coagulopathy	0	1 (2.9)	0	0	0
Hepatobiliary disorders					
Cholangitis	11 (27.5)	7 (20.0)	4 (14.3)	4 (16.7)	18 (28.1)
Drug-induced liver injury [c]	0	0	0	1 (4.2)	1 (1.6)
Hepatic function abnormal	0	0	0	1 (4.2)	1 (1.6)
Hyperbilirubinaemia	0	1 (2.9)	0	0	0
Jaundice	1 (2.5)	0	1 (3.6)	0	2 (3.1)
Liver injury	0	0	0	1 (4.2)	1 (1.6)
Infections and infestations					
Rotavirus infection	0	0	0	1 (4.2)	1 (1.6)
Injury, poisoning and procedural complications					
Accidental exposure to product by child	0	0	0	1 (4.2)	1 (1.6)
Investigations					
Alanine aminotransferase increased	4 (10.0)	4 (11.4)	2 (7.1)	0	5 (7.8)
Blood bilirubin increased	1 (2.5)	1 (2.9)	1 (3.6)	0	2 (3.1)
Hepatic enzyme increased	3 (7.5)	0	0	1 (4.2)	4 (6.3)
International normalised ratio increased	1 (2.5)	0	0	0	1 (1.6)
Liver function test increased	1 (2.5)	0	0	0	1 (1.6)

AE=adverse event; MRX=maralixibat; MRX-MRX=participants who received maralixibat in the double-blind portion of the study and received maralixibat in the OLE; OLE=open-label extension; PBO=placebo; PBO-MRX=participants who received placebo in the double-blind portion of the study and received maralixibat in the OLE; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
a Events that occurred during the OLE period.
b Events that occurred while receiving maralixibat during the double-blind and OLE study periods.
c Reported as verbatim term Drug induced liver injury due to Bactrim (see narrative for Participant [redacted]).
Notes: Percentages are 100*n/N. AEs are coded using MedDRA Version 26.1. Multiple TEAEs were counted only once per participant for each SOC and PT.
Source: Table 14.3.2.4.

Deaths

Participant [redacted] was [redacted] [redacted] with portoenterostomy/Kasai surgery on [redacted] (aged 85 days), cytomegalovirus (CMV) infection, coagulopathy, anaemia, and malnutrition.

Relevant concomitant medications taken within 30 days prior to the onset of the event of pneumonia included cefazolin, metronidazole, and ursodeoxycholic acid. Relevant concomitant medications taken within 30 days prior to the onset of the event of hepatic cirrhosis included ursodeoxycholic acid and cefotaxime.

On [redacted] (Study Day 1) the participant received the first dose of double-blind study medication (maralixibat). On [redacted] (Study Day 10; maralixibat), the participant experienced a serious adverse event of pneumonia (Grade 3) and was hospitalised with cough, mild fever, chest retractions, moist rales, thoracic indrawing breathing, pink lips, jaundice, and pale stool. Chest X-ray findings included exaggerated heart size but no damage on lung parenchyma. Safety lab. Values including liver function tests were in the same range as at the baseline.

On [redacted] (Study Day 12), the participant was stable and completely breastfed, and liver and spleen were enlarged. On [redacted] (Study Day 14), findings included liver 2 cm below the ribs, mean spleen size below costal margin 1 cm; the participant was stable with little cough, no fever, and no rales. Viral hepatitis, autoimmune hepatitis, and cholangitis had been ruled out.

Treatment for the event included IV cefotaxime sodium. No action was taken with the study medication due to the event. On [redacted] (Study Day 16), the event of pneumonia was considered resolved (participant stable with cough resolved), and the participant was discharged from the hospital. Worsening in total and direct bilirubin values was observed.

On [redacted] (Study Day 19), the participant received that last dose of study medication but remained in the study.

On [redacted] (Study Day 20), the participant experienced a serious adverse event of hepatic cirrhosis (Grade 4). The reported event was considered serious due to the seriousness criteria of hospitalisation and other medically important event.

On [redacted] (Study Day 30), local laboratory results included ALT 346 U/L, AST 573 U/L, ALP 455 U/L, GGT 58 U/L, total bilirubin 26.37 mg/dL, direct bilirubin 14.92 mg/dL, albumin 2.5 g/dL, and INR 1.8 (normal range 0.8–1.1). Treatment for the event included oral spironolactone. The event of hepatic cirrhosis was considered not resolved.

On [redacted] (Study Day 39), central laboratory results included ALT 435 U/L, AST 602 U/L, ALP 378 U/L, GGT 54 U/L, total bilirubin 27.61 mg/dL, and direct bilirubin 15.66 mg/dL. On that same day, the participant discontinued the study due to the adverse event of hepatic cirrhosis.

It was reported that the participant was hospitalised on [redacted] and died on [redacted] (71 days after the last dose of study medication). Cause of death was not provided, and an autopsy was not performed.

The investigator assessed the causality of the event of hepatic cirrhosis as not related to the double-blind study medication but rather that the medical history of cirrhosis and underlying biliary atresia provide plausible etiology. The sponsor assessed the causality of the event of hepatic cirrhosis as not related to double-blind study medication and agreed with the possible etiology provided by the investigator.

Participant [redacted], and with HPE surgery on the same day, cytomegalovirus infection, and hepatic cirrhosis (both ongoing; 93 days prior to baseline) started treatment with MRX on [redacted].

On [redacted], 2 days prior to the first dose of double-blind study medication, the screening physical examination findings included liver 3 cm below the costal margin, mild yellow sclera, and mild jaundice of the skin overall. On that same day, screening laboratory results included ALT 214 U/L (normal range 3–30 U/L), ALP 155 U/L (normal range 124–341 U/L), GGT 837 U/L (normal range 15–132 U/L), total bilirubin 4.17 mg/dL (normal range 0–1.99 mg/dL), albumin 4.2 g/dL (normal range 2.9–4.2 g/dL), INR 0.99 (normal range 0.9–1.2). On [redacted] (Study Day 1), central laboratory results included AST 184 U/L (normal range 0–78 U/L) and direct bilirubin 2.81 mg/dL (normal range 0–0.5 mg/dL).

Relevant concomitant medications taken within 30 days prior to the onset of the event of diarrhoea included ursodeoxycholic acid, valganciclovir hydrochloride, tobramycin sulfate, cefotaxime, esomeprazole sodium, cefoperazone/sulbactam sodium, methylprednisolone, and cefixime.

On [redacted] (Study Day 2), the participant was hospitalised due to diarrhoea (Grade 3; SAE), that was considered study drug-related by the investigator. No action was taken with the study medication due to the SAE. It resolved on [redacted] (Study Day 10) and the participant was discharged. The investigator assessed the causality of the event of diarrhoea as related to the double-blind study medication. A day before starting the blinded study medication, the participant had also experienced diarrhoea. Treatment for the event included IV cefoperazone/sulbactam, glucose, potassium chloride, sodium chloride, and sodium citrate dihydrate; and oral racecadotril and saccharomyces boulardii. Therefore, the MAH considers the causal relationship inconclusive, as this might have been continuation of the previous episode or aggravation due to treatment; however, as diarrhoea is a known adverse drug reaction with maralixibat, the sponsor agreed with the investigator's assessment of the causality between the event of diarrhoea and double-blind study medication as related. Confounding factors included the use of saline laxatives and ongoing cytomegalovirus infection.

On study day 16 the participant was hospitalised due to the AE (SAE) of pneumonia that resolved on day 21, and the participant was discharged from the hospital. The investigator assessed the causality of the event of pneumonia as not related to the double-blind study medication. The sponsor assessed the causality of the event of pneumonia as not related to double-blind study medication and considered the infectious etiology of the event, the age of the patient, concomitant methylprednisolone, and an immature immune system as confounding factors.

On [redacted] (Study Day 37), the participant had a nonserious adverse event of cholangitis (Grade 3) that was upgraded to a serious adverse event (Grade 3), as the participant was hospitalised on the next day. At the time of the event, the participant was receiving double-blind study medication (maralixibat). On the same day, the participant had a serious adverse event of pneumonia (Grade 3). Treatment for the event of cholangitis included IV cefoperazone/sulbactam sodium. On [redacted] (Study Day 43) recorded physical examination findings were stomach distension and malnutrition. Study medication was interrupted due to the event of cholangitis on [redacted]. Other medications given during hospitalization included IV and oral furosemide; oral and IV spironolactone; IV potassium chloride, amikacin, meropenem trihydrate, and sodium chloride; and oral paracetamol. The patient improved and on [redacted] study medication was resumed (maralixibat).

On [redacted] (Study Day 55), local laboratory results included ALT 53.8 U/L, AST 58.4 U/L, total bilirubin 2.15 mg/dL, direct bilirubin 1.83 mg/dL, leukocytes 14.78×103/µL, and neutrophils 3.72×103/µL. On [redacted] (Study Day 59), the events of cholangitis and pneumonia were considered resolved, and the participant was discharged from the hospital. The investigator and MAH assessed the causality of the events of cholangitis and pneumonia as not related to the double-blind study medication and considered the participant's underlying disease, immature immune system, cytomegalovirus infections in the medical history, previous episode of pneumonia resulting in hospitalization less than a month before the current one, and HPE procedure (as cholangitis is one of the most common complications after surgery) as confounding factors.

On [redacted] (Study Day 70; on maralixibat), the participant had a nonserious adverse event of hepatic enzyme increased (Grade 3) with ALT 725 U/L, AST 704.2 U/L, ALP 329.6 U/L, GGT 316.7 U/L, total bilirubin 1.04 mg/dL, direct bilirubin 0.46 mg/dL, albumin 4.26 g/dL (normal range 2.8–4.8 g/dL), platelets 312×103/µL (normal range 140–440×103/µL), and INR 1.22. The participant was hospitalised on [redacted], and the event was considered an SAE. The study medication was interrupted due to the serious event of hepatic enzyme increased. Treatment for the event included IV glucose, sodium chloride, potassium chloride, and cefotaxime.

On (Study Day 74), the participant experienced a nonserious adverse event of ascites (Grade 2). On [redacted] (Study Day 76), the participant experienced a serious adverse event of cholangitis (Grade 3) resulting in prolonged hospitalization. The reported event was considered serious due to the seriousness criterion of hospitalization. At the time of the event, the participant was not receiving double-blind study medication and did not restart the blinded study drug due to subsequent withdrawal from the study. On the same day, local laboratory results included ALT 135.3 U/L (normal range 6–50 U/L), AST 85.9 U/L (normal range 19–61 U/L), GGT 405.8 U/L (6–92 U/L), leukocytes 5.26×103/µL, and neutrophils 2.9×103/µL. Treatment for the event throughout hospitalization included oral paracetamol, spironolactone, tobramycin, and rehydration therapy; and IV glucose, potassium chloride, sodium chloride, albumin, cefoperazone/sulbactam sodium, levofloxacin, furosemide, and meropenem trihydrate.

On [redacted] (Study Day 80), local laboratory results included ALT 46.5 U/L, AST 50 U/L, ALP 280 U/L, GGT 417.3 U/L, total bilirubin 4 mg/dL (normal range 0.1–0.7 mg/dL), direct bilirubin 3.18 mg/dL (normal range 0–0.2 mg/dL), albumin 3.03 g/dL, and INR 1.19 (normal range 0.9–1.2). On the same day the event of hepatic enzyme increased was considered resolved. The investigator assessed the causality of the event of hepatic enzyme increased as related to the double-blind study medication. The sponsor assessed the causality of the event of hepatic enzyme increased as not related to blinded study medication; recent infections, including pneumonia, cytomegalovirus infection, and cholangitis (including their corrective treatment), and the participant's ongoing malnutrition, ascites and cirrhosis provided plausible alternative etiology for the increased liver enzyme values.

On [redacted] the participant had respiratory failure due to large ascites, and the participant was discharged from the hospital at the parents' request; the site confirmed that the participant was discharged in a not-recovered condition. Consequently, the event of cholangitis was ongoing, and the outcome of the event was unknown following hospital discharge. The investigator assessed the causality of the event of cholangitis as not related to the double-blind study medication. The sponsor assessed the causality of the event of cholangitis as not related to the blinded study medication. The alternative explanation for the event of cholangitis was that cholangitis is a common complication in patients with biliary atresia who have undergone HPE surgery.

On [redacted], the participant discontinued the study; the caregiver had taken the baby back home on [redacted] and rejected any further healthcare activities, including study procedures, and so the participant was withdrawn from the study at the parents' request. The participant died on [redacted] (81 days after the last dose of study medication), and the cause of the death was assessed by the investigator as being due to progression of the underlying disease. An autopsy was not performed due to lost to follow-up.

Laboratory evaluations and concomitant treatments

Throughout the course of the study, selected liver parameters (ALT, total serum bilirubin, conjugated bilirubin) and INR were monitored against pre-HPE and post-HPE values for safety and drug interruption decisions. LSV deficiency occurs in most patients with BA due to their underlying disease. Therefore, LSV values were closely monitored and compared with screening values for safety and drug interruptions.

Overall, mean values of TSB, ALT, AST, direct (conjugated) bilirubin and GGT decreased after baseline in both groups. ALP increased after baseline, with a higher increase from baseline observed in the placebo group, with no clinically relevant differences when compared with the maralixibat group. There were no relevant changes in albumin after baseline.
For all other chemistry parameters, there were overall no clinically relevant changes from baseline to post-baseline assessment, and there were no differences between treatment groups.

Overall, there were no clinically relevant changes from baseline to post-baseline assessment or differences between treatment groups for haematology laboratory parameters.

There was a larger decrease (improvement) in cholesterol from baseline to Week 26 in the maralixibat group compared with the placebo group; the mean changes observed at Week 26 were -65.74 mg/dL and -47.51 mg/dL respectively.
There was a larger decrease (improvement) in LDL cholesterol from baseline to Week 26 in the maralixibat group compared with the placebo group; the mean changes observed at Week 26 were -77.53 mg/dL and -48.98 mg/dL respectively.
There were decreases in triglycerides observed in both treatment groups, with a larger mean change of -66.62 mg/dL in the placebo group compared with a mean change of -26.00 mg/dL in the maralixibat group at Week 26.

The baseline mean (SD) vitamin A level was 37.84 (36.74) µg/dL in the maralixibat group and 51.19 (52.54) ng/mL in the placebo group. Fluctuations were seen in the maralixibat group, whereas decreases were seen consistently in the placebo group compared with baseline. The mean changes from baseline at Weeks 6 and 14 in the maralixibat group were 0.43 (34.19) µg/dL and -8.70 (38.74) µg/dL, respectively. The mean changes from baseline at Weeks 6 and 14 in the placebo group were -15.81 (63.16) µg/dL and -20.96 (55.63) µg/dL, respectively. Limited data were available for a Week 26 comparison.
The baseline mean vitamin D (25-hydroxy vitamin D) level was 19.86 (29.56) ng/mL in the maralixibat group and 13.62 (18.76) ng/mL in the placebo group. Increases in vitamin D levels occurred in both the maralixibat and placebo groups from baseline to Week 26, with a greater mean change seen in the placebo group; mean changes from baseline observed at Week 26 were 10.15 (37.84) ng/mL in the maralixibat group and 42.28 (21.57) ng/mL in the placebo group. There were no clinically relevant changes in vitamin E levels from baseline to postbaseline assessment or differences between the treatment groups.

There were no clinically relevant changes from baseline to postbaseline assessment or differences between the treatment groups for coagulation laboratory parameters.

There were fluctuations in LSVs throughout the double-blind and OLE periods with shifts from normal or abnormal at baseline to normal or abnormal at subsequent visits for 25-hydroxy vitamin D, alpha tocopherol, INR, and vitamin A.

Seven participants had laboratory abnormalities that were Grade ≥3 in severity: hyperbilirubinaemia (1 maralixibat in double-blind period), increased ALT (1 placebo in double-blind period, 1 MRX-MRX in OLE), increased hepatic enzyme (2 maralixibat in double-blind period and 1 MRX-MRX and 1 PBO-MRX in OLE).

No clinically relevant trends or findings were observed in vital signs, ECG, or physical findings.

All participants (100%) took concomitant medications during the double-blind period of the study. In the OLE period, 85.7% of MRX-MRX participants and 91.7% of PBO-MRX participants took concomitant medications.
The most common concomitant therapies/medications (in ≥50% of maralixibat or placebo participants) taken during the double-blind period included the following (maralixibat, placebo, respectively): ursodeoxycholic acid (97.5%, 100%); sulfamethoxazole, trimethoprim (60.0%, 54.3%); DL-methionine, glycine, glycyrrhizic acid, ammonium salt (37.5%, 51.4%); methylprednisolone (40.0%, 57.1%); and vitamin A and D in combination (50.0%, 54.3%).
The most common concomitant therapies/medications (in ≥30% of MRX-MRX or PBO-MRX participants) taken during the OLE period included the following (MRX-MRX, PBO-MRX, respectively):

ursodeoxycholic acid (46.4%, 58.3%), paracetamol (39.3%, 29.2%), ibuprofen (32.1%, 25.0%), and budesonide (10.7%, 33.3%).

Cross-study comparisons

The MAH has presented comparison of safety data across MRX-701 and MRX-801 studies based on the main rationale that both studies included population of similar age (infants). Key differences between the 2 studies concern their design, duration and size. Study MRX-701 had a double-blind period of 26 weeks followed by an open-label extension of up to 78 weeks. Study MRX-801 was an open-label study, with a core period of 13 weeks followed by a long-term extension, with a study participation up to 89 weeks. Only 10 patients were included in the MRX-801 study.

Data showed similar safety profiles for maralixibat in both PFIC and BA populations, as per MAH. The most common TEAEs for Study MRX-801 were vomiting (50%); nasopharyngitis (40%); diarrhoea, pyrexia, upper respiratory tract infection, viral infection, cough, and rhinorrhea (30% each); and coagulopathy, coronavirus infection, influenza, rhinitis, and teething (20% each). The most common TEAEs for Study MRX-701 were diarrhoea (37.5%); pyrexia (34.4%); cholangitis (32.8%); pneumonia, upper respiratory tract infection, and vitamin D deficiency (23.4% each); and cough (21.9%).

TEAEs that occurred only in Study MRX-701 Overall Population and not in Study MRX-801 included cholangitis, pneumonia, and vitamin D deficiency. It is not surprising that cholangitis occurred only in Study MRX-701 since cholangitis is a common complication in patients with BA (Shiau et al. 2023). This event is more likely due to the underlying disease rather than a drug effect as evidenced by the higher incidence of cholangitis in the placebo arm (54.3%) than in the maralixibat arm (37.5%) of the DBP of Study MRX-701. Although pneumonia occurred more predominantly in Study MRX-701, it is of note that the highest incidence of TEAEs for both studies occurred in the System Organ Class (SOC) of Infections and Infestations (100% in Study MRX-801 PFIC population and 76.6% in Study MRX 701 Overall Population). In both indications, infections are common complications. It is not uncommon for patients with BA to experience various infections such as cholangitis and viral respiratory infections (Shiau et al. 2023) such as pneumonia.

Table 12 Most Common (>20%) Treatment-Emergent Adverse Events (Studies MRX-701 and MRX-801 Safety Population)

	No. (%) of Participants					
		MRX-701 BA				
		Double-blind Period		OLE Period [a]		Overall [b]
System Organ Class Preferred Term	MRX-801 PFIC MRX (N=10)	MRX (N=40)	PBO (N=35)	MRX-MRX (N=28)	PBO-MRX (N=24)	MRX (N=64)
Blood and lymphatic system disorders						
Coagulopathy	2 (20.0)	3 (7.5)	4 (11.4)	1 (3.6)	1 (4.2)	4 (6.3)
Gastrointestinal disorders						
Diarrhoea	3 (30.0)	13 (32.5)	8 (22.9)	6 (21.4)	6 (25.0)	24 (37.5)
Vomiting	5 (50.0)	4 (10.0)	6 (17.1)	0	2 (8.3)	6 (9.4)
Teething	2 (20.0)	0	0	0	0	0
General disorders and administration site conditions						
Pyrexia	3 (30.0)	15 (37.5)	9 (25.7)	8 (28.6)	4 (16.7)	22 (34.4)
Hepatobiliary disorders						
Cholangitis	0	15 (37.5)	19 (54.3)	4 (14.3)	4 (16.7)	21 (32.8)
Infections and infestations						
Pneumonia	0	10 (25.0)	6 (17.1)	1 (3.6)	4 (16.7)	15 (23.4)
Upper respiratory tract infection	3 (30.0)	7 (17.5)	4 (11.4)	8 (28.6)	5 (20.8)	15 (23.4)
Nasopharyngitis	4 (40.0)	1 (2.5)	1 (2.9)	3 (10.7)	0	4 (6.3)
Influenza	2 (20.0)	0	0	3 (10.7)	0	3 (4.7)
Viral infection	3 (30.0)	0	0	0	3 (12.5)	3 (4.7)
Coronavirus infection	2 (20.0)	0	0	0	0	0
Rhinitis	2 (20.0)	0	0	0	0	0
Metabolism and nutrition disorders						
Vitamin D deficiency	0	7 (17.5)	10 (28.6)	3 (10.7)	5 (20.8)	15 (23.4)
Respiratory, thoracic, and mediastinal disorders						
Cough	3 (30.0)	8 (20.0)	5 (14.3)	3 (10.7)	5 (20.8)	14 (21.9)
Rhinorrhoea	3 (30.0)	1 (2.5)	0	2 (7.1)	0	3 (4.7)

AE=adverse event; BA=biliary atresia; PFIC=progressive familial intrahepatic cholestasis; TEAE=treatment emergent adverse event; OLE=open-label extension.
Notes: Percentages are 100*n/N. At each level of summarization (System Organ Class and Preferred Term), participants who reported >1 AE were only counted once. System organ class term sorted alphabetically, and preferred terms sorted in descending order of incidence in Study MRX-701 MRX overall column.
[a] Only events during OLE are presented. They are presented by the treatment the participants received during double-blind period. OLE treatment is MRX for everyone.
[b] Presents events while receiving maralixibat only.
Data cut: 12 April 2024

SAEs

In Study MRX-801, 2 (20%) of 10 participants experienced ≥1 SAE (none were considered related to maralixibat). In Study MRX-701, there were 39 (60.9%) of 64 participants who experienced ≥1 SAE (3 were assessed as related to maralixibat); however, in the DBP, SAEs occurred more frequently in the placebo arm (71.4%) than in the maralixibat arm (65%). None of the SAEs in Study MRX-801 met the 20% incidence rate cutoff. Cholangitis was the most common SAE and only occurred in Study MRX-701. See Table 3.

Adverse Events of Special Interest

Similar to SAEs, cholangitis was the most frequently reported AESI for Study MRX-701. There was only one AESI (ALT increased that led to treatment discontinuation) that occurred in Study MRX-801.

2.3.3. Updated Discussion on clinical aspects

Livmarli (maralixibat) is currently licenced in two indications related to cholestasis, for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older, and for treatment of progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older.

The submitted abbreviated report concerns the study MRX-701 in new target population with biliary atresia (BA) and was planned to support extension of indication in "treatment of biliary atresia". Of note, multiple parameters which were collected in the study are listed in various individual patient listings and have not been summarised as tables. These are partly also not reported in the study report body.

The study included 26-week, multicenter, double-blind, placebo-controlled, randomized parallel-group phase, followed by an OLE with analyses up to Week 104, in 20 to 90 days old patients with BA. The study design is similar to the program submitted for PFIC and is acceptable.

The Primary Objective of the placebo-controlled portion of this study was to evaluate the efficacy of maralixibat on biliary drainage after HPE in participants with BA.

The Secondary Objectives of the placebo-controlled portion of this study were to evaluate the rate of clinically relevant reductions in cholestatic biomarkers, the rate of liver-related clinical events, and the safety, tolerability, and pharmacokinetics of maralixibat.

The OLE objectives included the same primary and secondary objectives analysed over the full study duration, including the OLE period.

The protocol was amended 5 times, but 4 amendments were introduced before enrolment of the first subject and the fifth amendment concerned removal of fibrosis-4. Thus, relevant adaptations were all made prospectively.

Up to 600 µg/kg MRX BID (as maralixibat chloride, equivalent to 570 µg/kg maralixibat) was tested which is similar to the recommended dose of Livmarli® to treat patients with PFIC. Notably, several formulations (with different concentrations of MRX) were applied. No explanation could be located. It is assumed that this was done to limit exposure to the excipient propylene glycol in the patients.

During the study, participants received standard-of-care treatment in line with investigator and caregiver preference in addition to study medication. This is acceptable. However, it is unclear whether change in dose of the concomitant medication was allowed and/or took place, which renders the data difficult to interpret.

The study included patients with BA after Kasai procedure. No additional specific selection criteria to ensure presence of a certain level of cholestasis, e.g., presence of elevated (above predefined threshold) sBA, TBS, or other relevant parameters, were defined. Notably, current label of Livmarli does not recommend use of the medicinal product in patients with severe hepatic impairment and PFIC because of potential risks of PG-related toxicity. The MRX-701 study did not exclusion such patients and a number of patients with cirrhosis was included. Also, overall, clinical picture and course of the BA differs from those in PFIC and ALGS, with patients requiring surgical interventions, including liver transplant early in life (Mysore et al. 2019; Wehrman and Loomes 2024).

A total of 75 participants enrolled in the study, 40 were randomized to receive maralixibat, and 35 participants were randomized to receive placebo in the DB phase. In the OLE period of the study, 52 participants received maralixibat. The size of the study is small, but not unexpected given the rare occurrence of the disease.

This was the youngest population studied to date for maralixibat, with baseline mean (SD) age of 76.1 (17.63) days and an age range from 41 to 109 days. Mean TSB was 7.40 mg/dL and mean sBA was 149.20 µmol/L at baseline. Baseline data were not discussed in detail and medical history was collected (judging from CRFs) but not summarised.

The majority of participants were able to dose escalate to the maximum dose of 600 µg/kg BID in both the double-blind and OLE periods.

The study did not meet its primary or secondary efficacy endpoints. The Applicant is of the opinion that numerically better results were achieved with MRX in mean change and in categorical analyses done for TSB levels <2 mg/dL and ≤1.2 mg/dL as well as a mean sBA level ≤40 mmol/L through Weeks 14–26 of treatment. However, this opinion is not supported. The differences are minimal, and the thresholds have not been justified.

It is agreed that LS mean change in sBA was more pronounced on MRX compared to placebo (where no change was observed). Also, 7αC4 (ng/mL) increased gradually on MRX in contrast to placebo, suggesting presence of effect of MRX on uptake of bile acids in the intestines.

The CSR does not contain detailed presentation and discussion of a large number of relevant parameters, such as liver function tests, pruritus, etc. However, data in the tables indicate that no relevant positive effects were observed with MRX.

In conclusion, the study results are not supportive of the indication of "treatment of BA" and the Applicant's conclusion that "maralixibat treatment is not promising in this cholestatic population" is agreed to. Indeed, it seems that additional treatment with maralixibat in the patients with HPE procedure does not provide any sizable benefit. The Applicant intends to evaluate alternative patient subgroups, who may benefit from treatment with Livmarli, e.g., in the patients with BA and pruritus.

The Applicant concludes that the study results do not trigger any changes in the label. This is agreed in relation to efficacy/benefits in ALGS and PFIC. BA can be considered to be remotely similar to the patients with PFIC2 who have a complete absence or lack of function of Bile Salt Export Pump protein (i.e., patients with BSEP3 subtype of PFIC2). Patients with BSEP3 are also not expected to gain benefit from treatment with Livmarli (see the SmPC section 4.4).

With respect to safety, the Applicant's conclusion that no changes in the labelling are necessary, is overall agreed. Provided information shows that frequency/number of TEAEs, SAEs and TEAEs leading to discontinuation of the study did not differ relevantly between MRX and placebo arms, and safety profile of maralixibat in BA population cannot be readily extrapolated to the approved indications (PFIC and ALGS). Also, small size of the study does not allow to draw firm conclusions.

Some inconsistencies in the reporting and coding of AEs were detected. However, updated tables with similar events pooled under the same medical term, provided on request of the CHMP were largely in line with the summary submitted initially.

It was also noticed that some relevant events, e.g., cirrhosis, ascites, were reported in the narratives, but did not appear in the list of AE/SAEs, or the list of liver-related events. As an example, patient [redacted] developed all of the above events (see the respective narrative), but these could not be located in the AE/SAEs, or liver-related events in the CRF. The MAH has explained that per definition in the study protocol liver related events considered to be triggered by the disease progression were recorded separately. Only selected events which were considered not to fit in the symptomatology/natural course of the background disease were reported as AEs and/or liver-related events. The MAH has also checked and confirmed that all events reported in the narratives have been reflected in the individual patient listings. This is agreed. However, review of the listings 16.8.1 - Adverse Events (Safety Population), 16.5.2 - Liver Associated Events (ITT Population), 16.5.3 - Liver Transplant List (ITT Population), and 16.4.2 - Long Term Follow-up Informed Consent and Disease Progression (ITT Population) show that liver-related events were reported across various listings inconsistently. As an example, patient [redacted] who developed ascites and cirrhosis on MRX was listed in the list of "liver-related events", but not in the list of "disease progression", although the list 16.5.2 mentions "disease progression" as well. Also, ascites is mentioned in the free text describing the AE of Rotavirus infection, but not as a separate AE. Other examples are patients [redacted] on placebo who are listed as having "disease progression" but have not been listed in the list of patients with "liver-related events", although patients treated with maralixibat and having disease progression were listed also in the list of "liver-related events". This complicates evaluation of the submitted data.

Moreover, since it was intended to develop the product for treatment of biliary atresia, all liver-related events should have been summarised as clinical outcomes (relevant for efficacy), including those presumably related to disease progression. Therefore, the MAH was requested to provide an overview

table including liver-related events (worsening in liver function tests, cirrhosis, ascites, bleeding, increased INR, end-stage liver disease, listing of LT, LT, etc.) per treatment arm, and a separate listing with details on these events. The MAH was also requested to specify whether there were cases of DILI observed during the study. The requested information was provided. Based on the summary table and the listing of the AEs no pattern that might have suggested causal relationship between the events and treatment with maralixibat could be identified. The reported events mostly represent various types of bleeding events and/or INR increased, worsening of liver function tests/elevated bilirubin, occurrence of cirrhosis, ascites, and listing for LT/LT. These events occurred on both, maralixibat and placebo treatment. No temporal relationship can be identified between the start of these events and treatment with MRX. Additionally, the Applicant confirmed that no cases of drug-induced liver injury (DILI) were observed throughout the conduct of Study MRX-701. Safety data from Study MRX-701 were reviewed quarterly by the Data Monitoring Committee (DMC); the DMC did not identify any cases of potential DILI attributable to maralixibat in this study. Thus, no new safety concerns have been raised based on these, additional information.

It has been noted (in the narratives) that several patients had strong increase in GGT on MRX, which do not necessarily seem to be related to ongoing AEs. Elevated levels of GGT occur commonly in patients with BA. Also, patients with such events had other confounders reported. At group level no differences were observed in the GGT over time. Thus, no specific concerns are being raised.

No deaths were reported during the study. However, two patients [redacted] died after premature cessation of study treatment (maralixibat in both cases) and withdrawal from the study. Detailed information provided on these cases shows presence of progressed disease already at study entry, as well as multiple confounders like recurrent AEs (e.g., cholangitis, infections/pneumonia) and related various concomitant treatments which are known to have risks of hepatotoxicity (e.g., antibiotics, paracetamol). Consequently, drawing of firm conclusions regarding causal relationship to MRX is not possible. In any case, hepatotoxicity is acknowledged as a potential important risk of MRX and respective warnings are already included in the SmPC as risk minimisation measures. No further actions for the approved indications are deemed necessary.

It is agreed that the most common AEs (e.g., diarrhoea) reflect the known safety profile of Livmarli and/or are age-typical (e.g., infections). It is also agreed that cholangitis is probably related to the HPE procedure.

Of note, Livmarli is not recommended in patients with PFIC who have severe hepatic and/or renal impairment due to the potential risk of toxicity from the excipient propylene glycol. As it seems, the MTX-701 study included a number of patients with cirrhosis, as well as progressed liver disease already at the baseline.

Systemic exposure to MRX was low.

The chosen study for cross-study comparison (MRX-801) is considered not optimal due to its very small size and differences in the design and duration. However, it is acknowledged that selection of other studies with older patient population would also face relevant limitations.

Comparison of the safety data between the two studies MRX-801 and MRX-701 showed similar safety profiles for maralixibat in both PFIC and BA populations. The most common AEs in both studies were predominantly gastrointestinal in nature such as diarrhoea, which is consistent with the known mechanism of action and established safety profile of maralixibat. All the other AEs such as pyrexia, cholangitis, upper respiratory tract infections, and influenza, among others point toward an infectious etiology, which is not unexpected in infants with cholestatic liver disease and in infants in general.

Overall, currently safety data collected in MRX-701 are very limited and do not allow to draw firm conclusion in patients with BA. No new safety signals have become apparent, and the observed safety profile appears to be largely in line with the one observed in the approved indications. Relevant differences in the BA vs. PFIC and ALGS populations suggest that extrapolation of the observed safety profile in the MRX-701 to the approved indications would be inappropriate. Therefore, benefit-risk ratio for the approved indications is considered not affected and remains unchanged.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**

4. MAH responses to the FIRST Request for supplementary information

Question 1

It may be that the submitted data have not been adequately "cleaned". E.g.,

a. **It has been noticed that some relevant events, e.g., cirrhosis, ascites, were reported in the narratives, but did not appear in the list of AE/SAEs, or the list of liver-related events. As an example, patient [redacted] developed all of the above events (see the respective narrative), but these could not be located in the AE/SAEs, or liver-related events in the CRF.**

b. **Unclear terms, e.g., "liver enzyme increased", have been used and sometimes also coded under different SOCs. This does not allow for pooling of these AEs.**

These examples suggest that the data submitted are likely insufficiently "cleaned"/"processed" and the outputs are not reliable for interpretation. Consequently, potential impact of the safety information on the benefit/risk in the approved indication and on the label cannot be assessed either. Therefore, the Applicant is requested to carefully review the raw data, properly clear the database, and re-do the analyses.

Summary of the Applicant's response

a. The Applicant has explained that the events which were considered related to the background disease were not reported as AEs (provided a clear changed compared to baseline too place) but were listed as liver-related events.

An extensive review of all of the narratives submitted was performed to identify any discrepancy between the events reported in the narratives and the corresponding listings. The events described in the narratives were cross-checked with the following listings:

- 16.8.1 Adverse Events (Safety Population)
- 16.8.2.1 Adverse Events of Special Interest (Safety Population)
- 16.8.3 Treatment Related Adverse Events (Safety Population)
- 16.8.4.1 Serious Adverse Events (Safety Population)
- 16.8.4.2 Serious Related Adverse Events (Safety Population)

- 16.8.5 Adverse Events Leading to Study Discontinuation (Safety Population)
- 16.5.2 Liver Associated Events (ITT Population)
- 16.5.3 Liver Transplant List (ITT Population)
- 16.3.3 Listing of Death (Safety Population)
- 16.4.2 Long Term Follow-up Informed Consent and Disease Progression (ITT Population)
- 16.2.2.2 Subject disposition and completion (ITT Population)

Per Section 7.3.6 of the MRX-701 Study Protocol, an event that is considered to be a progression of the underlying disease is not necessarily an AE unless it is atypical in presentation or considered by investigator to be related to the study drug. It was up to the investigator to determine if the event met either of these criteria and should be deemed an AE or a Liver Associated Event (LAE). The liver related events meeting these protocol-defined criteria can be found in Listing 16.5.2 Liver Associated Events (Safety Population).

As an example, the investigator for participant [redacted] reviewed the events of ascites, cirrhosis, and disease progression and determined that the events should be reported in the LAE listing (16.5.2) and not in the AE listing (16.8.1) based on the above-mentioned criteria. During the narrative review process, the information was checked, and the events are reported in the corresponding listing (16.5.2).

For participants who had the event of "listing for liver transplantation" reported in the LAE listing (16.5.2), the information was further captured in the corresponding eCRF page "Liver transplant list" (Listing 16.5.3) and not captured as an AE, as per eCRF completion guideline.

Results of this review were recorded and provided along with all listings for all the events reported in the narratives. It was concluded that all of the events described in the narratives were reported in the corresponding listing based on the event classification.

As a result of the above review, there are no changes needed to the adverse events listings provided in the MRX-701 CSR.

b. Updated tables of AEs and SAEs using a list of medically similar terms (including those that arise from different MedDRA SOCs) have been provided. Review of these updated tables using pooled terms by medical concept does not identify any new safety concerns and the safety profile observed in Study MRX-701 is consistent with the maralixibat safety information described in the current SmPC for Livmarli®.

Assessment of the Applicant's response

a. The MAH has explained that per definition in the study protocol liver related events considered to be triggered by the disease progression were recorded separately. Only selected events which were considered not to fit in the symptomatology/natural course of the background disease were reported as AEs and/or liver-related events. The MAH has also checked and confirmed that all events reported in the narratives have been reflected in the individual patient listings. This is agreed. However, review of the listings 16.8.1 - Adverse Events (Safety Population), 16.5.2 - Liver Associated Events (ITT Population), 16.5.3 - Liver Transplant List (ITT Population), and 16.4.2 - Long Term Follow-up Informed Consent and Disease Progression (ITT Population) show that liver-related events were reported across various listings inconsistently. As an example, patient [redacted] who developed ascites and cirrhosis on MRX was listed in the list of "liver-related events", but not in the list of "disease progression", although the list 16.5.2 mentions "disease progression" as well. Also, ascites is mentioned in the free text describing the AE of Rotavirus infection, but not as a

separate AE. Other examples are patients [redacted], on placebo who are listed as having "disease progression", but have not been listed in the list of patients with "liver-related events", although patients treated with maralixibat and having disease progression were listed also in the list of "liver-related events". This complicates evaluation of the submitted data.
Moreover, since it was intended to develop the product for treatment of biliary atresia, all liver-related events should have been summarised, including those presumably related to disease progression. Therefore, the MAH is requested to provide an overview table where all patients with any liver-related event (worsening in liver function tests, cirrhosis, ascites, bleeding, increased INR, end-stage liver disease, listing of LT, LT, etc.) will be considered per treatment arm. Also, a separate listing that includes such patients should be provided. The MAH is requested to also specify whether there were cases of DILI observed during the study. The updated information should be integrated in the study report and the old report should be replaced with the new one in the dossier for the sake of completeness. (OC)

b. The provided updated tables are in line with the previously submitted tables.

Conclusion

Issue partly resolved. The MAH is requested to provide an overview table where all patients with any liver-related event (worsening in liver function tests, cirrhosis, ascites, bleeding, increased INR, end-stage liver disease, listing of LT, LT, etc.) will be considered per treatment arm. Also, a separate listing that includes such patients should be provided. The MAH is requested to also specify whether there were cases of DILI observed during the study. (OC)

Question 2

Summary tables comparing AEs/SAEs/AEs of special interest from the MRX-701 study (only DB phase and OLE) against similar study in the PFIC population should be provided. Differences in the safety profile should be discussed and addition of new ADRs in the PI should be considered (e.g., hypersensitivity).

Summary of the Applicant's response

The MAH has briefly summarised key characteristics of BA and presented differences between BA and PFIC. Most relevant difference aside that in pathophysiology is more severe and fast progression of liver damage in biliary atresia (BA), use of surgical treatment very early in young children and different types of surgeries applied. Due to the rapidly progressive and unpredictable nature of the disease, BA remains the leading cause of pediatric liver transplantation worldwide. The two most important improvements in the care of patients with BA to date have been the hepatoportoenterostomy (HPE) and orthotopic liver transplantation. If the HPE is successful, the remaining small patent bile ducts will drain into the Roux limb, and jaundice will start to resolve in the weeks following surgery. Even if bile flow is established and cholestasis improves, many patients will have progressive liver disease despite undergoing the HPE procedure, and **approximately 40%–50% of patients will require a liver transplant by 2 years of age.**

Cholangitis is a common complication in patients with BA who have undergone a successful HPE. **The incidence of cholangitis** in these patients is **between 40% and 90%**, with most patients experiencing at least one episode prior to 2 years of age (Wehrman and Loomes 2024). Cholangitis can occur in single or multiple episodes (Gad et al. 2021). By contrast, patients with an unsuccessful HPE (i.e., in which bile drainage is not achieved) have a low risk for ascending cholangitis but **are still at risk for other infections like urinary tract infection, chest infection, and sepsis.**

The majority of BA patients with effective HPE surgery **will have normal bilirubin levels by the age of 1 year. However, decreases in the blood plasma levels of GGT, ALT, and AST may take**

much longer to improve, and for some patients, the elevations may persist for >5 years (Degtyareva et al. 2020).

The MAH has presented comparison of safety data across MRX-701 and MRX-801 studies based on the main rationale that both studies included population of similar age (infants). Key differences between the 2 studies concern their design, duration and size. Study MRX-701 had a double-blind period of 26 weeks followed by an open-label extension of up to 78 weeks. Study MRX-801 was an open-label study, with a core period of 13 weeks followed by a long-term extension, with a study participation up to 89 weeks. Only 10 patients were included in the MRX-801 study.

Data showed similar safety profiles for maralixibat in both PFIC and BA populations, as per MAH. The most common TEAEs for Study MRX-801 were vomiting (50%); nasopharyngitis (40%); diarrhoea, pyrexia, upper respiratory tract infection, viral infection, cough, and rhinorrhea (30% each); and coagulopathy, coronavirus infection, influenza, rhinitis, and teething (20% each). The most common TEAEs for Study MRX-701 were diarrhoea (37.5%); pyrexia (34.4%); cholangitis (32.8%); pneumonia, upper respiratory tract infection, and vitamin D deficiency (23.4% each); and cough (21.9%).

TEAEs that occurred only in Study MRX-701 Overall Population and not in Study MRX-801 included cholangitis, pneumonia, and vitamin D deficiency. It is not surprising that cholangitis occurred only in Study MRX-701 since cholangitis is a common complication in patients with BA (Shiau et al. 2023). This event is more likely due to the underlying disease rather than a drug effect as evidenced by the higher incidence of cholangitis in the placebo arm (54.3%) than in the maralixibat arm (37.5%) of the DBP of Study MRX-701. Although pneumonia occurred more predominantly in Study MRX-701, it is of note that the highest incidence of TEAEs for both studies occurred in the System Organ Class (SOC) of Infections and Infestations (100% in Study MRX-801 PFIC population and 76.6% in Study MRX 701 Overall Population). In both indications, infections are common complications. It is not uncommon for patients with BA to experience various infections such as cholangitis and viral respiratory infections (Shiau et al. 2023) such as pneumonia.

Table 13 Most Common (>20%) Treatment-Emergent Adverse Events (Studies MRX-701 and MRX-801 Safety Population)

	No. (%) of Participants					
		MRX-701 BA				
		Double-blind Period		OLE Period [a]		Overall [b]
System Organ Class Preferred Term	MRX-801 PFIC MRX (N=10)	MRX (N=40)	PBO (N=35)	MRX-MRX (N=28)	PBO-MRX (N=24)	MRX (N=64)
Blood and lymphatic system disorders						
Coagulopathy	2 (20.0)	3 (7.5)	4 (11.4)	1 (3.6)	1 (4.2)	4 (6.3)
Gastrointestinal disorders						
Diarrhoea	3 (30.0)	13 (32.5)	8 (22.9)	6 (21.4)	6 (25.0)	24 (37.5)
Vomiting	5 (50.0)	4 (10.0)	6 (17.1)	0	2 (8.3)	6 (9.4)
Teething	2 (20.0)	0	0	0	0	0
General disorders and administration site conditions						
Pyrexia	3 (30.0)	15 (37.5)	9 (25.7)	8 (28.6)	4 (16.7)	22 (34.4)
Hepatobiliary disorders						
Cholangitis	0	15 (37.5)	19 (54.3)	4 (14.3)	4 (16.7)	21 (32.8)
Infections and infestations						
Pneumonia	0	10 (25.0)	6 (17.1)	1 (3.6)	4 (16.7)	15 (23.4)
Upper respiratory tract infection	3 (30.0)	7 (17.5)	4 (11.4)	8 (28.6)	5 (20.8)	15 (23.4)
Nasopharyngitis	4 (40.0)	1 (2.5)	1 (2.9)	3 (10.7)	0	4 (6.3)
Influenza	2 (20.0)	0	0	3 (10.7)	0	3 (4.7)
Viral infection	3 (30.0)	0	0	0	3 (12.5)	3 (4.7)
Coronavirus infection	2 (20.0)	0	0	0	0	0
Rhinitis	2 (20.0)	0	0	0	0	0
Metabolism and nutrition disorders						
Vitamin D deficiency	0	7 (17.5)	10 (28.6)	3 (10.7)	5 (20.8)	15 (23.4)
Respiratory, thoracic, and mediastinal disorders						
Cough	3 (30.0)	8 (20.0)	5 (14.3)	3 (10.7)	5 (20.8)	14 (21.9)
Rhinorrhoea	3 (30.0)	1 (2.5)	0	2 (7.1)	0	3 (4.7)

AE=adverse event; BA=biliary atresia; PFIC=progressive familial intrahepatic cholestasis; TEAE=treatment emergent adverse event; OLE=open-label extension.
Notes: Percentages are 100*n/N. At each level of summarization (System Organ Class and Preferred Term), participants who reported >1 AE were only counted once. System organ class term sorted alphabetically, and preferred terms sorted in descending order of incidence in Study MRX-701 MRX overall column.
[a] Only events during OLE are presented. They are presented by the treatment the participants received during double-blind period. OLE treatment is MRX for everyone.
[b] Presents events while receiving maralixibat only.
Data cut: 12 April 2024

SAEs

In Study MRX-801, 2 (20%) of 10 participants experienced ≥1 SAE (none were considered related to maralixibat). In Study MRX-701, there were 39 (60.9%) of 64 participants who experienced ≥1 SAE (3 were assessed as related to maralixibat); however, in the DBP, SAEs occurred more frequently in the placebo arm (71.4%) than in the maralixibat arm (65%). None of the SAEs in Study MRX-801 met the 20% incidence rate cutoff. Cholangitis was the most common SAE and only occurred in Study MRX-701.

Adverse Events of Special Interest

Similar to SAEs, cholangitis was the most frequently reported AESI for Study MRX-701. There was only one AESI (ALT increased that led to treatment discontinuation) that occurred in Study MRX-801.

Conclusion

Comparison of the safety data between the two studies MRX-801 and MRX-701 showed similar safety profiles for maralixibat in both PFIC and BA populations. The most common AEs in both studies were predominantly gastrointestinal in nature such as diarrhoea, which is consistent with the known mechanism of action and established safety profile of maralixibat. All the other AEs such as pyrexia, cholangitis, upper respiratory tract infections, and influenza, among others point toward an infectious etiology, which is not unexpected in infants with cholestatic liver disease and in infants in general. No new safety concerns or risks were identified in Study MRX-701 and therefore, it is the Applicant's position that no change to the Product Information of Livmarli is warranted.

Assessment of the Applicant's response

The chosen study for comparison is considered not optimal due to its very small size and differences in the design and duration. However, it is acknowledged that selection of other studies with older patient population would also face relevant limitations.

Overall, due to the small size of the compared populations (and other limitations) interpretation of the data is difficult. Considering the above limitations and the intrinsic differences between BA and PFIC observed difference in the safety profile (frequent cholangitis in BA) appear logical.

Conclusion

Issue considered resolved.

Question 3

It has been noted (in the narratives) that several patients had strong increase in GGT on MRX, which do not necessarily seem to be related to ongoing AEs. Possible explanation for these events should be provided.

Summary of the Applicant's response

The increased activity of GGT and transaminases in the early HPE postoperative period was observed in most BA patients with effective HPE surgery (as compared with the values before the surgery). It is the Applicant's position that this may reflect the liver compensatory reaction to the surgical intervention per se, as well as to the use of potentially hepatotoxic pharmaceuticals (anaesthetics, antibacterials, etc.). In the follow-up period, the GGT/ALT/AST activities gradually decreased.

Considering the specificity of the patient population, the Applicant conducted an analysis for all the cases where there was an increase in the GGT level of 5 times baseline (BL) value, and the Applicant identified a total of 13 participants. See table below for the detailed overview of the 13 participants analysed.

Table 14 MRX-701 Participants with Increases in GGT Level of 5 Times Baseline (BL) Value

Participants with increase in GGT during MRX treatment				
Participant Number	Associated with ALT Increase (Y/N)	Associated with Serum Bilirubin Increase (Y/N)	Associated with AEs (Y/N)	List of AEs Associated with GGT Increase
[redacted]	N	N	N	NA
[redacted]	N	Y	Y	Jaundice
[redacted]	N	N	Y	Pyrexia
[redacted]	N	Y	N	NA
[redacted]	Y	N	Y	Gastroenteritis Hepatic function abnormal
[redacted]	Y	N	Y	Cholangitis
[redacted]	N	Y	Y	Cholangitis
Participants with increase in GGT during PBO treatment				

[redacted]	Y	N	Y	Vomiting Haematochezia Cholangitis Eczema
[redacted]	Y	N	Y	ALT increased Vomiting Respiratory tract infection Sepsis
[redacted]	Y	N	Y	Cholangitis ALT increased
[redacted]	Y	N	N	NA
Participants with increases in GGT during PBO treatment and again during MRX treatment				
[redacted] during PBO	N	N	N	NA
[redacted] during MRX	Y	N	Y	Gastroenteritis adenovirus Diarrhoea Vomiting Cholangitis
[redacted] during PBO	Y	N	Y	ALT increased Vitamin A deficiency Vitamin D deficiency
[redacted] during MRX	N	N	Y	Upper respiratory tract infection Vitamin A deficiency Vitamin D deficiency

AE=adverse event; MRX=maralixibat; NA=Not applicable; N=No; PBO=placebo; Y=Yes.

The majority of patients with BA with effective HPE surgery will have normal bilirubin levels by the age of 1 year. However, decreases in the blood plasma levels of GGT, ALT, and AST may take much longer to improve and for some patients, elevations may persist for >5 years (Degtyareva et al.2020). This finding can explain these cases seen during maralixibat and placebo treatment periods, during which participants had increases in GGT without an associated adverse event. Importantly, no pattern or prevalence differences between active treatment versus placebo were identified suggesting these GGT elevations are not related to maralixibat treatment.

Assessment of the Applicant's response

The MAH analysed the cases of increased GGT in the study population. Only the patients with strongly increased GGT (5 times baseline or higher) were reviewed in detail. All patients seem to have had other possible reasons for increased GGT. Increased levels of GGT were also observed on placebo, albeit in smaller number of patients. The explanation is somewhat reassuring. Overall, low number of patients and the background disease that is the key confounder of GI/liver-related events, no conclusions can be drawn with sufficient certainty. Notably, GGT increase was no identified as ADR in PFIC and ALGS populations.

Conclusion

Issue resolved/no longer pursued as no additional certainty can be gained from the data.

Question 4

Patient [redacted] should be discussed in detail in regard to possible MRX-related liver decompensation as a possible cause of the event of cirrhosis. This patient died 1 month after stop of treatment.

Summary of the Applicant's response

Participant [redacted] had a past medical history of HPE surgery performed at 85 days old, close to the upper age limit at which HPE surgery should be performed to ensure the best outcome (Gutierez et al.2024). In addition, the participant had a medical history of blood clotting disorder, ankyloglossia congenital, anaemia, malnourishment, vitamin A & D deficiency. Most notably, the participant had a diagnosis of cytomegalovirus infection that was made approximately 22 days before the participant entered the study.

On [redacted] (18 days prior to the participant's baseline visit) local laboratory values included ALT 111.2 U/L (normal range 0–50 U/L), total bilirubin 15.58 mg/dL (normal range 0.3–1.2 mg/dL) and direct bilirubin 7.75 mg/dL (normal range 0–0.2 mg/dL). On [redacted] (1 day prior to the participant's baseline visit), the participant was noted to have a "big liver" and "jaundice". During the baseline visit, prior to initiating the study medication, the participant's central laboratory values revealed an increase in liver enzymes that included ALT 250 U/L (normal range 4–35 U/L) and total bilirubin 22.36 mg/dL (normal range 0–1.99 mg/dL). This steady increase in their liver enzymes continued during study participation as well as after the participant received the last dose. As stated in the previous response above, the two most important improvements in the care of patients with BA to date have been HPE and orthotopic liver transplantation. If the HPE is successful, the remaining small patent bile ducts will drain into the Roux limb, and jaundice will start to resolve in the weeks following surgery. If the HPE is unsuccessful, bile drainage is not achieved, and the child remains jaundiced. Participant [redacted] entered the study with hepatomegaly, a significant past medical history, and a lack of bilirubin clearance indicated by the jaundiced appearance and persistently increasing liver enzymes. Despite undergoing an HPE procedure on [redacted], the participant did not clear the bilirubin and subsequently developed hepatic cirrhosis on [redacted] (38 days after the procedure and 20 days after entering the study). This development of cirrhosis is typical in patients where the HPE procedure has failed to establish bile drainage and indicative of the natural history of the underlying disease.

Therefore, the development of hepatic cirrhosis in participant [redacted] can be attributed to the underlying disease. This is characterized by the obstruction of extrahepatic bile ducts, not relieved by the HPE procedure, which eventually led to cirrhosis. The participant's lack of bilirubin clearance that was exhibited by a steady increase in liver enzymes, seen even before study medication was initiated, indicated a possible failed HPE procedure. These factors compounded by significant past medical history played a role in the development of hepatic cirrhosis.

Assessment of the Applicant's response

The MAH has provided detailed information on the patient stating that this patient had failed HPE in medical history and already had significantly progressed disease at the time of study entry. In the response to question 2 the MAH has summarised characteristics of the disease and mentioned that even if bile flow is established and cholestasis improves after HPE, many patients will have progressive liver disease, and approximately 40%–50% of patients will require a liver transplant by 2 years of age. It is obvious that maralixibat did not provide adequate efficacy in this patient to lessen the burden of cholestasis. Whether the substance might have contributed to liver damage is difficult to establish but seems unlikely due to the progressed and severe course of the disease.

Conclusion

Issue considered resolved.

Question 5

An updated list of liver-related events should be provided after "data cleaning" and causal relationship of the events with MRX should be discussed

Summary of the Applicant's response

Per Section 7.3.6 of the MRX-701 protocol, events that are considered to be a progression of the underlying disease are not necessarily AEs unless they are atypical in presentation or considered by the investigator to be related to the study drug. It was up to the investigator to determine if the event met either of these criteria and should be deemed an AE. In such cases, the liver-related events meeting these criteria can be found in Listing 16.8.1 Adverse Events (Safety Population). Listing 16.5.2 (Liver Associated Events) includes events that did not meet the criteria of an AE and were not assessed by the investigator for causality since this listing captured events that were considered due to typical progression of the underlying disease.

As described in the response to the major observation #1, an extensive review of all the narratives submitted was performed to identify any discrepancy between the events reported in the narratives and the corresponding listings (16.8.1 and 16.5.2). After the completion of the review, it was concluded that all the events described in the narratives could be found in the corresponding listings, based on the event classification (Appendix 1). As a result, there were no liver associated events reported in the narratives missing from Listing 16.5.2 (Liver Associated Events). Therefore, no additional data cleaning or update to the respective listing is needed.

Assessment of the Applicant's response

Reference is made to the assessment of the response to Question 1.

Even if per definition some events are assigned to disease progression and may not count as safety issue, to assess efficacy of MRX in this population complete listing of such events needs to be presented.

Conclusion

Issue not resolved. Reference is made to the conclusion to Question 1.

Question 6

No deaths were reported during the study. However, at least one patient [redacted] died after withdrawal from the study. Such cases should be presented.

Summary of the Applicant's response

BA is a rare, inflammatory condition of the biliary tree that presents in the first weeks of life and involves extrahepatic bile duct obstruction. This is associated with consequent liver injury, fibrosis, and cirrhosis that leads to portal hypertension and a decline in hepatic synthetic function (Chardot 2006). Once a diagnosis of BA is made, patients will require an HPE procedure as soon as possible to relieve the obstruction and reestablish bile flow. If left untreated (without HPE), patients will rapidly develop cirrhosis, which will then progress to end stage liver disease resulting in the need for liver transplantation (Mysore et al. 2019). Overall survival with native liver (without performing a liver transplant) ranges from 30%–55% at 5 years. (Wehrman and Loomes 2024). The vast majority of individuals with BA, even with optimal management of the disease, will eventually require liver transplantation.

A thorough review of the MRX-701 database was performed, and there were 2 participants [redacted] identified with events of death reported after study discontinuation. Participant had no reported event of death either during the study or after study discontinuation at the time of the database closure or completion of the Clinical Study Report. Of note, both participants with reports of death after study discontinuation were from [redacted]. In this country, access to liver transplant is limited, with patients having limited survival if HPE fails to re-establish bile flow (Liu et al. 2017).

Participant [redacted] was [redacted] [redacted] at the time of enrollment in Study MRX-701 on [redacted]. The participant had received the diagnosis of biliary atresia on [redacted] and had HPE surgery on [redacted] (aged 85 days). Additional relevant medical history included cytomegalovirus (CMV) infection, coagulopathy, anaemia and malnutrition.

Relevant concomitant medications taken within 30 days prior to the onset of the event of pneumonia included cefazolin, metronidazole, and ursodeoxycholic acid. Relevant concomitant medications taken within 30 days prior to the onset of the event of hepatic cirrhosis included ursodeoxycholic acid and cefotaxime.

On (Study Day 1), the baseline visit, the participant received the first dose of double-blind study medication while enrolled in Study MRX-701. On [redacted] (Study Day 19), the participant received the last dose of double-blind study medication.

On [redacted] (a screening visit 18 days prior to the first dose of study medication) local laboratory results included ALT 111.2 U/L (normal range 0–50 U/L), total bilirubin 15.58 mg/dL (normal range 0.3–1.2 mg/dL), and direct bilirubin 7.75 mg/dL (normal range 0–0.2 mg/dL). On [redacted] (a screening visit, 1 day prior to the first dose of study medication), the participant was noted to have a "big liver" on physical examination. On [redacted] (Study Day 1), the baseline visit, central laboratory results included ALT 250 U/L (normal range 4–35 U/L), AST 493 U/L (normal range 0–64 U/L), ALP 690 U/L (normal range 82–383 U/L), GGT 353 U/L (normal range 12–122 U/L), total bilirubin 22.36 mg/dL (normal range 0–1.99 mg/dL), and albumin 3.1 g/dL (normal range 2.8–4.6 g/dL). Of note ALT and total bilirubin showed a slight increase compared with the screening results prior to the initiation of the study medication.

On [redacted] (Study Day 10), the participant experienced a serious adverse event of pneumonia (Grade 3) and was hospitalised that same day with cough, mild fever, chest retractions, moist rales, thoracic indrawing breathing, pink lips, jaundice, and pale stool. Chest X-ray findings included exaggerated heart size but no damage on lung parenchyma. The reported event was considered serious due to the seriousness criterion of hospitalization. At the time of the event, the participant was receiving double-blind study medication (maralixibat). On that same day, local laboratory results included ALT 288.5 U/L (normal range 0–50 U/L), AST 451.7 U/L (normal range 15–60 U/L), total bilirubin 23.76 mg/dL (normal range 0.3–1.2 mg/dL), direct bilirubin 11.41 mg/dL (normal range 0–0.2 mg/dL), and leukocytes 6.82×103/µL (normal range 6–14×103/µL). Of note ALT, total bilirubin, and direct bilirubin continued to show a steady increase in their values as compared with the 10 March 2023 screening visit results (see laboratory results reported above) possibly indicating a failed HPE procedure (insufficient bile drainage).

On [redacted] (Study Day 11), the participant was arousable and had pink lips, warm hands and feet, regular breathing, slightly thoracic indrawing breathing, and noisy breathing; the participant was stable with partial breast feeding. On [redacted] (Study Day 12), the participant was stable and completely breastfed, and liver and spleen were enlarged. On [redacted] (Study Day 14), findings included liver 2 cm below the ribs, mean spleen size below costal margin 1 cm; the participant was stable with little cough, no fever, and no rales. On that same day, laboratory tests revealed a negative antinuclear antibodies (ANA) test (ELISA), CMV DNA below detection limit, Epstein-Barr virus DNA not detected,

CMV DNA qPCR positive detection limit, and immunofluorescence tests negative for SMA, LKM1, AMA, and FACTIN and positive for ANA. It was reported that all viral hepatitis, autoimmune hepatitis, and cholangitis had been ruled out. On [redacted] (Study Day 15), the participant was considered stable with a little cough and no fever. Treatment for the event included IV cefotaxime sodium. No action was taken with the study medication due to the event. On [redacted] (Study Day 16), the event of pneumonia was considered resolved (participant stable with cough resolved), and the participant was discharged from the hospital. On that same day (Study Day 16), central laboratory results included ALT 289 U/L (normal range 4–35 U/L), AST 584 U/L (normal range 0–64 U/L), ALP 649 U/L, total bilirubin 24.38 mg/dL (normal range 0–1.99 mg/dL), direct bilirubin 14.15 mg/dL (normal range 0–0.5 mg/dL), albumin 2.6 g/dL, leukocytes 8.81×103/µL (normal range 7.91–13.41×103/µL), and neutrophils 5.29×103/µL (normal range 2.57–7.54×103/µL).

The investigator assessed the causality of the event of pneumonia as not related to the double-blind study medication. The sponsor assessed the causality of the event of pneumonia as not related to double-blind study medication. The sponsor considered the infectious etiology of the event, the age of the participant, and the participant's immature immune system as alternate etiologies for the event.

As of [redacted], the total bilirubin and direct bilirubin continued their steady upward trajectory that had been present since the participant's screening visit (see laboratory results reported above).

On [redacted] (Study Day 19), the participant received the last dose of study medication. On [redacted] the participant experienced a serious adverse event of hepatic cirrhosis (Grade 4). The reported event was considered serious due to the seriousness criteria of hospitalization and other medically important event. Study medication was not given on [redacted] due to the event of hepatic cirrhosis; it was considered withdrawn due to adverse event. On [redacted] (Study Day 30), 11 days after the last dose of study medication, the participant's ALT, total bilirubin, and direct bilirubin continued to steadily increase while the albumin decreased. On that same day (Study Day 30) local laboratory results included ALT 346 U/L, AST 573 U/L, ALP 455 U/L, GGT 58 U/L, total bilirubin 26.37 mg/dL, direct bilirubin 14.92 mg/dL, albumin 2.5 g/dL, and INR 1.8 (normal range 0.8–1.1). Treatment for the event included oral spironolactone. The event of hepatic cirrhosis was considered not resolved.

On [redacted] (Study Day 39), central laboratory results included ALT 435 U/L, AST 602 U/L, ALP 378 U/L, GGT 54 U/L, total bilirubin 27.61 mg/dL, and direct bilirubin 15.66 mg/dL. On that same day the participant discontinued the study due to the adverse event of hepatic cirrhosis.

After the participant left the study, it was reported that the participant was hospitalised on [redacted] and died on [redacted] (71 days after the last dose of study medication). Cause of death was not provided on the death certificate, and an autopsy was not performed.

The investigator assessed the causality of the event of hepatic cirrhosis as not related to the double-blind study medication but rather that the medical history of cirrhosis and underlying biliary atresia provide plausible etiology. The sponsor assessed the causality of the event of hepatic cirrhosis as not related to double-blind study medication and agreed with the possible etiology provided by the investigator. Additionally, the sponsor has also considered the participants medical history of cytomegalovirus infection as a possible contributor to the event of hepatic cirrhosis.

Participant [redacted], was [redacted] old at the time of enrolment in Study MRX-701 on [redacted]. The participant had received the diagnosis of biliary atresia on and had HPE surgery on the same day (age [redacted]). Additional relevant medical history included cytomegalovirus infection and hepatic cirrhosis (both ongoing [redacted], 93 days prior to baseline).

Relevant concomitant medications taken within 30 days prior to the onset of the event of diarrhoea included ursodeoxycholic acid, valganciclovir hydrochloride, tobramycin sulfate, cefotaxime, esomeprazole sodium, cefoperazone/sulbactam sodium, methylprednisolone, and cefixime.

Relevant concomitant medications taken within 30 days prior to the onset of the first event of pneumonia included ursodeoxycholic acid, saccharomyces boulardii, cefixime, racecadotril, cefoperazone/sulbactam sodium, and methylprednisolone.

Relevant concomitant medications taken within 30 days prior to the onset of the first event of cholangitis and the second event of pneumonia included ursodeoxycholic acid, cefoperazone/sulbactam sodium, tobramycin sulfate, racecadotril, cefixime, and azithromycin.

Relevant concomitant medications taken within 30 days prior to the onset of the event of hepatic enzyme increased included ursodeoxycholic acid, cefoperazone/sulbactam sodium, azithromycin, vancomycin, cefixime trihydrate, spironolactone, meropenem, sulfamethoxazole/trimethoprim, ambroxol, and ciprofloxacin. Relevant concomitant medications taken within 30 days prior to the onset of the second event of cholangitis included all previously mentioned for hepatic enzyme increased with the addition of cefotaxime.

On [redacted], 2 days prior to the first dose of double-blind study medication, the screening physical examination findings included liver 3 cm below the costal margin, mild yellow sclera, and mild jaundice of the skin overall. On that same day, screening laboratory results included ALT 214 U/L (normal range 3–30 U/L), ALP 155 U/L (normal range 124–341 U/L), GGT 837 U/L (normal range 15–132 U/L), total bilirubin 4.17 mg/dL (normal range 0–1.99 mg/dL), albumin 4.2 g/dL (normal range 2.9–4.2 g/dL), INR 0.99 (normal range 0.9–1.2), leukocytes 14.23×103/µL (normal range 6.85–12.84×103/µL), and neutrophils 7.04×103/µL (normal range 2.22–7.11×103/µL). On [redacted] (Study Day 1), central laboratory results included AST 184 U/L (normal range 0–78 U/L) and direct bilirubin 2.81 mg/dL (normal range 0–0.5 mg/dL).

On [redacted] (Study Day 1), the baseline visit, the participant received the first dose of doubleblind study medication (maralixibat) while enrolled in Study MRX-701. On [redacted] (Study Day 71), the participant received the last dose of double-blind study medication (maralixibat).

On [redacted] (Study Day 2), the participant experienced a serious adverse event of diarrhoea (Grade 3) and was hospitalised that same day. The reported event was considered serious due to the seriousness criterion of hospitalization. At the time of the event, the participant was receiving double-blind study medication (maralixibat). It was noted that on [redacted], 1 day before starting the blinded study medication, the participant had also experienced diarrhoea. Treatment for the event included IV cefoperazone/sulbactam, glucose, potassium chloride, sodium chloride, and sodium citrate dihydrate; and oral racecadotril and saccharomyces boulardii. No action was taken with the study medication due to the event. On [redacted] (Study Day 10), the event of diarrhoea was considered resolved, and the participant was discharged from the hospital. The investigator assessed the causality of the event of diarrhoea as related to the double-blind study medication. As the participant had previously experienced diarrhoea before study initiation, it is not conclusive if the reported event was a continuation of the previous episode or aggravation due to treatment; however, as diarrhoea is a known adverse drug reaction with maralixibat, the sponsor agreed with the investigator's assessment of the causality between the event of diarrhoea and double-blind study medication as related. Confounding factors included the use of saline laxatives and ongoing cytomegalovirus infection.

On [redacted] (Study Day 16), the participant experienced a serious adverse event of pneumonia (Grade 3) and was hospitalised that same day. The reported event was considered serious due to the seriousness criterion of hospitalization. At the time of the event, the participant was receiving double-

blind study medication (maralixibat). On the same day local laboratory results included ALT 155.4 U/L (normal range 6–50 U/L), AST 194.7 U/L (normal range 19–61 U/L), total bilirubin 1.23 mg/dL (normal range 0.1–0.7 mg/dL), direct bilirubin 0.61 mg/dL (normal range 0–0.2 mg/dL), leukocytes 15.38×103/µL (normal range 6.8–12.8×103/µL), and neutrophils 2.78×103/µL (normal range 2.2–7.1×103/µL). Local laboratory results on (Study Day 17) included bicarbonate 16 mmol/L (normal range 18–28 mmol/L), potassium 4.9 mmol/L (normal range 3.5–5.1 mmol/L), and sodium 137 mmol/L (normal range 136–145 mmol/L). On the same day the recorded physical examination findings were severe malnutrition and moist rale[s] on both sides of the lung. Treatment for the event included IV cefoperazone/sulbactam sodium, sodium chloride, potassium chloride, and glucose, and oral azithromycin. No action was taken with the study medication due to the event. (Study Day 21), it was reported that the participant had no fever, was breathing spontaneously, had pink lips and open airways, and was no longer in critical condition. On the same day the event of pneumonia was considered resolved, and the participant was discharged from the hospital. The investigator assessed the causality of the event of pneumonia as not related to the double-blind study medication. The sponsor assessed the causality of the event of pneumonia as not related to double-blind study medication and considered the infectious etiology of the event, the age of the patient, concomitant methylprednisolone, and an immature immune system as confounding factors.

On [redacted] (Study Day 37), the participant had a high fever (39°C) and experienced a nonserious adverse event of cholangitis (Grade 3). No treatment was reported for the event. On [redacted] (Study Day 38), increases in local laboratory results when compared with the prior laboratory values were observed and included total bilirubin 1.39 mg/dL (normal range 0.1–0.7 mg/dL), direct bilirubin 1 mg/dL (normal range 0–0.2 mg/dL), ALT 426.5 U/L (normal range 6–50 U/L), AST 287.9 U/L (normal range 19–61 U/L), ALP 417U/L, GGT 348.2 U/L (normal range 6–92 U/L), leukocytes 23.2×103/µL (normal range 6.8–12.8×103/µL), and neutrophils 9.38×103/µL (normal range 2.2–7.1×103/µL).

On [redacted] (Study Day 38), the cholangitis was upgraded to a serious adverse event (Grade 3), as the participant was hospitalised; the event was also considered an. At the time of the event, the participant was receiving double-blind study medication (maralixibat). On the same day the participant had a serious adverse event of pneumonia (Grade 3). The reported events were considered serious due to the seriousness criterion of hospitalization. Treatment for the event of cholangitis included IV cefoperazone/sulbactam sodium. On [redacted] (Study Day 43) recorded physical examination findings were stomach distension and malnutrition. Study medication was interrupted due to the event of cholangitis. Other medications given during hospitalization included IV and oral furosemide; oral and IV spironolactone; IV potassium chloride, amikacin, meropenem trihydrate, and sodium chloride; and oral paracetamol. It was reported that the participant's cough decreased, and fever disappeared. On [redacted], study medication was resumed (maralixibat).

On [redacted] (Study Day 55), local laboratory results included ALT 53.8 U/L, AST 58.4 U/L, total bilirubin 2.15 mg/dL, direct bilirubin 1.83 mg/dL, leukocytes 14.78×103/µL, and neutrophils 3.72×103/µL.

On [redacted] (Study Day 59), the events of cholangitis and pneumonia were considered resolved, and the participant was discharged from the hospital. The investigator assessed the causality of the events of cholangitis and pneumonia as not related to the double-blind study medication. The sponsor assessed the causality of the events of cholangitis and pneumonia as not related to double-blind study medication, and considered the participant's underlying disease, immature immune system, cytomegalovirus infections in the medical history, previous episode of pneumonia resulting in hospitalization less than a month before the current one, and HPE procedure (as cholangitis is one of the most common complications after surgery) as confounding factors.

On [redacted] (Study Day 70), the participant had a nonserious adverse event of hepatic enzyme increased (Grade 3). On that same day, local laboratory results included ALT 725 U/L, AST 704.2 U/L, ALP 329.6 U/L, GGT 316.7 U/L, total bilirubin 1.04 mg/dL, direct bilirubin 0.46 mg/dL, albumin 4.26 g/dL (normal range 2.8–4.8 g/dL), platelets 312×103/µL (normal range 140–440×103/µL), and INR 1.22. The following day (Study Day 71), the participant was hospitalised, and the hepatic enzyme increased (Grade 3) was considered a serious event, due to the seriousness criterion of hospitalization, and was also an adverse event of special interest. At the time of the event, the participant was receiving double-blind study medication (maralixibat). On the same day the central laboratory results included ALT 691 U/L (normal range 3–30 U/L), AST 603 U/L (normal range 0–78 U/L), ALP 350 U/L, GGT 325 U/L (normal range 15–132 U/L), total bilirubin 0.99 mg/dL (normal range 0–1.99 mg/dL), direct bilirubin 0.74 mg/dL (normal range 0–0.5 mg/dL), albumin 4.2 g/dL (normal range 2.9–4.2 g/dL), and INR 1.3 (normal range 0.8–1.1). Treatment for the event included IV glucose, sodium chloride, potassium chloride, and cefotaxime. On the same day the study medication was interrupted due to the serious event of hepatic enzyme increased.

On [redacted] (Study Day 74), the participant experienced a nonserious adverse event of ascites (Grade 2). On [redacted] (Study Day 76), the participant experienced a serious adverse event of cholangitis (Grade 3) resulting in prolonged hospitalization. The reported event was considered serious due to the seriousness criterion of hospitalization. At the time of the event, the participant was not receiving double-blind study medication and did not restart the blinded study drug due to subsequent withdrawal from the study. On the same day the local laboratory results included ALT 135.3 U/L (normal range 6–50 U/L), AST 85.9 U/L (normal range 19–61 U/L), GGT 405.8 U/L (6–92 U/L), leukocytes 5.26×103/µL, and neutrophils 2.9×103/µL. Treatment for the event throughout hospitalization included oral paracetamol, spironolactone, tobramycin, and rehydration therapy; and IV glucose, potassium chloride, sodium chloride, albumin, cefoperazone/sulbactam sodium, levofloxacin, furosemide, and meropenem trihydrate.

On [redacted] (Study Day 80), local laboratory results included ALT 46.5 U/L, AST 50 U/L, ALP 280 U/L, GGT 417.3 U/L, total bilirubin 4 mg/dL (normal range 0.1–0.7 mg/dL), direct bilirubin 3.18 mg/dL (normal range 0–0.2 mg/dL), albumin 3.03 g/dL, and INR 1.19 (normal range 0.9–1.2). On the same day the event of hepatic enzyme increased was considered resolved. The investigator assessed the causality of the event of hepatic enzyme increased as related to the double-blind study medication. The sponsor assessed the causality of the event of hepatic enzyme increased as not related to blinded study medication; recent infections, including pneumonia, cytomegalovirus infection, and cholangitis (including their corrective treatment), and the participant's ongoing malnutrition, ascites and cirrhosis provided plausible alternative etiology for the increased liver enzyme values.

On [redacted], the participant had respiratory failure due to large ascites, and the participant was discharged from the hospital at the parents' request; the site confirmed that the participant was discharged in a not-recovered condition. Consequently, the event of cholangitis was ongoing, and the outcome of the event was unknown following hospital discharge. The investigator assessed the causality of the event of cholangitis as not related to the double-blind study medication. The sponsor assessed the causality of the event of cholangitis as not related to the blinded study medication. The alternative explanation for the event of cholangitis was that cholangitis is a common complication in patients with biliary atresia who have undergone HPE surgery.

On [redacted], the participant discontinued the study; the caregiver had taken the baby back home on and rejected any further healthcare activities, including study procedures, and so the participant was withdrawn from the study at the parents' request. The participant died on [redacted] (81 days after the last dose of study medication), and the cause of the death was assessed by the investigator as being

due to progression of the underlying disease. An autopsy was not performed due to lost to follow-up. This death was not considered treatment emergent.

Assessment of the Applicant's response

Two patients died after cessation of treatment with MRX. Detailed narratives were provided. Conclusion of the treated doctors and the MAH is that both events are related to progression of the background disease. In both cases the patients had progressed condition already at the baseline and multiple recurrent AEs (e.g., cholecystitis, pneumonia/infections, diarrhoea). Multiple concomitant treatments known to be hepatotoxic were administered including antibiotics, paracetamol, etc. It is not possible to draw firm conclusions on causal relationship (presence or absence) in presence of multiple confounders.

Conclusion

Issue resolved.

5. MAH responses to the SECOND request for supplementary information

Question

The MAH is requested to provide an overview table where all patients with any liver-related event (worsening in liver function tests, cirrhosis, ascites, bleeding, increased INR, end-stage liver disease, listing of LT, LT, etc.) will be considered per treatment arm. Also, a separate listing that includes such patients should be provided. The MAH is requested to also specify whether there were cases of DILI observed during the study.

Summary of the Applicant's response

As requested by the Agency, the Applicant has provided an overall summary table of all participants with any liver-related event reported in Study MRX-701.

In addition, a separate patient-level listing including all participants with liver-related events reported in Study MRX-701 is provided; reference is made to the listing in Appendix 1.

The Applicant confirms that no cases of drug-induced liver injury (DILI) were observed throughout the conduct of Study MRX-701. Safety data from Study MRX-701 were reviewed quarterly by the Data Monitoring Committee (DMC); the DMC did not identify any cases of potential DILI attributable to maralixibat in this study.

Table 15 Incidence of Treatment-Emergent Liver-Related Events by Preferred Term, Safety Population

	No. (%) of Participants				
	Double-blind Period		OLE Period [a]		Overall [b]
Event Term **Preferred Term (where applicable)**	**MRX (N=40)**	**PBO (N=35)**	**MRX-MRX (N=28)**	**PBO-MRX (N=24)**	**MRX (N=64)**
Worsening of liver function tests [c]	**10 (25.0)**	**8 (22.9)**	**5 (17.9)**	**3 (12.5)**	**16 (25.0)**
Alanine aminotransferase increased	5 (12.5)	6 (17.1)	3 (10.7)	1 (4.2)	7 (10.9)
Aspartate aminotransferase increased	1 (2.5)	1 (2.9)	2 (7.1)	0	2 (3.1)
Blood bilirubin increased	1 (2.5)	2 (5.7)	1 (3.6)	0	2 (3.1)
Hepatic enzyme increased	3 (7.5)	0	1 (3.6)	1 (4.2)	5 (7.8)
Hepatic function abnormal	0	0	0	1 (4.2)	1 (1.6)
Hyperbilirubinemia	1 (2.5)	1 (2.9)	0	0	1 (1.6)
Liver function test increased	1 (2.5)	0	0	0	1 (1.6)
Cirrhosis [c, d, e]	**2 (5.0)**	**0**	**0**	**0**	**2 (3.1)**
Development of liver cirrhosis [d]	2 (5.0)	0	0	0	2 (3.1)
Development of liver cirrhosis [e]	1 (2.5)	0	0	0	1 (1.6)
Hepatic cirrhosis [c]	1 (2.5)	0	0	0	1 (1.6)
Ascites [c, d, e]	**3 (7.5)**	**1 (2.9)**	**1 (3.6)**	**0**	**4 (6.3)**
Ascites [c]	2 (5.0)	1 (2.9)	0	0	2 (3.1)
Ascites [d]	2 (5.0)	1 (2.9)	1 (3.6)	0	3 (4.7)
Ascites [e]	1 (2.5)	0	0	0	1 (1.6)
Bleeding, including upper GI variceal bleeding [c, d]	**2 (5.0)**	**2 (5.7)**	**1 (3.6)**	**0**	**3 (4.7)**
Epistaxis [c]	1 (2.5)	0	0	0	1 (1.6)
Gastrointestinal haemorrhage [c]	1 (2.5)	0	0	0	1 (1.6)
Haematochezia [c]	0	2 (5.7)	0	0	0

	No. (%) of Participants				
	Double-blind Period		OLE Period [a]		Overall [b]
Event Term **Preferred Term (where applicable)**	**MRX (N=40)**	**PBO (N=35)**	**MRX-MRX (N=28)**	**PBO-MRX (N=24)**	**MRX (N=64)**
Upper GI variceal bleeding [d]	0	0	1 (3.6)	0	1 (1.6)
Upper gastrointestinal haemorrhage [c]	0	0	1 (3.6)	0	1 (1.6)
Increased INR [c]	**1 (2.5)**	**0**	**0**	**0**	**1 (1.6)**
Listing for Liver Transplant [d, f]	**3 (7.5)**	**1 (2.9)**	**0**	**0**	**3 (4.7)**
Listing for liver transplantation [d]	3 (7.5)	1 (2.9)	0	0	3 (4.7)
Listing for liver transplantation [f]	3 (7.5)	1 (2.9)	0	0	3 (4.7)

CRF=case report form; GI=gastrointestinal; INR=international normalized ratio; MRX=maralixibat; OLE=open-label extension; PBO=placebo.

Notes: The single event or single PT only has Event Term row.

Participants may report multiple Preferred Terms within an Event Term. The participant is only counted once per Event Term.

[a] Only events during OLE are presented. They are presented by the treatment the participants received during double-blind period. OLE treatment is MRX for everyone.

[b] Presents events while receiving MRX only.

[c] Adverse Events CRF

[d] Liver-Associated Events CRF

[e] Disease Progression Follow-Up CRF

[f] Study Completion or Discontinuation 2 CRF

Final study data from 12 Apr 2024

Assessment of the Applicant's response

The requested information was provided. Based on the summary table and the listing of the AEs no pattern that might have suggested causal relationship between the events and treatment with maralixibat could be identified. The reported events mostly represent various types of bleeding events and/or INR increased, worsening of liver function tests/elevated bilirubin, occurrence of cirrhosis, ascites, and listing for LT/LT. These events occurred on both, maralixibat and placebo treatment. No temporal relationship can be identified between the start of these events and treatment with MRX.

The Applicant confirms that no cases of drug-induced liver injury (DILI) were observed throughout the conduct of Study MRX-701. Safety data from Study MRX-701 were reviewed quarterly by the Data Monitoring Committee (DMC); the DMC did not identify any cases of potential DILI attributable to maralixibat in this study.

No new relevant information has, thus, been identified and no new safety concerns have been raised.

Conclusion

Issue resolved.

Appendix 1.

Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Livmarli Active substance: Maralixibat

Study title	Study number	Date of completion	Date of submission of final study report
Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Biliary Atresia after Hepatoportoenterostomy	MRX-701	07 February 2024	03 September 2024 (abbreviated study report submitted)