PROTOCOL: **MRX-701**

TITLE:	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
SHORT TITLE:	**EMBARK**: **E**valuation of **M**aralixibat in **B**iliary **A**tresia **R**esponse post-**K**asai
DRUG:	Maralixibat
IND:	147617
EUDRACT:	2020-000974-22
SPONSOR	Mirum Pharmaceuticals Inc. 950 Tower Lane Foster City, CA 94404
COORDINATING INVESTIGATOR:	[redacted]
PROTOCOL HISTORY:	Version 1, 26 June 2020 Version 2, 24 August 2020 Version 3, 3 February 2021 Version 4, 6 May 2021 Version 5, 25 March 2022 Version 6, 25 April 2023

This study will be performed in compliance with the International Council for Harmonisation Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents.

[redacted]

PROTOCOL SIGNATURE PAGE

Sponsor's (Mirum) Approval

Signature: DocuSigned by: [redacted]	**Date:**
[redacted] FD2E719A407... Medical Lead	5/8/2023

Investigator's Agreement

I have read this protocol for Mirum Pharmaceuticals, Inc. Study MRX-701 (EMBARK), Version 6.

Title: 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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a participant in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____
_____
_____

Signature: _____ **Date:** _____

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

LIST OF FIGURES

STUDY SYNOPSIS

Protocol Number: MRX-701	**Drug:** Maralixibat (SHP625, LUM001)
Title of the 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	
Short Title: EMBARK: **E**valuation of **M**aralixibat in **B**iliary **A**tresia **R**esponse post-**K**asai	
Number of Participants (total and for each treatment arm): Approximately 72 participants will be enrolled (36 per treatment group). Participants will be randomized 1:1 to maralixibat 600 µg/kg twice daily (BID) or placebo BID.	
Investigators: International, multicenter study	
Sites and Regions: The study will be conducted at multiple sites in North America, Europe, and Asia. Other regions may be added, if necessary.	
Clinical Phase: 2	

Background

Biliary atresia (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.

The two most important improvements in the care of patients with BA to date have been the Kasai hepatoportoenterostomy (HPE or Kasai) and orthotopic liver transplantation. HPE remains the standard of care as first-line intervention, generally being performed within the first 2 months of life. The procedure consists of surgically removing affected extrahepatic bile ducts and establishing bile flow by connecting a small bowel loop directly to the hepatic hilum, bypassing the obstructed bile ducts. HPE significantly improves long-term outcomes (native liver survival, mortality, morbidity), with approximately 40%–64% of patients experiencing clearance of jaundice. However, although HPE frequently improves the signs and symptoms of BA, a substantial proportion of patients do not respond fully. Approximately 40%–50% of patients will require a liver transplant by 2 years of age despite undergoing HPE, making BA the leading cause of pediatric liver transplantation worldwide. This population, therefore, has a clear unmet medical need to improve outcomes and reduce the need for liver transplantation and long-term immunosuppressive therapy. At present, there are no approved pharmacological agents that have demonstrated efficacy in achieving this goal.

Maralixibat is a minimally absorbed inhibitor of the ileal bile acid transporter (IBAT; also known as the apical sodium-dependent bile acid transporter or solute carrier family 10 member 2). By virtue of its ability to inhibit bile acid absorption and lower circulating bile acid levels, maralixibat is being developed by Mirum Pharmaceuticals, Inc. (Mirum), as a potential therapeutic agent for the treatment of BA.

Rationale

Clinical data from other forms of pediatric cholestatic diseases, including ongoing and completed Phase 2 studies in progressive familial intrahepatic cholestasis and Alagille syndrome, indicate that maralixibat improves signs and symptoms of cholestasis and may improve markers of liver injury as well as long-term liver-related outcomes. This includes reductions in serum bile acid (sBA), as well as improvements in growth and other measures suggestive of disease modification, including transplant and biliary diversion event-free survival. Maralixibat has demonstrated an acceptable

safety profile in more than 1600 exposed participants overall, including more than 119 children ≥12 months of age with cholestatic liver disease.

Elevated sBA levels are associated with increased morbidity and mortality in several cholestatic diseases. High bile acid levels are understood to be an important driver of liver disease in patients with BA after HPE. A consistent body of literature has demonstrated that biliary drainage, as measured by bilirubin levels at 3 and 6 months after HPE, is a prognostic indicator for long-term transplant-free survival in BA.

Given the above, a reduction in the levels of serum and hepatic bile acids in patients with BA is hypothesized to slow or prevent liver injury, and therefore improve long-term transplant-free survival. Based on the understanding of maralixibat's mechanism of action and its ability to durably reduce sBA in pediatric cholestasis for >6 years, maralixibat has the potential to reduce the long-term liver sequelae of BA.

Objectives and Endpoints

Objectives

Primary Objective:

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

Secondary Objectives:

- 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

Exploratory Objectives:

- [redacted]

Open-Label Extension Objectives:

- All of the above primary and secondary objectives analyzed over the full study duration, including the open-label extension (OLE) period

[redacted]

Endpoints

Primary Endpoint:

- Mean change in total serum bilirubin levels from baseline through Week 26

Secondary Endpoints of the Double-Blind Period:

- 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 10^9/L) or clinically evident ascites or endoscopic evidence of esophageal 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 pharmacokinetic profile

Exploratory Endpoints of the Double-Blind Period:

- [redacted]

- [redacted]

Open-Label Extension Endpoints:

- To assess all of the above primary and secondary endpoints but for study data through Week 104

Study Design

This is a 26-week, multicenter, double-blind, placebo-controlled, randomized parallel-group study, followed by an OLE period including analyses up to Week 104, in participants with BA. In the double-blind period of the study, participants will be randomized in a 1:1 fashion to receive either placebo or maralixibat up to 600 µg/kg BID. Treatment assignment will use a block randomization process scheme by study site (i.e., stratified by study site). The study periods are as follows:

1. Screening (1 week to 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 will receive standard-of-care treatment in line with investigator and caregiver preference and in addition to study medication.

Screening

The duration of the screening period is up to 3 weeks, during which all procedures listed for the screening visit in the Schedule of Assessments in the protocol must be completed.

Participants who meet eligibility criteria after completion of all screening visit assessments will be randomized and enter the 4- to 8-week double-blind dose-escalation period. This period should not start until all screening assessments required to confirm eligibility for randomization have been completed and study medication has been received at the site.

Double-Blind Period

Participants who meet all eligibility criteria will be randomized 1:1 at the baseline visit to receive maralixibat or placebo.

Dose Escalation: The double-blind dose-escalation treatment periods will comprise 4–8 weeks (maximum 8 weeks). Dose escalation should occur in the absence of major safety (e.g., liver parameters, biochemistry) or tolerability concerns (e.g., gastrointestinal-related, TEAEs) concerns related or possibly related to study medication. Participants may have doses reduced to a lower, previously tolerated dose level for 1 week before continuing dose escalation, as required. [redacted] participants who cannot tolerate the minimum dose of [redacted] µg/kg maralixibat BID will be removed from both the study and the per-protocol analysis.

[redacted]

Investigators have up to 8 weeks of dose escalation to determine the highest tolerated dose up to 600 µg/kg BID; if rechallenges or further dose escalations fail, the participant will remain at the highest tolerated dose level for the remainder of the treatment period, completing a minimum of 18 weeks within the stable dosing double-blind period.

Stable Dosing: During the double-blind stable-dosing period, participants/caregivers will receive emails and/or a phone calls during which the use of concomitant treatments, breastfeeding status, AEs, and study drug compliance will be reviewed. [redacted]

Open-Label Extension Period

All participants who complete the double-blind period will enter the OLE, in which all participants receive open-label maralixibat at a maximum tolerated dose of 600 µg/kg BID. [redacted]

Participants will remain in the OLE until at least Week 104. [redacted]

[redacted]

Dose Escalation: During the OLE, all participants, regardless of treatment assignment in the double-blind period, will receive maralixibat at a starting dose of [redacted] µg/kg BID (or [redacted] µg/kg BID [redacted]). Investigators have up to 8 weeks to determine the highest tolerated dose in the OLE. The dose will be escalated over a 4- to 8-week period, in a manner similar to the escalation in the double-blind period. If rechallenges or further dose escalations fail, the participant will remain on the highest tolerated dose level for the remainder of the OLE period to complete a minimum of 78 weeks of treatment in the OLE period (to Week 104). Dose reductions are allowed for safety or tolerability reasons down to a minimum level of [redacted] µg/kg BID. Participants who cannot tolerate this dose will be discontinued from the study.

Stable Dosing: In the OLE, guidelines for stable dosing will be the same as in the double-blind period, with the exception of the cumulative period of treatment interruption. [redacted]

Discontinuations

Medically important events that, in the opinion of the investigator or medical monitor, may compromise the participant's ability to safely continue the study would warrant the participant's discontinuation from the study. The reason for discontinuation must be recorded in the participant's source documents. If a participant is discontinued for more than 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated. See the protocol for reasons for discontinuation.

Inclusion and Exclusion Criteria

Inclusion Criteria

A participant will be considered eligible for the study if he or she meets all the criteria below:

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 ≥[redacted] weeks at birth (Those with gestational age <[redacted] 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 scheduled remote participant contacts

Exclusion Criteria

A participant will be considered ineligible for the study if he or she meets any of the criteria below:

1. Chronic diarrhea requiring ongoing IV fluid or nutritional intervention at screening, during the screening period, or in 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 ratio >1.5 after correction of possible vitamin K deficiency, history or presence of clinically significant ascites, known varices, variceal hemorrhage, 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

Investigational Product, Dose, and Mode of Administration

Maralixibat will be provided in the form of an oral solution (i.e., [redacted] mg/mL) along with either 0.5-, 1.0-, or 3.0- mL sized dosing dispensers, vials for formulation dilution, and bottle adapters (if required) to clinical sites. The reference/comparator product is a placebo, which will also be provided as an oral solution along with dosing dispensers of the same size (either 0.5 mL, 1.0 mL, or 3.0 mL).

[redacted]

Participants will be administered varying volumes of ready-to-use oral solution study medication at each dosing visit, starting with the baseline visit. The dosing volume is determined based on the individual body weight, the dose level according to the dose-escalation plan [redacted], or 600 µg/kg BID), and the strength of solution being administered. [redacted]

Statistical Methods

Power and Sample Size

[redacted]

Analysis Populations

- Intent-to-treat (ITT) population: all randomized participants. Additional subgroups of the ITT population will be specified based on the presence/absence of post-baseline efficacy assessments for particular efficacy endpoints.
- Per-protocol population: all participants in the ITT population who receive at least 1 dose of study medication and do not have any major protocol violations or deviations. Major protocol violations/deviations will be identified prior to database lock.
- Safety population: all participants who receive at least 1 dose of study medication.

Efficacy Analyses

The primary efficacy endpoint is defined as the mean change in total serum bilirubin levels from baseline to Week 26 for the maralixibat-treated cohort versus placebo.

[redacted]

The null hypothesis for the primary efficacy endpoint of the equality of maralixibat and placebo is:

H_0: mean change in total bilirubin baseline and Week 26 in the two treatment groups are equal

The null hypothesis of no treatment effect will be rejected if the statistical analysis results in a 2-sided p-value for treatment at Week 26 is <0.05. [redacted]

[redacted]

[redacted]

The study will be deemed successful if the hypothesis of no treatment effect on the primary efficacy endpoint over the primary cohort in the ITT population is rejected at the 0.05 (2-sided) significance level. Analysis similar to that described for the primary efficacy endpoint, including the sensitivity analyses, will be performed for each of the secondary efficacy endpoints.

[redacted]

Exploratory and OLE endpoints will be summarized descriptively.

Safety Analysis

All safety analyses will be performed on the safety population. Safety measures will be summarized descriptively. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation, minimum, and maximum will be presented for the observed and change from baseline values at each study visit. Qualitative variables will be summarized using counts and percentages at each study visit. AEs and concomitant treatments will be coded with standard dictionaries and will be summarized by treatment received.

[redacted]

Pharmacokinetic Analysis

Plasma maralixibat concentrations at each nominal time point and sampling time will be summarized using descriptive statistics. All data will be included in data listings.

[redacted]

Primary Analysis

A single and formal primary analysis will be performed after the last participant has completed Week 26 (or prematurely discontinued the study). All of the Week 26 endpoints will be tested as described above. A final analysis will be performed after all participants have left the study and will focus on the Week 104 endpoints from the OLE.

[redacted]

Table 1 Schedule of Assessments: Screening and Double-Blind Period

Procedure	Screening[a]	BL	Dose Escalation (Duration: 4–8 Weeks)[b,c,d]					Stable Dosing (Duration: 18–22 Weeks)						
Visit/Participant Contact	**VS**	**VBL**	[redacted]											
Study Week	**-3 to -1**	**0**												
Study Day	**-21 to -1**	**0**												
Window (days)														
Informed consent	X													
Eligibility assessment	X	X												
Demographics	X													
Medical history	X													
Breastfeeding status	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs[g]	X	X	X	X		X		X		X		X		X
[redacted]		X						X						X
[redacted]		X						X						X
[redacted]		X[j]												X
[redacted]		X												X
Electrocardiogram		X						X						X
[redacted]		X						X						X
[redacted]		X	X	X		X		X		X		X		X
CBC with differential[m]	X			X				X				X		X
Coagulation[m]	X					X		X		X		X		X
Chemistry panel[n]	X	X		X		X		X		X		X		X
sBA collection[o, p]		X		X		X				X		X		X
Retinol/Vitamin A, α-tocopherol/Vitamin E [p, q]	X					X				X				
25-hydroxy vitamin D[p, q]	X							X				X		X
[redacted]		X		X		X				X		X		X
PK sample[r, o]		X		X				X						X
[redacted]		X								X				X
[redacted]	X													
Study medication supplied[s]		X	X	X		X		X		X		X		
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X
Assess AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess participant dosing compliance[t]			X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

[redacted] AE=adverse event; BL=baseline; CBC=complete blood count; DMC=Data Monitoring Committee; [redacted] PK=pharmacokinetic; sBA=serum bile acid; V=visit.

a Participants who initially do not meet eligibility criteria may be reassessed during the 3-week screening period prior to being considered as a screen failure. [redacted]

b During the dose-escalation period, dose escalation should occur in the absence of major safety (e.g., liver parameters) or tolerability concerns (e.g., gastrointestinal-related treatment-emergent adverse events) related or possibly related to the study medication. [redacted]

c Additional study visits at the investigator's discretion.

d Dose escalation visit schedule may be updated per DMC recommendation after [redacted] participants have completed the dose-escalation period of the double-blind period, per Section 6.2.4.1.

e [redacted]

f Assessments at Week 26 of the double-blind period are combined with the assessments of the Week-26 OLE period at the same study visit. All assessments/measurements from this double-blind dosing period visit to also apply for the first visit of the open-label extension period.

g Length, weight, blood pressure, heart rate, temperature, and respiration rate. Spleen size below the lower costal margin (measured in centimeters) will be assessed and recorded by the investigator.

h [redacted]

j Should be performed within a [redacted] of the BL visit.

k [redacted]

m CBC and coagulation results performed as part of standard of care by the local laboratory may be used for the study if sample was collected within 3 days before or after the study visit.

n Clinical chemistry (including total and conjugated bilirubin, ALP, ALT, AST, GGT, and albumin) and sBA samples must always be sent to the central laboratory.

o The sBA, [redacted] and PK results will remain blinded to sites and to the blinded study team (see Section 6.1.2 for exceptional circumstances).

p Samples should be taken before feeding, with a suggested fasting of approximately 2 hours prior to collection and before administration of vitamin supplementation, when possible. Water intake, excluding milk, is permitted if necessary.

q Lipid-soluble vitamin values performed as part of standard of care by the local laboratory may be used for the study if samples were collected within ±14 days from the study visit. If blood volumes do not allow all assessments within a single visit, a separate clinical visit in which samples for retinol/Vitamin A, α-tocopherol/Vitamin E, and 25-hydroxy vitamin D are taken can be made.

r Blood samples should be collected before feedings and administration of vitamin supplementation, when possible. Systemic concentrations of maralixibat in plasma will be determined at predose and at approximately [redacted]. Predose samples are not required for measures made at BL.

s If needed, and where permitted, study medication may be supplied via direct shipment to participants between site visits.

t [redacted] compliance is assessed at each visit.

[redacted]

Table 2 Schedule of Assessments: Open-Label Extension and Follow-Up Periods

Procedure	Dose Escalation (Duration: 4–8 Weeks)[a,b,c]					OLE Stable Dosing (To Week 104)										OLE Stable Dosing (Beyond Week 104)[d]		ET[e] /EOT	Follow-Up after ET/EOT
Visit/Participant Contact	[redacted]																		
Study Week																			
Study Day																			
Window (days)																			
Breastfeeding status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs [h]		X	X		X		X		X		X		X		X	X		X	X
[redacted]							X		X		X		X		X	X		X	X
							X		X		X		X		X	X		X	X
Electrocardiogram																X			X[j]
[redacted]			X						X		X		X		X	X		X	X
		X	X		X		X		X		X		X		X	X		X	X
										X						X			
																			X
CBC with differential [n]					X		X		X		X		X		X	X		X	X
Coagulation [n]					X		X		X		X		X		X	X		X	X
Chemistry panel [o]			X		X		X		X		X		X		X	X		X	X
sBA collection [p,q]			X		X		X		X		X		X		X	X		X	X
Retinol/Vitamin A, α-tocopherol/Vitamin E [q,r]			X				X		X		X		X		X	X		X	X
25-hydroxy vitamin D [q,r]					X		X		X		X		X		X	X		X	X
[redacted]			X		X		X		X		X		X		X	X		X	X
										X						X			X
Study medication supplied [s]	X		X		X		X		X		X		X		X	X		X	
Study medication administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant treatments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess participant dosing compliance[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted] AE=adverse event; CBC=complete blood count; circ=circumference; DMC=Data Monitoring Committee; EOT=end of treatment; ET=early termination; OLE=open-label extension; [redacted] sBA=serum bile acid; V=visit.

a During the dose-escalation period, dose escalation should occur in the absence of major safety (e.g., liver parameters) or tolerability concerns (e.g., gastrointestinal-related treatment-emergent adverse events) related or possibly related to the study medication. [redacted]

[redacted]

b Additional study visits at the investigator's discretion.

c Dose escalation visit schedule may be updated per DMC recommendation after [redacted] participants have completed the dose-escalation period of the double-blind period, per Section 6.2.4.1.

d Study medication to continue twice daily in the setting of treatment continuation. [redacted]

e If the ET/EOT visit is within 7 days of the last repeating visit, blood and other clinical assessments do not need to be repeated if previously performed unless there is clinical suspicion of abnormality. Breastfeeding status, AEs, participant dosing compliance, and prior and concomitant treatments will be assessed regardless of timing of the last repeating visit.

f Assessments at Week 26 of the OLE period are combined with the assessments of the Week-26 double-blind period at the same study visit. All assessments/measurements from this double-blind visit to also apply for the first visit of the OLE period.

g [redacted]

h Length, weight, blood pressure, heart rate, temperature, and respiration rate. Spleen size below the lower costal margin (measured in centimeters) will be assessed and recorded by the investigator.

i [redacted]

j ECG is not required at ET/EOT if the ET/EOT visit occurs after Week 104.

k [redacted]

[redacted]

[redacted]

n CBC and coagulation results performed as part of standard of care by the local laboratory may be used for the study if sample was collected within 3 days before or after the study visit.

o Clinical chemistry (including total and conjugated bilirubin, ALP, ALT, AST, GGT, and albumin) and sBA samples must be sent to the central laboratory.

p The sBA [redacted] results will remain blinded to sites and to the blinded study team (see Section 6.1.2 for exceptional circumstances).

q Samples should be taken before feeding, with a suggested fasting of approximately 2 hours prior to collection and before administration of vitamin supplementation, when possible. Water intake, excluding milk, is permitted if necessary.

r Lipid-soluble vitamin values performed as part of standard of care by the local laboratory may be used for the study if samples were collected within ±14 days from the study visit. If blood volumes do not allow all assessments to be performed within a single visit, a separate clinical visit in which samples for retinol/Vitamin A, α-tocopherol/Vitamin E, and 25-hydroxy vitamin D are taken can be made.

s If needed, study medication may be supplied via direct shipment to participants between site visits.

t [redacted]

[redacted]

ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALGS	Alagille syndrome
ALP	alkaline phosphatase
[redacted]	[redacted]
AUC	area under the concentration-time curve
BA	biliary atresia
BID	twice daily (dosing)
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
CRO	contract research organization
CSR	clinical study report
CSS	Clinician Scratch Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DILI	drug-induced liver injury
EMA	European Medicines Agency
EOT	end-of-treatment
ET	early termination
fBA	fecal bile acid
FDA	US Food and Drug Administration
GI	gastrointestinal
GCP	Good Clinical Practice
GGT	γ-glutamlytransferase
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HPE	hepatoportoenterostomy
IBAT	ileal bile acid transporter
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

Abbreviation	Definition
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat (population)
IV	intravenous
[redacted]	[redacted]
LSV	lipid-soluble vitamin
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
OLE	open-label extension
[redacted]	[redacted]
[redacted]	[redacted]
PFIC	progressive familial intrahepatic cholestasis
PG	propylene glycol
PI	Principal Investigator
PK	pharmacokinetic
PND	postnatal day
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acids
TEAE	treatment-emergent adverse events
TK	toxicokinetic
UDCA	ursodeoxycholic acid

[redacted]

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Biliary atresia (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. Infants with BA are often born at-term, have normal birth weight, and generally considered to be thriving well. The first symptoms appear in the first weeks of life, with prolonged jaundice (beyond 2 weeks of life), acholic stools, and dark urine (Chardot 2006). The jaundice is accompanied by irritability and weight loss.

Untreated, the outcome of BA is uniformly fatal (Karrer et al. 1996). The etiology and pathogenesis of BA, however, remain largely unknown and are likely multifactorial (Wehrman et al. 2019). That stated, genetic, infective, inflammatory/immunological, and toxicological factors have been implicated (Hartley et al. 2009; Verkade et al. 2016; Kilgore and Mack 2017). BA is a recognized orphan disease. Recent BA estimates in Western countries show a prevalence between 0.5 and 0.8 per 10,000 live births, corresponding to 16,450 to 22,320 annual cases in the United States (Sanchez-Valle et al. 2017).

The two most important improvements in the care of patients with BA to date have been the Kasai hepatoportoenterostomy (HPE or Kasai) and orthotopic liver transplantation. HPE remains the standard of care as first-line intervention, generally being performed within the first 2 months of life. The procedure consists of surgically removing affected extrahepatic bile ducts and establishing bile flow by connecting a small bowel loop directly to the hepatic hilum, bypassing the obstructed bile ducts. HPE significantly improves long-term outcomes (native liver survival, mortality, morbidity), with approximately 40%–64% of patients experiencing clearance of jaundice (Chardot et al. 1999; McKiernan et al. 2000; Davenport et al. 2004; Wildhaber et al. 2008; Pakarinen et al. 2018). However, although HPE frequently improves the signs and symptoms of BA, a substantial proportion of patients do not respond fully. Approximately 40%–50% of patients will require a liver transplant by 2 years of age despite undergoing HPE, making BA the leading cause of pediatric liver transplantation worldwide. This population, therefore, has a clear unmet medical need to improve outcomes and reduce the need for liver transplantation and long-term immunosuppressive therapy. At present, there are no approved pharmacological agents that have demonstrated efficacy in achieving this goal.

1.2 Product Background and Clinical Information

Maralixibat chloride (hereafter referred to as maralixibat) is an inhibitor of the ileal bile acid transporter (IBAT; also known as the apical sodium-dependent bile acid transporter or solute carrier family 10 member 2). The doses described in this document are of maralixibat chloride but are presented as “maralixibat.” For example, 600 µg/kg maralixibat chloride is equivalent to 570 µg/kg maralixibat free base but will be referred to as 600 µg/kg maralixibat throughout this document.

In a healthy individual, bile acids promote activation of digestive enzymes and micellization of fats and lipid-soluble vitamins (LSV), permitting their intestinal absorption. The IBAT is present in the terminal small intestine on the luminal surface of ileal enterocytes, where it mediates the uptake of conjugated bile acids across the brush border membrane of the enterocyte. It facilitates the recycling of 95% of bile acids that enter the gut lumen back into the bloodstream in a system known as enterohepatic recirculation.

The majority of bile acids (~95%) are absorbed by active transport in the terminal ileum, mediated by the IBAT. Pharmacological inhibition of bile acid uptake through inhibition of the IBAT has the potential for clinical benefit by reducing hepatic accumulation of toxic bile acids, which play an essential role in BA liver damage and disease burden. Due to its key role in bile acid re-uptake, IBAT is an ideal target for pharmacological interruption of bile acid transport. Given its location, IBAT is accessible by compounds that are restricted to the lumen of the gut and do not require systemic exposure for inhibition of bile acid reabsorption. As such, inhibiting the reuptake of bile acids via inhibition of IBAT may represent an ideal treatment for cholestatic disease in general and more specifically for BA (Neimark et al. 2004).

Maralixibat is a potent, highly selective inhibitor (IC_{50}=0.3 nM) of the IBAT. This transmembrane protein transporter, localized on the luminal surface of ileal enterocytes, is present in the terminal 25% of the small intestine and mediates uptake of conjugated bile acids across the brush border membrane of the enterocyte. Maralixibat is minimally absorbed due to its large molecular weight (710 Da) and the presence of a positively charged quaternary nitrogen atom, therefore maximizing the local exposure of the molecule to the receptor and minimizing unnecessary systemic exposure.

Maralixibat-mediated blockade of intestinal reabsorption of bile acids by IBAT interrupts the enterohepatic circulation, thereby increasing fecal bile acid (fBA) excretion and lowering serum bile acid (sBA) levels. Since reductions in sBA concentrations after surgical interruption of the enterohepatic circulation have been shown to be associated with improvements in cholestasis and outcomes in several pediatric cholestatic liver diseases (Emerick and Whitington 2002; Mehl et al. 2016; Bull et al. 2018; van Wessel et al. 2020), pharmacological interruption of the enterohepatic circulation by IBAT inhibition may be a nonsurgical and reversible alternative to achieve a similar reduction in sBA and thus improve disease outcomes.

The ability of maralixibat to reduce sBA and prevent liver injury has been demonstrated in a rodent model of BA, the rat partial bile duct ligation model of cholestasis. This animal model is relevant for BA because it replicates many details of the pathology and etiology as well as signs and symptoms of the disease. In this model, the atresia of bile ducts is mimicked by surgically induced partial ligation. Within 34 days following surgery, the animals develop increased levels of sBA, alkaline phosphatase (ALP), AST, ALT, γ-glutamyltransferase (GGT), and total bilirubin (Heinrich et al. 2011).

Three nonclinical studies support the rationale for efficacy (see the Maralixibat Chloride Investigator's Brochure [IB] for further details). In the first study, 0.3-mg/kg and 10-mg/kg

doses of maralixibat were compared with vehicle and sham surgery. After 14 days of treatment in the maralixibat-treated groups, sBA and liver enzymes were significantly improved compared with the vehicle groups. Consistent with improvements in functional liver biochemistry, histopathologic analysis of liver tissue showed a reduction in necrosis, inflammatory cell infiltration and the number of proliferating cholangiocytes 14 days after liver injury. Similar results were observed in a second study with 3 treatment arms (1 mg/kg and 10 mg/kg maralixibat, vehicle; Gedulin et al. 2013). In a final study, it was demonstrated that treatment with maralixibat (1 mg/kg) significantly improved outcome in terms of sBA, liver enzymes, and total bilirubin as well as showed numerical superiority over treatment with ursodeoxycholic acid (UDCA; 1 mg/kg).

Several safety and pharmacokinetic (PK) studies have also been performed. In a 13-week adult rat Good Laboratory Practice (GLP) daily oral toxicity study (SA4947; M3000008), maralixibat was administered at dose levels up to 150 mg/kg/day in male rats and up to 500 mg/kg/day in female rats; however, the bioavailability was <0.1% at these doses. The maximum serum concentration (C_{max}) and area under the concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) values generally increased with increasing dose. Because there were no maralixibat-related findings in this study that were considered to be adverse, the no observed adverse effect level (NOAEL) was the highest doses administered, which were 150 mg/kg/day for males and 500 mg/kg/day for females.

In a separate rodent study, no significant changes were observed in safety pharmacology studies following single oral or intravenous (IV) administration. No evidence of mutagenic or clastogenic activity was seen. In a GLP juvenile toxicity study (postnatal day [PND] 7 to 21) conducted in rats, no adverse effects were observed with oral doses of maralixibat that were 50 times greater than the current Phase 3 clinical dose of 1200 µg/kg/day (for an average 20-kg child).

A definitive GLP juvenile toxicity study was conducted in which maralixibat was administered to rat pups from PND 7 through 21 (Study 2939-001 [MRXNC-001]). Maralixibat doses of 50, 100, and 250 mg/kg/day were given to both sexes: the study included 20 male and 20 female animals per dose level in the main study and 60 animals of each sex per dose level in the toxicokinetic (TK) part of the study. In contrast to other nonclinical studies on maralixibat but in line with the TK results from the non-GLP pilot study in same-aged animals (Study R9976M-SHP625 described above), systemic exposures were seen in this study, with an average AUC of 13,900 hr*ng/mL on the first day of dosing (PND 7) at the highest tested dose (250 mg/kg). Plasma AUCs did not significantly increase with increases in dose, indicating saturation of absorption at the lowest dose (50 mg/kg) and thus a high estimated oral bioavailability (approximately 17%) at the lowest dose on the first day of dosing. Estimated bioavailability significantly decreased over the course of the study, to <0.5% at all dose levels after the last dose on PND 21. Thus, maralixibat absorption was highest in the youngest pups but similar to that seen in adult animals in the oldest pups, likely due to increased permeability in the immature gastrointestinal (GI) tract of neonatal pups. Despite these high plasma exposures, maralixibat was well tolerated in this study and showed no obvious signs of toxicity, with no effect on survival, clinical findings, body weights, food

consumption, sexual maturation, clinical pathology, or histopathologic examinations at any dose level evaluated.

Clinical data from other pediatric cholestatic diseases, including completed Phase 2 studies in progressive familial intrahepatic cholestasis (PFIC; Study LUM001-501) and Alagille syndrome (ALGS; Studies LUM001-301, -302, -303, -304, and -305), show consistent and clinically meaningful improvements in signs and symptoms of cholestasis in participants aged ≥1 year treated with maralixibat. This includes significant reductions in sBA, bilirubin, and ALT, as well as improvements in growth and other indicators of disease modification. Data also suggest that patients with PFIC treated for up to 5 years with maralixibat experience long-term avoidance of liver transplantation. Further, maralixibat has been shown to have an acceptable safety profile in more than 1600 exposed participants overall and more than 119 children ≥12 months of age with cholestatic liver disease. The most common treatment-related adverse events (AEs) were mechanism based, mild to moderate in nature, and included self-limited diarrhea, abdominal pain, and nausea. No worsening of LSV malabsorption was noted in clinical studies so far. In September 2021, LIVMARLI® (maralixibat) oral solution was approved in the United States for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older.

Please refer to the latest version of the Maralixibat IB for the overall benefit/risk assessment and the most current information regarding the drug metabolism, PK, efficacy, and safety of maralixibat.

By virtue of its ability to inhibit bile acid absorption and lower circulating bile acid levels, maralixibat is being developed by Mirum Pharmaceuticals, Inc. (Mirum) as a potential therapeutic agent for the treatment of BA.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Clinical data from other forms of pediatric cholestatic, including ongoing and completed Phase 2 studies in PFIC and ALGS, indicate that maralixibat improves the signs and symptoms of cholestasis and may improve markers of liver injury as well as long-term liver-related outcomes. This includes reductions in sBA, as well as improvements in growth and other measures suggestive of disease modification, including transplant and biliary diversion event-free survival. Maralixibat has demonstrated an acceptable safety profile in more than 1600 exposed participants overall, including more than 119 children ≥12 months of age with cholestatic liver disease.

In disease states, bile acids have been shown to induce damage and necrosis in hepatocytes and cholangiocytes (Monte et al. 2009). Elevated sBA levels are associated with increased morbidity and mortality in several cholestatic diseases. Specifically, large increases in sBA levels are a well-known feature of BA. For example, in one study, sBA levels at Kasai (88.96±28.70 µM) and liver transplantation (165.48±43.55 µM) greatly exceeded those of pediatric control patients with non-cholestatic liver disease (4.94±5.43 µM; Chen et al. 2008). The importance of bile acid toxicity to hepatocytes in BA is highlighted

by clinical data that show sBA levels to be inversely correlated with native liver survival and to be predictive of overall outcome (Harpavat et al. 2019). It is based on these findings that high bile acid levels are understood to be an important driver of liver disease in patients with BA after HPE.

Liver disease and failure are arguably the most important complications for patients with BA after HPE. Up to 50% of BA patients require liver transplantation at 2 years after HPE. Liver transplantation is an important clinical event for patients with end-stage liver disease in BA, carrying significant medical risk, both acutely and long term (e.g., immunosuppression). Importantly for this population, a consistent body of literature has demonstrated that biliary drainage, as measured by bilirubin levels at 3 and 6 months after HPE, is a clinically meaningful prognostic indicator for long-term native liver survival in BA (Kasai et al.1989; Chusilp et al. 2016; Shneider et al. 2016). Based on these data, serum bilirubin is frequently used as a clinical marker of HPE success and long-term outcome (including potential future requirement of liver transplantation).

Given the above, reducing the level of serum and hepatic bile acids in patients with BA is hypothesized to slow or prevent liver injury, and therefore improve long-term transplant-free survival. Based on the understanding of maralixibat's mechanism of action and its ability to durably reduce sBA in pediatric cholestasis for >6 years, maralixibat has the potential to reduce the long-term liver sequelae of BA. In the short term (<1 year), reductions in both the bile acid pool and markers of liver injury are anticipated, and these may translate into lower total serum bilirubin values, a prognostic marker for improved longer-term outcomes.

The primary endpoint for this study therefore compares mean change in total serum bilirubin from baseline to Week 26 of treatment between the placebo and maralixibat groups. In addition, the impact of maralixibat on transplant-free survival and the incidence of other liver-associated events will also be analyzed as important secondary outcomes, both in the double-blind portion of the study and during the long-term extension period. Given the importance of bile acids in BA liver disease and maralixibat's mechanism of action, changes in sBA levels will be a secondary endpoint for the double-blind portion of this study.

2.2 Study Objectives and Endpoints

2.2.1 Primary Objective and Endpoint

Objective **To evaluate the efficacy of maralixibat on biliary drainage after HPE in participants with BA**

Endpoint *Mean change in total serum bilirubin levels from baseline through Week 26*

[redacted]

2.2.2 Secondary Objectives and Endpoints of the Double-Blind Period

Objective	**To evaluate the rate of clinically relevant reductions in cholestatic biomarkers with maralixibat treatment**
Endpoints	*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
Objective	**To evaluate the rate of liver-related clinical events**
Endpoints	*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 10^9/L) or clinically evident ascites or endoscopic evidence of esophageal or gastric varices through Week 26
Objective	**To evaluate the safety, tolerability, and pharmacokinetics of maralixibat**
Endpoints	*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

2.2.3 Exploratory Objectives and Endpoints of the Double-Blind Period

[redacted]

[redacted]

[redacted]

2.2.4 Open-Label Extension Objectives and Endpoints

Objective	**To assess all of the above primary and secondary objectives analyzed over the full study duration, including the open-label extension period**
Endpoints	*All of the above primary and secondary endpoints but for study data through Week 104*

3 STUDY DESIGN

3.1 Study Design and Flow Chart

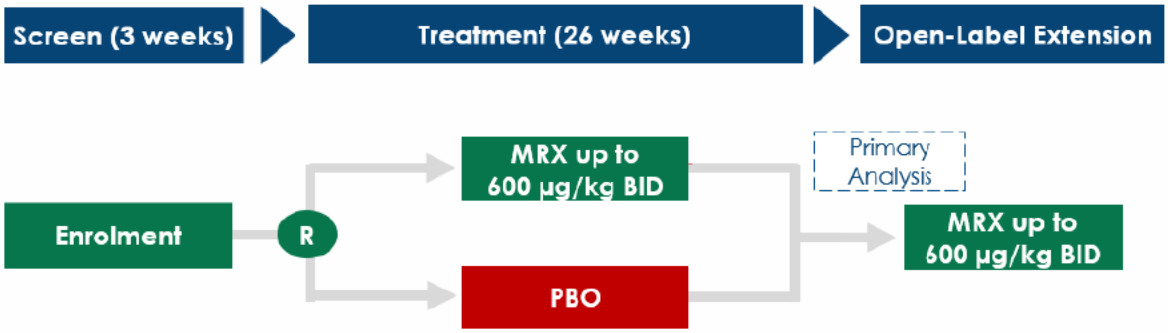
This is a 26-week, multicenter, double-blind, placebo-controlled, randomized parallel-group study, followed by an open-label extension (OLE) including analyses up to Week 104, in participants with BA. In the double-blind period of the study, participants will be randomized in a 1:1 fashion to receive either placebo or maralixibat- up to 600 µg/kg twice daily (BID; Figure 1). Treatment assignment will use a block randomization process scheme by study site (i.e., stratified by study site). The study periods are 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)

[redacted]

During the treatment period, participants will receive standard-of-care treatment in line with investigator and caregiver preference and in addition to study medication (for prohibited medications, see Section 5.2).

Figure 1 Study Design



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

All participants who complete the double-blind period will enter the OLE, in which all participants receive open-label maralixibat at a maximum tolerated dose of 600 µg/kg BID.

[redacted]

Participants will remain in the OLE to at least study Week 104. [redacted]

For information about the schedule of assessments throughout the study, refer to Table 1, Table 2, and Section 7. For information on dosing, including dose-escalation requirements, refer to Section 6.2.3.

3.1.1 Rationale for Treatment Dose

Maralixibat is a minimally absorbed inhibitor of the IBAT, the intestinal transporter responsible for the reabsorption of bile acids at the terminal ileum. Maralixibat is provided as an oral solution that is dosed on a weight basis (i.e., µg/kg), a standard pediatric dosing approach supported by clinical experience from the development program in pediatric cholestasis. Effective and clinically relevant inhibition of the IBAT using maralixibat has been demonstrated by durable reductions in sBA levels in children aged ≥1 year on treatment for over 5 years.

[redacted]

3.1.1.1 Clinical Efficacy

Available clinical data across multiple indications, including data from studies in children with cholestatic liver disease (PFIC and ALGS), suggests that IBAT inhibition leads to clinically meaningful treatment effects, including improvements in sBA levels, pruritus, growth, and possibly transplant-free survival.

Study LUM001-304 in participants with ALGS aged ≥1 year, was a 4-week, randomized placebo-controlled drug withdrawal study with a long-term treatment period up to 5 years using maralixibat doses of 400 µg/kg QD and then BID. Maralixibat led to significant and sustained reductions in sBA and pruritus, with a significant difference between maralixibat and placebo during the randomized withdrawal period. Over this period, improvement in linear growth as well as improvements in xanthomas were observed. BID doses (up to 400 µg/kg BID) led to further improvement in sBA and pruritus, although not in a statistically significant manner, while the safety profile was comparable between the two dose levels.

Study LUM001-501 in participants with PFIC aged ≥1 year was a single-arm study using maralixibat doses up to 280 µg/kg QD and then BID. A subset of participants showed a profound and sustained treatment response including normalization or ≥75% reduction from baseline in sBA levels, control of pruritus or ≥1.0-point reduction from Itch Reported Outcome (Observer) baseline, improvements in growth (height and weight), normalization of liver parameters, and remaining transplant-free with more than 5 years of maralixibat treatment. BID dosing (up to 280 µg/kg BID) led to similar rapid and sustained treatment response in additional participants while showing a similar safety profile as the QD dosing, indicating that higher doses and a BID dosing regimen may improve the responder rate to maralixibat treatment. Therefore, doses up to 600 µg/kg BID are evaluated in the ongoing Phase 3 randomized double blinded, placebo-controlled study in participants with PFIC.

The 600 µg/kg BID dosing regimen is further supported by documentation of dose-dependent increase in fBA excretion, the direct pharmacodynamic marker of IBAT inhibition, up to total daily doses of maralixibat 100 mg (weight-based equivalent of 1400 µg/kg/day) in the dose finding study (SHP625-101) conducted in overweight and obese healthy volunteers. BID dosing (50 mg BID; 700 µg/kg BID equivalent) led to a further increase in fBA excretion compared with 100 mg QD (1400 µg/kg QD equivalent). The safety profile was comparable across the tested dose range, with the exception of increased stool frequency at higher doses.

3.1.1.2 Clinical Safety and Tolerability

In the completed and ongoing Phase 2 studies, maralixibat has been administered to >119 pediatric participants (≥12 months age) with cholestatic liver disease at doses up to a maximum daily dose of 1200 µg/kg/day. Dosing of 400 and 800, as well as 280 and 560 µg/kg/day in Study LUM001-304 and LUM001-501, respectively, demonstrated a consistent safety profile. No maximal tolerated dose has been determined at single doses up to 7000 µg/kg and multiple doses up to 1400 µg/kg/day. Furthermore, no dose-related safety findings have been identified to date.

[redacted]

The maralixibat development program, conducted in >1600 participants across multiple indications as well as healthy volunteers, provides safety data for treatment exposures to over 5 years. GI symptoms (abdominal pain, diarrhea) were the most commonly reported treatment-related AEs and were mostly mild to moderate in severity and transient in nature.

Doses of maralixibat, up to 1200 µg /kg/day (600 µg /kg/day BID), are expected to be safe in children with cholestatic liver disease.

3.1.1.3 Nonclinical Safety Data Justify Dosing of Children <1 year of age

The use of maralixibat in children aged <1 year is supported by the absence of adverse effects in multiple GLP juvenile toxicity studies conducted in rats. In separate studies, rats were dosed from PND 7 to PND 21, and from PND 21 to PND 63. No adverse effects were observed in these GLP studies up to the highest doses tested. Rat pups were dosed starting as young as PND 7, which from a whole animal development perspective is generally representative of a preterm human infant. Therefore, data from these studies support the use of maralixibat in clinical studies in the youngest human infants. Large safety margins were established in these studies (the highest dose tested in the youngest rat pups was 250 mg/kg/day, equivalent to ~60,000 µg/kg/day in human infants) and predict a minimal risk of toxicity in human infants.

In summary, based on the absence of adverse effects in juvenile toxicity studies and the acceptable safety profile in >1600 participants across multiple indications, including 119 children with cholestatic liver disease, at single doses up to 7000 µg/kg and multiple doses up to 1400 µg/kg/day, maralixibat is expected to be safe at the doses proposed in the ongoing or planned clinical studies. Together with the dose-dependent increase in fBA excretion, and the documentation of higher responder rates in clinical studies in participants with cholestatic liver disease, doses up to 600 µg/kg BID are considered to have a favorable benefit-risk profile in patients with a potentially life-threatening progressive liver disease.

Several safeguards are foreseen in Study MRX-701 to ensure the safety and wellbeing of study participants. Doses will be increased in a stepwise fashion with careful monitoring of each individual participant's tolerability and safety parameters. In addition, throughout the study, pharmacokinetics and safety parameters will be reviewed on a frequent basis in an unblinded fashion by an independent data monitoring committee and will be monitored in real time by the Principal Investigator (PI) and medical monitor. In summary, given the safeguards in place to ensure participant's safety and the absence of safety signals from clinical and nonclinical studies conducted to date, as well as the clinically relevant treatment benefits documented with maralixibat in other pediatric cholestasis indications, the overall benefit-risk profile of Study MRX-701, including its dosing regimen, is considered favorable.

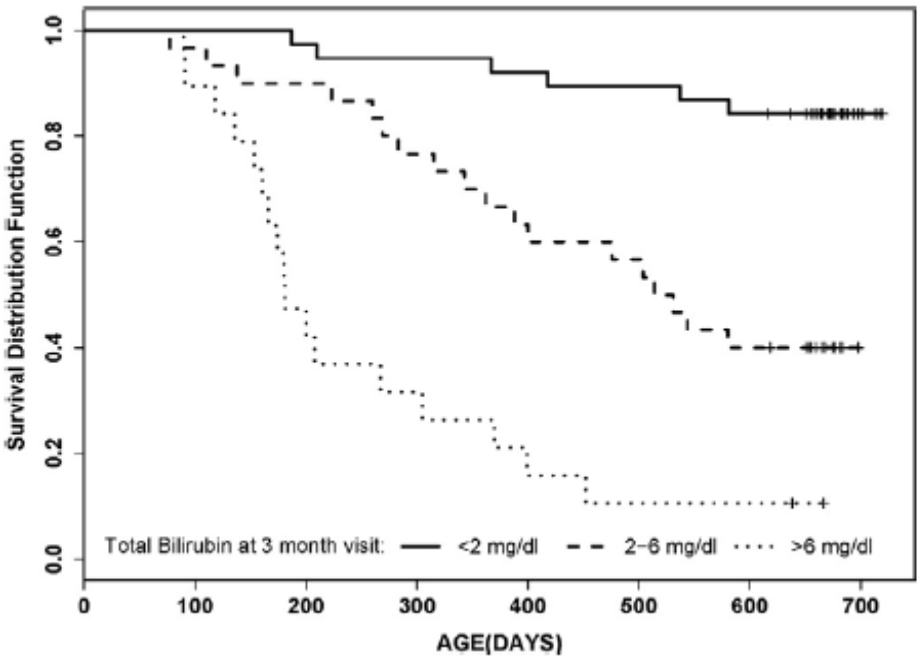
3.1.2 Rationale for Primary Endpoint

The primary endpoint is mean change from baseline in total bilirubin based on published data demonstrating that bilirubin levels at 6 months after HPE are predictive of long-term outcome (native liver survival; Kasai et al. 1989; Hung et al. 2006; de Vries et al. 2012; Chusilp et al. 2016; Shneider et al. 2016) in patients with BA. A reduction in bilirubin levels

after 26 weeks of treatment would indicate a potential improvement in long-term outcomes for patients with BA. In addition, bilirubin is a measure of the degree of cholestasis and is routinely monitored in patients with BA post-Kasai to determine the success of HPE surgery and for clinical decision making for subsequent a potential liver transplantation. In other pediatric cholestatic indications (PFIC and ALGS) with maralixibat treatment, reduction in sBA has led to normalization in bilirubin levels and other liver parameters indicating general improvements in liver function, growth, and symptoms associated with cholestasis.

Estimates for a clinically relevant treatment effect are assumed to be approximately 30%, or mean change in total bilirubin of -2.1 mg/dL between treatment groups, assuming that this would lead to a higher proportion of study participants with bilirubin in the low-risk category (<2.0 mg/dL) in the maralixibat group compared with the placebo group. This threshold of bilirubin has been linked with a significantly different treatment course with respect to native liver survival (see Figure 2; Shneider et al. 2016).

Figure 2 **Kaplan-Meier Analysis of Outcome Based on Total Bilirubin Level 3 Months after HPE**



HPE=hepatoportoenterostomy.
Note: Survival with native liver relative to age in days after HPE is shown in the 3 Kaplan-Meier curves, derived by dividing the cohort of participants on the basis of their total serum bilirubin level 3 months after HPE. At 3 months after HPE, total bilirubin level was <2 mg/dL in 38 children, between 2 and 6 mg/dL in 30 children, and >6 mg/dL in 19 children.

3.1.3 Rationale for Study Population

Maralixibat has the potential for meaningful clinical benefit in a disease with a high unmet medical need. There is currently no approved pharmacotherapy for BA, and available medical approaches (e.g., steroids, immunoglobulins) have failed to show efficacy in clinical studies (Davenport et al. 2013; Bezerra et al. 2014; Mack et al. 2019). Standard of care is therefore mainly supportive, focusing primarily on re-establishing bile flow via surgical HPE (Kasai procedure), usually performed within the first 2 months of life, and on promoting growth through nutritional support and preventing or treating secondary complications (Wong and Davenport 2019). However, despite this approach, HPE outcomes can vary widely, with approximately one-third of patients attaining a good long-term outcome (native liver and non-jaundice), one-third undergoing a progressive 2- to 4-year path of liver failure leading to an eventual liver transplant, and the final third undergoing rapid liver failure requiring transplant within 6 to 12 months (Shneider et al. 2006; Goda et al. 2013; Nightingale et al. 2017). Given this, BA remains the leading cause of pediatric liver transplant worldwide, with approximately 40% of patients requiring a transplant by 2 years of age despite undergoing HPE. No pharmacological therapy has been shown to delay the time to death or liver transplantation.

The early course of BA is characterized by an inflammatory condition. Due to the cholestasis, there is an accumulation of toxic bile acids, which likely contribute to the hepatocyte injury. This is followed by either a rapid reduction in liver function, leading to liver failure and the need for transplantation within 6 to 12 months, or a more slowly progressive fibrotic phase of hepatic disease that erodes function and results in failure over many years. The optimal therapeutic window for an IBAT inhibitor, such as maralixibat, in the treatment of BA is likely during the early, inflammatory phase of the disease before the fibrotic/cirrhotic phase of disease. Given this, the study has been designed to enroll participants shortly after the HPE procedure to reduce the pathophysiological effects of sBA exposure to the hepatocytes though pharmacological interruption of the enterohepatic circulation.

3.2 Duration and Study Completion Definition

A participant's duration of participation for the double-blind portion of MRX-701 is expected to be up to 26 weeks followed by an OLE of 78 weeks to at least Week 104. Participants who complete the double-blind phase of the study and continue in the OLE phase will receive maralixibat regardless of whether they were assigned to the maralixibat group or the placebo group in the double-blind phase of the study.

The study completion date is defined as the date the final participant, across all sites, completes his or her final protocol-defined assessment. Note that this includes the follow-up visit or contact, whichever is later (see Section 7.1.6 for the defined follow-up period for this study), but not the long-term clinical follow-up of persistent safety findings.

Participants who discontinue at any time during this study will have early termination (ET) assessments [redacted] days after the last dose of study medication and a safety follow-up phone call or email [redacted] days after last dose (see Section 7.1.6). Participants who discontinue from the

[redacted]

study for safety reasons will be followed as long as clinically indicated or until the safety finding is considered ongoing, stable, or resolved.

3.3 Sites and Regions

The study will be conducted in North America, Europe, and Asia. Other regions may be added.

4 STUDY POPULATION

4.1 Inclusion Criteria

A participant will be considered eligible for the study if he or she meets all the criteria below.

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 ≥[redacted] weeks at birth (Those with gestational age <[redacted] 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

4.2 Exclusion Criteria

A participant will be considered ineligible for the study if he or she meets any of the criteria below:

1. Chronic diarrhea 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 hemorrhage, 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

4.3 Reproductive Potential

Because this study will be conducted in prepubescent pediatric participants, discussion of reproduction is not applicable.

4.4 Withdrawal/Discontinuation from Study

A participant may be withdrawn from the study at any time for any reason without prejudice to his or her future medical care by the physician or at the institution. The investigator or sponsor may discontinue the participant from the study at any time (refer to Section 4.4.1). The investigator is encouraged to discuss discontinuation of a participant with the medical monitor when possible. The reason for termination and the date of stopping study medication must be recorded in source documents. The evaluations listed for the ET/end-of-treatment (EOT) visit are to be performed as completely as possible for any participant who discontinues early.

Participants who discontinue from the study for safety reasons are to be followed as long as clinically indicated or until the safety finding is considered ongoing, stable, or resolved. Participants who discontinue from the study will not be replaced. [redacted].

4.4.1 Reasons for Discontinuation from Study

Medically important events that, in the opinion of the investigator or medical monitor, may compromise the participant's ability to safely continue the study would warrant the participant's discontinuation from the study. The reason for discontinuation must be recorded in the participant's source documents. If a participant is discontinued for more than 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

Reasons for discontinuation may include but are not limited to:

- Noncompliance with study procedures
- AE
- Prolonged study medication interruption (see Section 6.5)
- Inability to tolerate a dose of [redacted] µg/kg maralixibat BID
- Sustained, severe diarrhea that requires hospitalization and/or an IV or nutritional supplementation or leads to severe electrolyte disturbances
- Persistent LSV deficiency (per criteria in Section 7.4.5)
- Withdrawal by parent/guardian
- Physician decision
- Loss to follow-up
- Liver transplant or imminent need for liver transplantation
- Taking a prohibited concomitant treatment (see Section 5.2)
- Disease progression

[redacted]

4.4.2 Participants "Lost to Follow-Up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any participant lost to follow-up at any time before the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the participant's last known address via courier or registered mail (with an acknowledgment of receipt request) asking that the participant return to the site for final safety evaluations and return any unused study medication.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatments

Information on specific prior medications and therapies will be collected throughout the study. Prior treatments refer to treatments prior to the first dose of study medication. This information must be recorded in the participant's source documents and the relevant case report form (CRF) for data collection.

5.2 Concomitant Treatments

A participant should be instructed to continue use of any medication or treatment until informed consent (by the legally authorized representative) has been obtained. Concomitant treatments refer to all treatments, including concomitant therapies as well as herbal treatments, vitamins, and nonpharmacological treatments administered between the dates of the first dose of study medication and the end of the participant's participation in the study. Concomitant treatment information must be recorded in the participant's source documents. Investigators must ensure that participants receive LSV supplements, as needed, for the duration of the study.

Throughout this study, standard-of-care medications individual to the clinician/center will be allowed if this is 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.

Table 3 lists the prohibited treatments and the time restriction period prior to baseline.

Table 3 Prohibited Treatments and Time Restriction Prior to Baseline

	Restricted Period
[redacted]	During the study and 30 days prior to baseline
[redacted]	During the study and 30 days prior to baseline
[redacted]	Any time within 5 half-lives of the investigational drug, biologic or medical device (if applicable)
[redacted]	Any time before and during the study
[redacted]	During the study
[redacted]	For participants <1 month of age only
[redacted]	For participants <1 month of age only
[redacted]	During the study and 30 days prior to baseline

6 STUDY MEDICATION

6.1 Investigational Product

Maralixibat will be provided in the form of an oral solution (i.e., [redacted] mg/mL) along with 0.5-, 1.0-, or 3.0-mL sized oral dosing dispensers, vials for formulation dilution, and bottle adapters (if required) to clinical sites. The reference/comparator product is a placebo, which will also be provided as an oral solution along with oral dosing dispensers of the same size (0.5 mL, 1.0 mL, or 3.0 mL).

Maralixibat and placebo (the study medication) will be provided in 30-mL volumes packaged in amber-colored polyethylene terephthalate bottles and should be refrigerated at 2C°–8°C. [redacted] (see Section 6.2.3 and the Pharmacy Manual).

[redacted]

Additional information is provided in the Maralixibat IB and the Pharmacy Manual.

6.1.1 Investigational Product Benefit-Risk Guidance

Participants with BA have a high unmet clinical need. There are currently no available therapies that extend transplant-free survival beyond HPE. Liver transplantation is a high-risk procedure, with a life-long patient and societal burden. Based on maralixibat's mechanism of action, as well as clinical and outcomes benefits described in other pediatric

cholestatic indications, maralixibat has the potential to reduce liver injury, as represented by serum markers (i.e., bilirubin, liver enzymes) and possibly extend the transplant-free survival in patients with BA. Further, no significant safety concerns have emerged from either the juvenile animal toxicology study or from maralixibat's large safety database of >1600 exposed participants, including >119 children with cholestatic liver diseases. [redacted] Identified risks for maralixibat include diarrhea and abdominal pain, which are transient in nature and mostly mild to moderate in severity. See Section 7.4.8 for additional risk mitigation/management guidelines for these events. Given the above, the available nonclinical and clinical data indicates a favorable benefit-risk profile for the evaluation of maralixibat in participants with BA. Additional information is provided in the Maralixibat IB.

6.1.2 Blinding the Treatment Assignment

The placebo solution will contain all components of maralixibat solution except the active drug substance. All packaged study medication components, including the dosing dispensers, will be identical to those of maralixibat in order to maintain the blind.

Where possible without impacting standard of care, the sBA results will remain blinded to sites and to the blinded study team, with preferred processing at a central laboratory. The [redacted] PK results will also remain blinded to sites and to the blinded study team with processing to occur at a central laboratory.

6.2 Administration of Study Medication

6.2.1 Interactive Response Technology for Study Medication Management

An interactive response technology (IRT) will be used for screening and enrolling participants, randomization, dispensing and managing study medication, inventory management and supply ordering, study medication expiration tracking and management, and emergency unblinding. The investigator or designee will access the IRT at the screening visit (Visit VS) for participant-specific information (e.g., unique participant number, age, weight). Sites will be presupplied with bottles of [redacted] strengths as well as matching placebo.

At the baseline visit, the investigator or designee will again access the IRT to either document a screen failure or, if the participant has met all entry criteria, to randomize the participant. For randomized participants, the IRT will provide one or more bottle identification numbers to dispense for treatment.

A user manual with specific functions and instructions for the IRT will be provided to the site, and site personnel will receive IRT training.

[redacted]

6.2.2 Allocation of Treatment to Participants and Unblinding

Individual participant treatment is automatically assigned by the IRT. Participants will be randomized after confirmation of study eligibility in a 1:1 ratio via a computer-generated randomization schedule to receive maralixibat or placebo, stratified using block randomization by study site (refer to Section 3.1). The participant's randomization number will be a unique number that corresponds to the treatment allocated to the participant.

The treatment assignment must not be unblinded during the study except for expedited safety reporting and in emergency situations for which the identification of the study medication is required for further treatment of the participant. The investigator should make efforts to contact the medical monitor before emergency unblinding occurs or as soon as possible after the investigator has been unblinded, without revealing the treatment assignment to the medical monitor. In any event, the medical monitor and sponsor must be informed about the code break as soon as possible.

In the event that the treatment assignment is unblinded, the date and the signature of the person who was unblinded and the reason for unblinding must be recorded in the source documents. Upon breaking the blind in emergency situations, the participant will be withdrawn from the study but should be followed for safety purposes. Unblinding will be processed through the IRT vendor, and instructions will be available in the user manual.

6.2.3 Dosing

Participants will be administered varying volumes of ready-to-use oral solution study medication at each dosing visit, starting with the baseline visit. The dosing volume is determined based on the individual body weight, the dose level according to the dose-escalation plan (or 600 µg/kg BID), and the strength of solution being administered. Maralixibat solution strength will vary according to maralixibat dose, per Table 4, with new solution strengths required with dose escalation/reduction.

Table 4 Maralixibat Dose and Strength

600	20

At each dosing visit, the investigator or designee will access the IRT and enter the participant's weight and information on dose-escalation status. This information will be used by the IRT to identify the appropriate strength of solution and dosing volume and to assign a corresponding bottle number(s) to be dispensed to the participant. Additional details will be provided in the Pharmacy Manual.

[redacted]

All caregivers will receive detailed training by the investigator or designee on how to administer study medication.

If needed, study medication may be supplied via direct shipment to participants in between site visits.

6.2.4 Dose Escalation

In both the double-blind and OLE periods, study medication administration will take place during the dose-escalation and stable-dosing periods based on a BID regimen (Figure 3 and Figure 4).

For participants ≥1 month of age assigned to maralixibat in the double-blind period, the dose-escalation period (4–8 weeks) will consist of the following steps:

- Dose level 1: [redacted] µg/kg maralixibat BID for 1–2 weeks
- Dose level 2: [redacted] µg/kg maralixibat BID for 1–2 weeks
- Dose level 3: [redacted] µg/kg maralixibat BID for 1–2 weeks
- Dose level 4: 600 µg/kg maralixibat BID (or highest tolerated) for the remaining duration of the dosing period

[redacted]

Figure 3 [redacted]

BID=twice daily; BL=baseline; [redacted]

Dose escalation should occur in the absence of major safety (e.g., liver parameters, biochemistry) or tolerability (e.g., GI-related TEAEs) concerns related or possibly related to study medication. [redacted] For participants ≥1 month of age, the minimum dose to continue in the study will be [redacted] µg/kg maralixibat BID; participants who cannot tolerate the minimum dose of [redacted] µg/kg maralixibat BID will be removed from both the study and the per-protocol analysis. The investigator should also review study medication compliance during the dose-escalation period to ensure that participants have adequate exposure to study medication to assess safety and tolerability.

After [redacted] participants have completed dose escalation, there will be a DMC review to analyze the potential to simplify dose escalation [redacted].

[redacted] Once a participant reaches ≥1 month of age, he or she should dose escalate, using the same steps approved by the DMC at that time point for participants who are ≥1 month of age (see Section 6.2.4.1). In this situation, dose escalation can occur up to Week 8 (i.e., for the remainder of the dose escalation period).

[redacted] Any compliance concerns should be discussed with the medical monitor.

Investigators have until Week 8 to determine the highest tolerated dose up to 600 µg/kg BID; if rechallenges or further dose escalations fail, the participant will remain on the highest

[redacted]

tolerated dose level for the remainder of the treatment period, completing a minimum of 18 weeks within the stable dosing double-blind period.

During the OLE, all participants, regardless of treatment assignment in the double-blind period, will receive maralixibat at a starting dose of [redacted] µg/kg BID (or [redacted] µg/kg BID [redacted]). The dose will be escalated over a 4- to 8-week period, in a manner similar to the escalation in the double-blind period and will consist of the following steps.

- Dose level 1: [redacted] µg/kg maralixibat BID for 1–2 weeks
- Dose level 2: [redacted] µg/kg maralixibat BID for 1–2 weeks
- Dose level 3: [redacted] µg/kg maralixibat BID for 1–2 weeks
- Dose level 4: 600 µg/kg maralixibat BID (or highest tolerated) for the remaining duration of the dosing period

[redacted]

BID=twice daily; BL=baseline; [redacted].

[redacted]

Investigators have up to 8 weeks to determine the highest tolerated dose in the OLE. If rechallenges or further dose escalations fail, the participant will remain on the highest tolerated dose level for the remainder of the OLE period to complete a minimum of 78 weeks of treatment in the OLE period (to Week 104). Dose reductions are allowed for safety or tolerability reasons down to a minimum level of [redacted] µg/kg BID. Participants who cannot tolerate this dose will be discontinued from the study.

[redacted]

6.2.4.1 Data Monitoring Committee Review of Dose Escalation

As described in Section 7.4, throughout this study, the safety of participants will be closely monitored via an unblinded DMC review [redacted] until the DMC advises otherwise. This includes an MRX-701 study-specific meeting as well as the programwide DMC review (occurring approximately [redacted]). All laboratory values except sBA, [redacted] and pharmacokinetics will be monitored by the contract research organization (CRO) and sponsor medical monitors as well as the Principal Investigator. Stopping criteria in response to laboratory abnormalities are discussed in Section 7.4.2.

After [redacted] participants have completed the dose-escalation portion of the double-blind period, the DMC will complete an independent and unblinded review of data at its next scheduled meeting. [redacted] This change will impact all future participant dose escalations (i.e., those yet to dose escalate in either the double-blind or OLE periods). Participants whose doses have already been escalated do not need to escalate again, unless warranted by the study design (i.e., to start the OLE period). Any change to the dose-escalation regimen will be reflected in an update to the IRT. This change will not impact clinic schedules or assessments. Decisions made by the DMC will apply to dose escalation in both the double-blind and OLE periods of the study. The DMC may review this opinion and decision at later time points, as more data become available.

The DMC prespecified criteria to implement a [redacted] are as follows:

- [redacted]
- [redacted]

[redacted]

Figure 5 [redacted]

[redacted]

Investigators will have the option of lowering the dose to a minimum level of [redacted] µg/kg BID as well as requesting the addition of the [redacted] µg/kg BID dose if there are any safety or tolerability issues.

[redacted]

6.3 Labeling, Packaging, Storage, and Handling

All study medication will be labeled according to country-specific requirements. Additional labels may, on a case-by-case basis, be applied to the study medication in order to satisfy local or institutional requirements but must not contradict or obscure the clinical study label or identify the study participant by name. Additional labels may not be added without the sponsor's prior full agreement.

Study medication is packaged in labeled containers of ready-to-use oral solution of maralixibat [redacted] mg/mL or matching placebo. The sponsor or designee will provide 0.5-, 1.0-, and 3.0-mL-sized dosing dispensers, vials for formulation dilution, and bottle adapters (if required) to clinical sites.

The investigator has overall responsibility for ensuring that study medication is stored in a secure, limited-access location at refrigerated storage conditions (2°C–8°C). Temperature monitoring is required at the storage location to ensure that the study medication is maintained within an established temperature range. The sponsor or their agreed designee must be notified immediately upon discovery of any excursion from the established range or if there are any changes to the storage area of the study medication that could affect the integrity of the study medication.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the study medication to carry out this protocol for the agreed number of participants. The investigator or designee will acknowledge receipt of the study medication, documenting shipment content and condition. Accurate records of all study medication dispensed, used, returned, and/or destroyed must be maintained by the study site.

The investigator has overall responsibility for administering/dispensing study medication. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained on the protocol and who works under the direct supervision of the investigator. Study medication will be dispensed at baseline and each visit in quantities sufficient for dosing until the next scheduled visit. If necessary, and where permitted, direct medication shipment from site to participant is allowed between visits.

The investigator or designee will dispense the study medication only to the caregivers of participants included in this study following the procedures set out in the study protocol. Each participant's caregiver will be given only the study medication assigned.

The investigator is responsible for ensuring the retrieval of all study supplies from participants. Caregivers must be instructed to bring their unused and empty/used study medication to every visit. Drug accountability must be assessed at the bottle level. The pharmacist/delegated person will record details on the drug accountability form or similar.

Based on entries in the site drug accountability forms, it must be possible to reconcile study medication delivered with those used and returned. All study medication must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

Other than study medication dispensed to participants, no stock or returned inventory may be removed from the site where originally shipped without prior knowledge and written consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or representatives must be permitted access to review the supplies storage, distribution procedures, and records, provided that the study blind is not compromised.

At the end of the study or as instructed by the sponsor, all unused stock, participant-returned study medication, and empty/used study medication packaging are to be returned to the sponsor or destroyed. Study medication must be counted and verified by clinical site personnel and the sponsor (or designated CRO) prior to return or destruction. Shipment return or destruction forms must be completed prior to shipment from the site or destruction. Shipment of all returned study medication must comply with local, state, and national laws.

6.5 Participant Compliance

Participant compliance with study procedures and treatment compliance will be assessed at each treatment visit by the site staff.

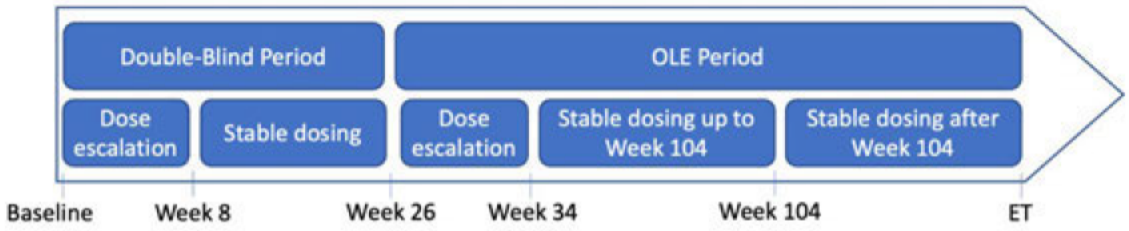
The allowed maximum number of days of dose interruption by study period is summarized in Figure 7.

Across the study, from baseline to Week 104, participants will be allowed a maximum of [redacted] cumulative dose interruption (both morning and evening dose), with no more than [redacted] consecutive days at a time.

During stable dosing in the double-blind period (Weeks 8–26), participants will be allowed a maximum of [redacted] days of cumulative dose interruption [redacted] with no more than [redacted] consecutive days at a time. During dose interruptions, participants should continue to complete all regularly scheduled study visits and assessments as outlined in Table 1. [redacted]

[redacted]

Figure 7 Treatment Compliance Rules



[redacted]

EOT=end of treatment; OLE=open-label extension.

[redacted]

7 STUDY PROCEDURES

7.1 Study Schedule

The study procedures and assessments to be performed throughout the study can be found in the schedule of assessments in Table 1 and Table 2. Further instructions about study assessments are provided in this section and in Section 7.2.

Prior to performing any study-related procedures (including those related to screening), the investigator or designee must obtain written informed consent (by the legally authorized representative) from the participant's caregiver (as per local requirements). For information about the informed consent process, see Section 9.8.1.

Participant numbers are assigned to all participants when consent is obtained to take part in the study. Within each site, the participant number is assigned to participants according to the sequence of presentation for study participation.

[redacted]

For management of clinical study procedures during a pandemic or other force majeure, please see Appendix 4.

7.1.1 Screening Period (Day –21 to -1)

The screening period starts when informed consent (by the legally authorized representative) is signed. The duration of the screening period is up to 3 weeks, during which all procedures listed for the screening visit (Visit VS) in Table 1 must be completed.

Participants who meet eligibility criteria after completion of all screening visit assessments will be randomized and enter the 4- to 8-week double-blind dose-escalation period. This period should not start until all screening assessments required to confirm eligibility for randomization have been completed and study medication has been received at the site.

If the participant does not meet eligibility criteria following completion of screening assessments, the investigator or designee will document the participant as a screen failure in the IRT. A screen failure is a participant who has given informed consent but has not been randomized because the participant has failed to meet the inclusion and/or has met at least 1 exclusion criterion. Participant numbers for screen failures cannot be reassigned to any other participants.

[redacted]

7.1.2 Baseline and Dose-Escalation Period: Double-Blind Visits Baseline to Week 8

Participants who meet all eligibility criteria will be randomized 1:1 at the baseline visit to receive maralixibat or placebo, as described in Section 6.2.3. The investigator or assigned site staff will access the IRT to randomize the participant and dispense the study medication (Section 6.2.1).

The double-blind dose-escalation treatment periods will comprise 4–8 weeks (maximum 8 weeks). Assessments and procedures for these periods, as detailed in Table 1, should be completed during the dose-escalation period. [redacted] In the event of escalation to the maximum dose ahead of 8 weeks, participants will continue with the same cadence of visits for the remainder of the dose-escalation period, as laid out in the schedule of assessments.

[redacted]

During dose escalation, a [redacted] day visit window will be permitted, unless otherwise specified. Visit dates and acceptable windows are calculated from the baseline visit.

7.1.3 Stable-Dosing Period: Double-Blind Visits from Week 10 to Week 26

Assessments and procedures will be performed as outlined in Table 1. A [redacted] day visit window will be permitted. Visit dates and acceptable windows are calculated from the baseline visit.

During the double-blind stable-dosing period, participants/caregivers will receive emails and/or a phone calls during which the use of concomitant treatments, breastfeeding status, AEs, and study drug compliance will be reviewed, as outlined in Table 1.

7.1.4 Dose-Escalation Period: OLE Visits from Week 26 to Week 34

The open-label dose escalation will comprise 4 to 8 weeks (maximum 8 weeks). During the OLE, all participants, regardless of treatment assignment in the double-blind period, will receive maralixibat. The assessments detailed in Table 2 should be completed during this period. In the event of escalation to the maximum dose ahead of 8 weeks, participants will continue with the same cadence of visits for the remainder of the dose-escalation period, as laid out in the Table 2.

During dose escalation, a [redacted] day visit window will be permitted, unless otherwise specified. Visit dates and acceptable windows are calculated from Week 26.

The Week 26 visit will be 1) the final visit of the double-blind stable dosing period and 2) the first visit of the open-label period.

7.1.5 Stable-Dosing Period: OLE Visits at Week 36+

During the first stage of the OLE stable-dosing period, participant contact will alternate between a phone or email contact and a clinical visit. This will comprise the following:

- Participants/caregivers will receive an email or a phone call, during which the use of concomitant treatments, breastfeeding status, AEs, and study drug compliance will be reviewed as outlined in Table 2.

- Alternating with emails or phone calls, participants will return to the site for a study clinic visit. Assessments and procedures will be performed as outlined in Table 2. A 7-day visit window will be permitted.

7.1.6 Early Termination/End of Treatment

Participants will return to the site at EOT or upon ET, and the procedures and assessments outlined in Table 2 will be performed. If a participant has undergone a clinic visit for the study within the preceding 7 days, blood and other clinical assessments do not need to be repeated unless there is clinical suspicion of abnormality. Breastfeeding status, AE assessment, participant dosing compliance, and prior and concomitant treatments will be

assessed regardless of timing of the timing of the preceding visit. If study medication is permanently discontinued early, regardless of the reason, the participant will be discontinued from the study, and the evaluations listed for the ET/EOT visit are to be performed. The participant should undergo the ET assessments at the visit during which study medication was discontinued, or the participant should be scheduled for an additional ET visit as soon as possible if study medication was discontinued between visits.

7.1.7 Follow-Up After Early Termination/End of Treatment

All participants who complete an ET/EOT visit (see Section 7.1.6) will be contacted by phone or email [redacted] days after the visit. This visit will not be required for those participants who are undergoing study drug interruption at the time of study discontinuation. Concomitant treatments, AEs, and breastfeeding status will be recorded by site personnel during this phone call.

7.1.8 [redacted]

[redacted]

7.2 Study Evaluations and Procedures

7.2.1 Efficacy

7.2.1.1 Biomarkers

Blood samples will be collected as described in schedules of assessments (Table 1 and Table 2) to measure safety parameters, and, if blood volumes allow, [redacted]

[redacted]

[redacted]

7.2.1.2 Other Efficacy Assessments

Liver-associated events, such as hepatic encephalopathy, variceal bleeding, new ascites, spontaneous bacterial peritonitis, liver-related death, and liver transplantation will be assessed by the investigator over the course of the study.

[redacted]

Spleen size, measured in centimeters below the lower costal margin, will be assessed and recorded by investigators during routine clinical visits.

7.2.2 Safety

7.2.2.1 Physical Examination, Vital Signs, and Neurodevelopmental Examination

Abnormalities (including presence of hepatomegaly, splenomegaly, edema, ascites, jaundice, or icterus) identified at the screening visit will be documented in the participant's source documents. Significant changes after the screening visit should be assessed as potential AEs. Physical examination assessments at each onsite visit should also include specific assessments for signs of such as hepatomegaly, splenomegaly, edema, ascites, jaundice, and scleral icterus.

Vital signs include systolic and diastolic blood pressure, heart rate, temperature, and respiration rate. Blood pressure should be determined following 5 minutes of rest by cuff using the same method, the same arm, and the same position throughout the study. Any deviations from baseline vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

[redacted]

[redacted]

For participants <2 years of age, or participants who cannot stand on their own, length will be measured using a calibrated headboard via 2 independent measurements, recorded to the nearest 0.1 cm (and a third measurement if values differ by >1.0 cm).

For participants ≥2 years of age or for participants who can stand on their own, height will be measured using a calibrated stadiometer via 2 independent measurements, recorded to the nearest 0.1 cm (and a third measurement if values differ by >0.5 cm).

For Participants <2 years of age or for participants who cannot stand on their own, weight will be assessed using a calibrated infant scale via 2 independent measurements and recorded to the nearest 0.1 kg (and a third measurement if values differ by >0.3 kg).

For participants ≥2 years of age or for participants who can stand on their own, weight will be assessed using a calibrated scale via 2 independent measurements and recorded to the nearest 0.1 kg (and a third measurement if values differ by >0.3 kg).

[redacted]

7.2.2.2 Electrocardiograms

All participants will undergo a standard triplicate 12-lead ECG at baseline, Week 10, Week 26, Week 104, and ET/EOT. An ECG is not required during the ET/EOT visit if the ET/EOT visit occurs after Week 104. ECGs should be recorded in the supine position, if possible, after at least 5 minutes of rest. ECGs will be locally read for diagnostic purposes and also centrally read by a Central ECG Reader with pediatric ECG expertise. The centrally read ECG data will be used for analysis. Each ECG tracing should be labeled with the study

[redacted]

and participant number, participant initials (if applicable), and date and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the relevant section of the Medical History/AE electronic CRF, as appropriate.

Additional ECGs may be performed based on clinical indication as per investigator and/or medical monitor judgment.

7.2.2.3 Clinical Laboratory Evaluations

Venous blood samples are required for samples analyzed by the central laboratory. For local safety assessments, if the investigator is unable to collect a venous sample, capillary blood samples may be used if compliant with local laboratory standard operating procedures.

Clinical laboratory assessments are listed in Appendix 3. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator or subinvestigator must assess out-of-range clinical laboratory values for clinical significance, indicating whether the values are clinically significant. Abnormal clinical laboratory values that are unexpected or not explained by the participant's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Complete blood count and coagulation results may be collected as part of standard of care (local laboratory) if blood is drawn within 3 days before or after the study visit. In such case, the investigator or designee will be asked to provide the reference ranges.

Unscheduled local laboratory values relevant to the monitoring of an AE/serious adverse event (SAE) or clinically significant laboratory abnormalities must be captured in the relevant CRF; collection of other local laboratory values may be requested by the sponsor.

The sBA, [redacted] and PK results will remain blinded to sites and to the blinded study team (see Section 6.1.2 for exceptional circumstances).

Clinical chemistry samples must be sent to the central laboratory. Total bilirubin is the primary endpoint of the study and must be measured by the central laboratory.

Anion gap and osmolar gap (when clinically indicated), corrected sodium, α-tocopherol/total lipids ratio, retinol/retinol-binding protein molar ratio (when clinically indicated), [redacted]. Total lipids will be approximated by the sum of triglycerides and total cholesterol.

Where possible and permitted, home care may be organized through qualified healthcare professionals to collect samples at the participant's home (or other agreed-upon location). This applies to all types of blood-based assessments.

[redacted]

7.2.3 Demographics, Medical History, Disease History, and Medication History

Participant demographic information including sex, age (months and days), and race, as allowed per local regulations, will be collected at the screening visit. Medical history is to include conditions the participant had prior to the first dose of study drug, with the exception of SAEs occurring during the screening period, which should be reported on the AE CRF. Breastfeeding status will be assessed at screening and throughout the study.

At the screening visit, the investigator must record all clinically or medically relevant information, including BA disease history.

Refer to Section 5.1 for details on collection of medication history. Prior treatment information, including any prior treatments for BA, must be recorded on the appropriate CRF page.

7.2.4 Other Assessments

7.2.4.1 Clinical Pharmacology Assessments

Blood samples will be drawn before dosing at [redacted] and [redacted] after dosing at baseline, [redacted] to assess the plasma level of maralixibat. Collection of the sample is at the investigator's discretion per clinically allowable blood volume draws. If only one draw is allowable, preference can be given to the postdose sample over the predose sample. The PK blood sample collection time relative to the time of dosing will be recorded. The investigator should ensure that every effort is made to collect all PK blood samples at the precise protocol-scheduled time in the schedule of assessments (see Table 1 and Table 2). Blood samples should be drawn before feedings and administration of vitamin supplementation, when possible. Systemic concentrations of maralixibat in plasma will be determined at predose and at approximately [redacted] hours after dosing. The PK blood collection should not deviate from the nominal collection time set forth in the protocol by more than the allowable window [redacted]

7.2.4.2 [redacted]

[redacted]

[redacted]

7.2.5 Volume of Blood to Be Drawn from Each Participant

Approximately [redacted] of blood will be drawn during the blinded portion of the study. In addition, approximately [redacted] may be required to complete assessments during the screening period. During the OLE, up to Week 104, approximately [redacted] mL of blood will be drawn.

According to the Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population (2017), the volume of blood drawn from a participant should not exceed 3% of the total blood volume over a period of 4 weeks and should not exceed 1% of the total blood volume per day. Should the volume of blood required for a single visit or a 4-week period exceed the maximum allowable amount, the investigator will draw blood according to the order of priority as specified for each clinic visit in Table 5 until the maximum amount has been reached. The order of priority is specific for each study visit. If the next sample in the priority list cannot be collected due to blood volume limits, a sample farther down the priority list can be collected if the total volume does not exceed the blood volume limits.

The order of priority identifies which samples should be collected until the blood sample volume limit is reached and not the sequence of blood draws (the sequence of blood draws by collection tube type is specified in the laboratory manual).

If CBC or coagulation were tested [redacted] days before or after the study clinic visit by a local laboratory (e.g., as part of standard of care), these results can be used for the study and the tests do not need to be done again.

If vitamin A (retinol), vitamin E (α-tocopherol), or Vitamin D are tested [redacted] days before or after the study clinic visit by the local laboratory (e.g., as part of standard of care), these results can be used for the study and the tests do not need to be repeated.

Due to the allowable blood sample volume limit that can be drawn as screening, LSV samples should be collected on a separate day during the screening period. If LSVs were not collected during the previous study visit due to volume limitations, consider collecting these samples during standard-of-care visits or during study visits without blood sampling (according to the Schedule of Assessments [Table 1 and Table 2]).

If possible, standard-of-care visits that require the same laboratory assessments as the study protocol should occur on the same day as the study visit to further limit the blood sampling.

Laboratory draws missing due to the maximum allowable blood volume being reached will not be considered protocol deviations.

Clinical chemistry samples must be sent to the central laboratory. Total bilirubin is the primary endpoint of the study and must be measured by the central laboratory.

Measures to minimize the pain and distress to study participants during blood draws (e.g., pediatric staff, minimize number of punctures, use of local anesthetics) are recommended. Further instructions are provided in the laboratory manual.

Table 5 **Order of Priority for Blood Sample Collection and Volume of Blood to be Withdrawn by Study Visit (Double-Blind Period)**

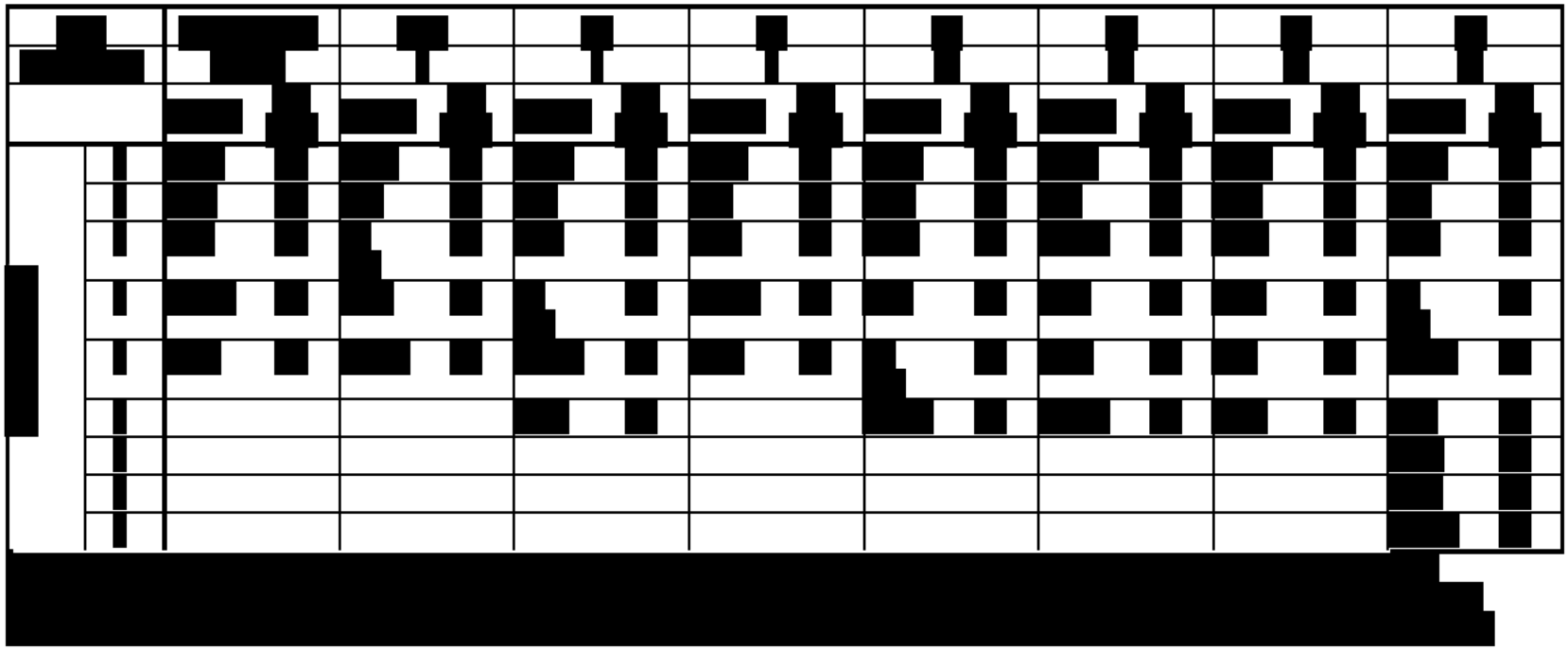


Table 6 Order of Priority for Blood Sample Collection and Volume of Blood to be Drawn by Study Visit (OLE period)

[redacted]

7.3 Adverse Event Collection

At each study visit, participants or their caregivers will be questioned in a general way to ascertain whether AEs have occurred since the previous visit (e.g., "Has your child had any health problems since your last visit?").

The investigator and/or designees are responsible for detecting, documenting, and recording events that meet the AE/SAE/adverse event of special interest (AESI) reporting criteria described in this section.

7.3.1 Adverse Event Collection Period

All SAEs will be recorded from the signing of the informed consent form (ICF) until the end of study visit at the time points specified in the schedule of assessments.

All AE/AESIs will be collected from first dose of study drug until the end of study visit at the time points specified in the schedule of assessments.

All SAE/AESIs will be reported to the sponsor or designee immediately but no later than 24 hours after awareness.

7.3.2 Follow-Up

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All events will be followed until the event resolves, stabilizes, is otherwise explained, or the participant is lost to follow-up.

Investigators are not obligated to actively seek AEs or SAEs after study participants exit the study. However, if the investigator learns of any SAEs that occurred in a participant after study exit and the investigator considers the event to be possibly related to the study treatment, the investigator must notify the sponsor immediately, but no later than 24 hours after awareness.

7.3.3 Expedited Safety Reporting

The sponsor will comply with country-specific regulatory requirements relating to expedited safety reporting to regulatory authorities, IRBs/IECs, and investigators.

An investigator who receives safety information (e.g., expedited safety report, periodic safety summaries) from the sponsor may need to notify the local IRB/IEC, according to local requirements.

7.3.4 Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to the sponsor's product or program.

The following events are AESIs for participants in this study and must be reported to the sponsor within 24 hours after awareness, irrespective of regulatory seriousness criteria or causality:

- [redacted] requiring study drug discontinuation (per Section 7.4.5)
- [redacted] requiring study drug interruption and/or dose modification (per Section 7.4.2.3)
- [redacted]

7.3.5 Overdose and Special Reporting Situations

Overdose is defined as intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed daily dose. Treatment of overdose with maralixibat would be consistent with general supportive measures, if applicable, including hydration and monitoring for LSV deficiencies. In the event of an overdose, the investigator should contact the medical monitor within 24 hours after awareness. The investigator must closely monitor the participant for any AE/AESI/SAEs and laboratory abnormalities (and for at least 24 hours).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant. Mirum does not recommend specific treatment for an overdose.

Abuse, misuse, overdose, or medication errors are not considered AEs on their own; however, they must be reported to the sponsor regardless of whether they result in an AE/AESI/SAE. All AEs associated with abuse, misuse, overdose, or medication errors should be reported as per the standard process for reporting any AE. The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse: Persistent or sporadic intentional intake of investigational product when used for a nonmedical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- Misuse: Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol.)
- Overdose: Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed daily dose

- Medication Error: An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.
    - Medication errors should be collected/reported for all products under investigation. The administration and/or use of the unassigned treatment is/are always reportable as a medication error.
    - The administration and/or use of an expired investigational product should be considered as a reportable medication error.

  Note: Cases of participants missing doses of the investigational product are not considered reportable as medication errors.

7.3.6 Disease Progression

Disease progression itself is not considered an AE unless it is considered atypical in presentation or considered to be related to the study drug. Signs of symptoms of disease progression do not need to be reported as AEs/SAEs; however, if there is uncertainty as to their cause, they may be reported as AEs.

7.3.7 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events meeting the AE definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Elective procedures and preplanned interventions for preexisting conditions that did not worsen since the start of the study
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

7.3.8 Serious Adverse Event Definition

An AE is considered serious if it meets at least 1 of the following criteria:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization signifies that the participant has been admitted (for at least 24 hours) at the hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

- Results in persistent disability/incapacity

  A substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect

- Important Medical Events

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events, that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an Emergency Department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.3.9 Recording and Follow-Up of AEs, AESIs, and SAEs

When an AE/AESI/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator should report all relevant AESI/SAE information within 24 hours after awareness following the instructions provided by the sponsor. It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF. There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) should be documented as the event term. If a participant dies during participation in the study or during a recognized follow-up period, the investigator should provide the sponsor or designee with a copy of any postmortem findings, including histopathology.

7.3.10 Assessment of Severity

The investigator will make an assessment of the maximum intensity for each AE and SAE according to the National Cancer Institute Common Terminology Criteria for Adverse Events

(CTCAE), version 5.0. Should a participant experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

NOTES: An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is graded as severe. A semicolon indicates "or" within the description of the grade, not "and."

7.3.11 Assessment of Causality

The investigator is obligated to assess the relationship (related or not related) between study treatment and each occurrence of each AE. Causal assessment is either "related" (which encompasses possibly related, probably related, or certainly related) or "not related" (which encompasses possibly unrelated, probably unrelated, or certainly unrelated). The investigator will use clinical judgment to determine the relationship. A "related possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship rather than that a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. For each AE/AESI/SAE, the investigator must document in the medical notes that he or she has reviewed the AE/AESI/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. An assessment of causality must be reported for every event, even when only limited data are available.

The investigator may change his or her opinion of causality in light of follow-up information and provide an SAE follow-up report with the updated causality assessment.

The following additional guidance may be used to determine the relationship:

Term	Relationship Definition
Related	• Absence of alternative causes (or difficult to assign to an alternative cause) • AE follows a strong or reasonable temporal sequence from administration of study drug • AE could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient • Occurrence of the AE follows a known response pattern to study drug • The AE is confirmed with a positive rechallenge or supporting laboratory data
Not Related	• An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medications, disease under study) • Occurrence of the AE does not follow a reasonable temporal sequence from administration of the study drug • AE does not follow a known pattern of response to study drug • AE does not reappear or worsen when study drug is restarted • An alternative explanation is likely but not clearly identifiable

AE=adverse event.

7.4 Safety Monitoring Guidelines

All laboratory values will be monitored by the sponsor medical monitor as well as the PI. The only exceptions are sBA, [redacted] and PK values, which will remain blinded until the Study MRX-701 database is locked.

A complete overview of safety monitoring guidelines pertaining to clinical laboratory tests, including DILI and associated stopping criteria, can be found in Section 7.4.2.

7.4.1 Data Monitoring Committee

Throughout this study, the safety of participants will be closely monitored by an unblinded DMC. The DMC will comprise [redacted] and will be governed by a DMC charter.

Regular review will occur on a rolling basis approximately [redacted] until the DMC advises otherwise. This includes an MRX-701 study meeting that alternates with the programwide DMC review ([redacted]). Enrollment will not be paused for the review.

In addition, ad hoc and/or offline DMC reviews will occur in the following situations:

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

The DMC will be provided with all available study data at the time of the meeting data cutoff; data will be provided in an unblinded fashion. The data include liver-related blood tests, vital signs and growth/nutritional parameters, AE listings, concomitant treatment listings, drug exposure listings, treatment allocation, protocol deviation listings, past medical history, and demographics. The DMC will make recommendations to the sponsor following Committee review regarding individual cases, changes to the protocol and/or ad hoc DMC reviews, and benefit-risk assessments as well as the appropriate interval for the next scheduled DMC review.

In addition to the DMC across both study and standard-of-care monitoring, assessments of growth, nutrition, and development will be conducted by the site investigators and analyzed by the sponsor.

As described in Section 6.2.4.1, the DMC will conduct an independent review of unblinded participant data after [redacted] participants have completed the dose escalation period of the double-blind portion of the study. The DMC will then use its own judgment, alongside the prespecified criteria set forth in Section 6.2.4.1, to approve or deny the alteration of the dose escalation regimen for participants in both the double-blind and OLE portions of the study.

7.4.2 Liver Parameters

7.4.2.1 General Guidelines

The following guidelines are provided for the monitoring of selected laboratory parameters. Signs and symptoms of liver injury will be monitored closely throughout the study per below guidelines. In this setting, the differential diagnosis of ascending cholangitis must also be considered (diagnostic guidance given in Section 7.4.3).

Confirmation Guidance: At any time during the study, the initial clinical laboratory results that meet the safety monitoring criteria presented below must be confirmed by performing measurements on new specimens (retest).

Retests should be conducted by the central laboratory. Retests at a local laboratory are acceptable on an as-needed basis. Local laboratory results are to be sent to the investigator and medical monitor for review. These results should be captured in the relevant CRF.

Retest collection should take place within 48 to 72 hours after availability of the initial findings of potential concern or as clinically indicated.

7.4.2.2 Enhanced Monitoring Criteria for Liver Parameters

Throughout this study, liver parameters will be monitored as part of standard of care as well as part of the schedule of assessments for this study. In addition, to address the period of BA after HPE, specific criteria will be used to assess for liver injury and to determine whether study medication should be temporarily interrupted. These values should be considered in the setting of the natural course of BA liver disease alongside clinician judgment. Other causes of liver injury should also be considered; specifically, a differential diagnosis of cholangitis should be investigated if clinically indicated, according to the criteria listed in this protocol and based on clinician judgment.

Table 7 provides the criteria for enhanced monitoring of liver parameters in the absence of a plausible alternative explanation for the observed abnormalities. If an alternative explanation has been identified, medical treatment and monitoring should be guided by that diagnosis.

The baseline values for the purpose of the liver safety monitoring differ according to the study period:

- Weeks 0 to 8 of study: Values taken within 1 week of the procedure (referred to here as pre-HPE value)
- Week 8 onward: Lower of the two values recorded during Week 2 and Week 6 visits of the study period (referred to here as post-HPE value). In the case of abnormal liver parameters that are secondary to an identified cause not related to study treatment during Weeks 2 and 6, investigators and medical monitor can agree on the most appropriate alternative post-HPE value to be used for further monitoring.

Table 7 Enhanced Liver Injury Monitoring Criteria (Adverse Event)

Frequency of repeat measurements: If at any time during the study, any of the above results meets the enhanced monitoring criteria, the measurement(s) must be reconfirmed, as outlined above, and followed up in regular intervals, as clinically appropriate. Participants with a confirmed abnormality in liver parameters should have their liver chemistry retested as clinically indicated, until levels stabilize or begin to recover.

Diagnostic workup for alternative explanations: Because the diagnosis of DILI is a diagnosis of exclusion, it is recommended that other explanations be investigated in case of clinically relevant elevations of liver parameters above the enhanced monitoring criteria. The diagnostic workup may include the following, as clinically indicated, but other investigations may be considered:

- Close and frequent monitoring of liver enzyme and serum bilirubin tests as clinically indicated
- Signs/symptoms, including body temperature, as well as prior, current, and intercurrent diseases/illnesses

- Use of or recent change in use of concomitant treatment (including non-prescription medications, herbal and dietary supplement preparations), exposure to alcohol or recreational drugs, and special diets
- History for exposure to environmental chemical agents and travel
- Serology for viral hepatitis (hepatitis A virus IgM, hepatitis B surface antigen, hepatitis C virus [HCV] antibody, HCV RNA, cytomegalovirus IgM, and Epstein Barr virus antibody panel)
- Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])
- AST, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH)
- CBC with differential blood count (eosinophils)
- Reticulocyte count, prothrombin time (PT)/INR
- Infection screen (white cell count, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], blood cultures [as appropriate])

Additional investigations of liver parameters, including gastroenterology/hepatology consultations, and/or hepatic imaging, may be requested at the discretion of the investigator, in consultation with the medical monitor. The diagnosis of ascending cholangitis should be investigated, if clinically indicated (see Section 7.4.3).

7.4.2.3 Guidelines for Interruption of Study Medication for Specific Liver Parameters

If the confirmed laboratory results meet any of the criteria below, after administration of the study medication, and the event is without an alternative explanation (i.e., intercurrent illness, disease progression, natural history of the disease, possible post-HPE surgical elevation), interruption of study medication should be considered. If an alternative explanation has been identified, study medication may continue if deemed appropriate by the PI and medical monitor; medical treatment and monitoring should be guided by that diagnosis. The medical monitor informs the DMC, if appropriate.

- [redacted]

Table 8 Treatment Interruption Criteria (Serious Adverse Event)

If these values occur on the first measurement after HPE, an additional measurement [redacted] days after HPE should be performed.

In addition, the PI and medical monitor retain the discretion to withhold study treatment based on the clinical suspicion of a treatment liver-related event even if the aforementioned criteria are not met.

Study medication should not be restarted if:

- The participant had a probable DILI in the opinion of the investigator and medical monitor (in case of disagreement, cases may be subject to independent expert adjudication by the DMC).
- The participant displays signs/symptoms of acute hepatitis, liver decompensation (i.e., variceal hemorrhage, ascites, hepatic encephalopathy), or hypersensitivity reaction.
- The participant had liver parameter elevations that met discontinuation criteria as listed above without alternative explanations or that are inconsistent with the natural history of the disease.

- The participant meets stopping criteria subsequent to a rechallenge (i.e., meeting stopping criteria after reintroduction of study medication) that are likely related to study medication.
- The participant had [redacted] previous interruptions for safety reasons, unless there is a compelling reason why the participant should continue with dosing (i.e., interruptions were due to disease progression, natural history, intercurrent illness) and provided that the participant is still compliant with the study protocol as per Section 6.5.
- The participant has LSV deficiency (see Section 7.4.5). In this case, study medication must be interrupted if clinical symptoms of deficiency occur in participants. Participants may restart dosing once clinical symptoms resolve and LSV levels begin to improve unless the participant has been previously discontinued for the same symptomatic LSV deficiency. [redacted]
- The participant has LSV deficiency after supplement escalations over a [redacted]-week period (per Section 7.4.5). In this case of LSV deficiency, if levels are persistently below the participant's baseline value or the lower limit of normal, [redacted]

7.4.3 Cholangitis Diagnostic Criteria

Cholangitis must be considered as differential diagnosis in participants showing abnormalities of liver parameters during the treatment period. Investigation for cholangitis should be considered if a participant exceeds conjugated bilirubin enhanced liver injury monitoring criteria (Table 7) and must be performed if a participant fulfills conjugated bilirubin treatment interruption criteria (Table 8). Suggested diagnostic criteria are:

- Fever >38°C or elevated inflammatory markers (white cell count, CRP, procalcitonin) in a child with no other obvious source of infection
- Evidence of cholestasis
  - Elevation of direct bilirubin by 25% or at least >1.0 mg/dL above current reference value,

    AND

  - Abnormal liver function tests: Increase in 2 or more of AST, ALT, ALP, or GGT to 1.5x the upper limit of normal (ULN) or >25% above current reference value if previously elevated

These criteria are based on the Tokyo guidelines and have been modified for this patient setting (Kiriyama et al. 2018). Other signs (e.g., decreased stool pigmentation in a child who previously had stool pigmentation, identified dominant biliary stricture) should also be

considered. Cases of cholangitis with positive bacterial culture of blood or ascites should be categorized as being "culture proven cholangitis," whereas, culture-negative cholangitis cases should be categorized as being "culture-unproven cholangitis."

The diagnosis of cholangitis will be captured as a safety endpoint. Further, for participants with a positive diagnosis of cholangitis, temporary interruption of study medication must occur until the episode has stabilized or resolved. Once the cholangitis episode has improved and in the investigator's judgment the study medication can be resumed, use of the Enhanced Monitoring and Treatment Interruption criteria will revert to the aforementioned guidelines for monitoring.

7.4.4 Growth and Development

Assessments of growth, nutrition, and development will take place throughout Study MRX-701 as both standard of care and as part of the study assessment regimen. This will be reviewed by medical monitors (blinded) and the DMC.

7.4.4.1 Growth

The following parameters should be assessed at the time points indicated in the schedules of assessments (Table 1 and Table 2):

- Weight, length, and head circumference; z-scores will be calculated using appropriate reference data.
- Physical examination

7.4.4.2 Nutrition

The following parameters should be assessed at the time points indicated in the schedules of assessment (Table 1 and Table 2):

- Albumin
- LSV (per Section 7.4.5)
- Nutritional support (captured as concomitant treatment): total parenteral nutrition, enteral supplements (oral, nasogastric or percutaneous endoscopic gastronomy tube delivered), albumin infusions, LSV supplements
- [redacted]

Nutrition should be optimized as per standard of care to prevent and treat nutritional deficiencies throughout the study period.

[redacted]

[redacted]

7.4.4.3 [redacted]

[redacted]

7.4.5 Lipid-Soluble Vitamins

LSV levels (serum vitamin A [retinol], serum 25-hydroxy vitamin D, and vitamin E [α-Tocopherol]) and INR will be assessed at the study visits indicated in the schedules of assessments (Table 1 and Table 2). In addition, in the case of abnormal serum retinol or INR levels, retinol-binding protein and Vitamin K levels will be determined, respectively. Blood samples will be obtained at the study visit before the daily dose of vitamins is administered. Throughout this study, supplementation of LSVs should be provided as clinically indicated.

In participants with LSV deficiency, study medication must be interrupted if clinical symptoms of deficiency occur in the absence of another identifiable cause. Clinical symptoms include but are not limited to:

- Vitamin A: night blindness, degeneration of the retina, xerophthalmia, follicular hyperkeratosis, keratomalacia, or Bitot's spots
- Vitamin D: rickets, osteomalacia, costochondral beading, epiphyseal enlargement, cranial bossing, bowed legs, ALP monitoring, fractures
- Vitamin E: numbness/tingling, decreased deep tendon reflexes, limb ataxia, hemolytic anemia, limited extraocular movements
- Vitamin K: easy bruising, excessive bleeding (e.g., epistaxis), blood in the urine or stool, anemia

Participants may restart dosing once clinical symptoms resolve and LSV levels begin to improve unless the participant has been previously discontinued for the same symptomatic LSV deficiency. Each participant may be rechallenged after symptomatic LSV deficiency only [redacted]

In the event that a confirmed vitamin (vitamin A, D, or E) or INR (as a proxy for vitamin K) level falls either below the participant's baseline or below the lower limit of normal (refer to reference ranges of the central or local laboratory), whichever is lower, and the participant is without clinical symptoms of deficiency, the investigator should make the appropriate modification to the participant's vitamin supplementation regimen.

In the case of identified vitamin A deficiency, investigators should test retinol binding protein levels and perform an eye examination, including extraocular muscles, skeletal examination, and reflexes, with referral to neurology, ophthalmology, and/or imaging if the concern persists.

Appropriate starting doses and vitamin formulations should be used for new cases of LSV deficiency (see Table 9, adapted from Shneider et al. 2012). Doses should be increased, as clinically indicated, to optimize the LSV levels. Parenteral formulations should be used (where available) if enteral supplements are unsuccessful at improving LSV deficiency.

Table 9 Recommended Starting Doses for Lipid-Soluble Vitamins

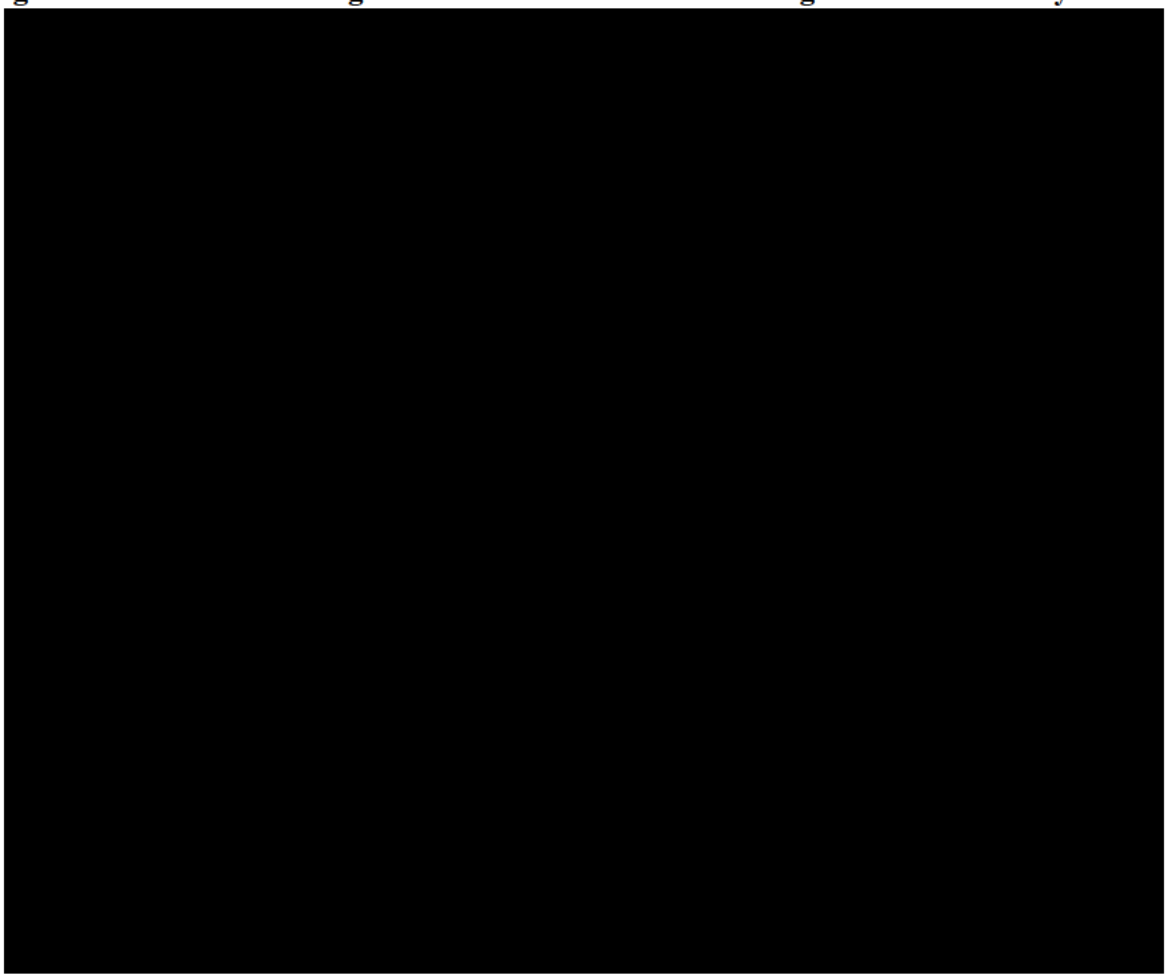
Vitamin	Starting Dose
Vitamin A (retinol)	5000 IU orally of water miscible product (or appropriate intramuscular dose)
Vitamin D (25-hydroxy vitamin D)	2000 IU orally daily of cholecalciferol (appropriate ergocalciferol or intramuscular dose may be used) or ultraviolet B phototherapy at the discretion of the investigator
Vitamin E (α-tocopherol)	25 IU/kg of D-α-tocopherol polyethylene glycol succinate (appropriate intramuscular dose vitamin E can be given if available)
Vitamin K	2.5 mg orally for weight ≤30 kg or 5 mg for weight >30 kg (appropriate intramuscular or IV dose may be used)

The response to the change in regimen will be assessed at the next scheduled study visit. Supplements should be escalated in [redacted]. If, during this period, the LSV levels are persistently below the participant's baseline value or the lower limit of normal, whichever is lower, and there is an absence of clinical symptoms, the investigator will [redacted].

Figure 8 provides a flow diagram representing the protocol recommendations for treatment of and discontinuation due to worsening of LSV deficiency.

[redacted]

Figure 8 Flow Diagram for Treatment of Worsening of LSV Deficiency



7.4.5.1 Rules for Study Medication Discontinuation Following LSV Deficiency

- The participant has LSV deficiency (see Section 7.4.5). In this case, study medication must be interrupted if clinical symptoms of deficiency occur, and participants may restart dosing once clinical symptoms resolve and LSV levels begin to improve unless the participant has been previously discontinued for the same symptomatic LSV deficiency. Each participant may be rechallenged after symptomatic LSV deficiency .
- The participant has LSV deficiency after supplement escalations over a week period (per Section 7.4.5). In this case of LSV deficiency, if levels are persistently below the participant's baseline value or the lower limit of normal, whichever is lower, and there is an absence of clinical symptoms, the investigator will

Results of LSV investigations will be reviewed and discussed by the investigator and medical monitor, as well as analyzed at the DMC meeting.

7.4.6 Safety Monitoring for Coagulation Panel Results

In the event of a confirmed laboratory result for INR >1.3 ( ) or INR >1.5) or an increase of >0.4 despite adequate vitamin K supplementation, the investigator and the medical monitor may consider a temporary interruption of study medication. Dosing may resume when the INR falls below 1.5 or returns to the participant's baseline level.

7.4.7

7.4.8 Study Medication Discontinuation Rules for Diarrhea

Study medication should be withheld if a participant sustains severe diarrhea that requires:

- Hospitalization

  AND/OR

- IV fluid or nutritional supplementation or leads to severe electrolyte disturbances

Rechallenge should not occur until the GI disturbance has improved. The exact duration of this hold will be based on the clinical judgment of the investigator and medical monitor.

Diarrhea is an identified risk with maralixibat. It is usually transient in nature and mild to moderate in severity. In most instances, diarrhea does not require dose modifications with maralixibat, and if necessary, can be treated with a short course of an appropriate pharmacological intervention (as per standard of care). In the event of significant diarrhea, the investigator should consider lifestyle interventions (including the monitoring of daily fluid balance), educate caregivers and guardians on the common signs and symptoms of dehydration (e.g., skin or mucosal dryness, reduction of diuresis, lethargy), and administration of oral rehydration, according to local standard-of-care guidelines.

7.4.9 Study Medication Discontinuation Rules for Grade 4 AEs

In the event of a Grade 4 AE, study drug interruption should take place.

Rechallenge should not occur until there has been consultation with the investigator and medical monitor or the event is in resolution.

8 STATISTICAL ANALYSIS

All predefined statistical analyses will be performed after the database is locked. All statistical analyses will be performed using SAS software (SAS Institute, Cary, NC, USA) version 9.4 or higher.

The statistical analysis plan (SAP) will provide the comprehensive statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as participant disposition, demographics and baseline characteristics, medical and BA disease history, study medication exposure, and prior medications. All study data will be presented in participant listings.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

8.1 Sample Size Calculation and Power Considerations

Estimates for placebo response and variance are drawn from Bezerra et al. (2014). [redacted]

8.2 Analysis Populations

The following analysis populations will be used:

- Intent-to-treat (ITT) population: all randomized participants. Additional subgroups of the ITT population will be specified based on the presence/absence of post-baseline efficacy assessments for particular efficacy endpoints.
- Per-protocol population: all participants in the ITT population who receive at least 1 dose of study medication and do not have any major protocol violations or deviations. Major protocol violations/deviations will be identified prior to database lock.
- Safety population: all participants who receive at least 1 dose of study medication.

[redacted]

8.3 Participant Disposition and Demographic and Baseline Characteristics

Participant disposition, demographics and baseline characteristics, BA disease history, prior medications, treatment exposure, and compliance will be summarized by treatment group. Study completion status and reasons for discontinuation will also be displayed. The safety population will be used for these summaries. Medical and surgical history and protocol violations/deviations will be presented in participant listings.

8.4 Efficacy Analyses

8.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as:

- Mean change in total serum bilirubin levels from baseline through Week 26

8.4.1.1 Primary Analysis for Primary Efficacy Endpoint

The primary analysis on the primary efficacy endpoint will be conducted in the ITT population. [redacted]

[redacted] The first (co)variance structure that does not have a convergence problem will be the one used for the analysis. [redacted]

[redacted]

[redacted]

[redacted]

The null hypothesis for the primary efficacy endpoint of the equality of maralixibat and placebo is:

H_0: mean change in total bilirubin baseline and Week 26 in the two treatment groups are equal

The null hypothesis of no treatment effect will be rejected if the statistical analysis results in a 2-sided p-value for treatment at Week 26 is <0.05. [redacted]

The study will be deemed successful if the hypothesis of no treatment effect on the primary efficacy endpoint over the primary cohort in the ITT population is rejected at the 0.05 (2-sided) significance level.

8.4.1.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

combined to produce a unique point estimate and standard error taking into account the [redacted]

[redacted]

[redacted]

8.4.1.6 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are described in Section 2.2.2.

For continuous endpoints, an analysis similar to that described for the primary efficacy endpoint, including the sensitivity analyses, will be performed for each of the secondary efficacy endpoints. [redacted]

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 will be summarized by treatment group. Barnard's exact test will be used to calculate the p-value for the difference between treatment groups.

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

8.4.3 Adjustment for Multiplicity

[redacted]

[redacted]

8.4.4 Exploratory Efficacy Endpoints

[redacted]

8.4.5 Open-Label Efficacy Endpoints

The open-label efficacy endpoints are described in Section 2.2.4.

OLE endpoints will be summarized descriptively.

8.5 Safety and Tolerability Analyses

All safety analyses will be performed on the safety population. Safety measures will be summarized descriptively. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation, minimum, and maximum will be presented for the observed and change from baseline values at each study visit. Qualitative variables will be summarized using counts and percentages at each study visit. AEs and concomitant treatments will be coded with standard dictionaries and will be summarized by treatment received.

8.5.1 Safety and Tolerability Endpoints

The following safety and tolerability endpoints will be evaluated for the double-blind and OLE periods:

- Incidence of 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 and neurodevelopmental assessment

8.6 Pharmacokinetic Analyses

Plasma maralixibat concentrations at each nominal time point and sampling time will be summarized using descriptive statistics. All data will be included in data listings.

8.7 Other Analyses

[redacted]

8.8 Primary Analysis

A single and formal primary analysis will be performed after the last participant has completed Week 26 (or prematurely discontinued the study). All of the Week 26 endpoints will be tested as described above. A final analysis will be performed after all participants have left the study and will focus on the Week 104 endpoints from the OLE.

9 STUDY CONDUCT

This study is conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH), EU Directive 2001/20/EC and its updates, and local ethical and legal requirements. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigator and sponsor files, as appropriate.

9.1 Sponsor and Investigator Responsibilities

9.1.1 Sponsor Responsibilities

The sponsor, including any third party to whom aspects of the study management or monitoring have been delegated, is obligated to conduct the study in accordance with strict ethical principles. The sponsor reserves the right to withdraw a participant from the study, to terminate participation of a study site at any time, and/or to discontinue the study.

The sponsor agrees to provide the investigator with adequate material and support to permit the investigator to conduct the study according to the study protocol.

9.1.2 Good Clinical Practice Compliance

The sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996) and

E6 R2 (2017), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, participants' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national governmental regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of study medication for shipment to the site.

9.1.3 Indemnity/Liability and Insurance

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study.

If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

9.1.4 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

9.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason.

If the study is terminated, the sponsor will notify all investigators to schedule safety follow-up visits for participants who at that time are still receiving treatment with maralixibat, or who have not yet had their safety follow-up visits.

If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs/IECs are notified as appropriate.

Should the study be temporarily suspended due to safety concerns, re-initiation will follow local laws and regulations.

The discontinuation of a registered clinical study that has been posted to a designated public website will be updated accordingly.

9.2 Investigator Responsibilities

9.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research participant has a primary care physician, the investigator should, with the caregiver's consent, inform them of the participant's participation in the study.

9.2.2 Protocol Adherence and Investigator Agreement

The investigator and any subinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those participants who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries, as required by (inter)national regulations.

To ensure compliance with the protocol and with guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

9.2.3 Documentation and Retention of Records

9.2.3.1 Data Collection and Case Report Forms

The investigators' authorized site personnel must enter the information required by the study CRF Completion Guidelines for all data requiring transcription of the source. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data

discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Unscheduled assessments (e.g., local laboratories) are not required to be collected in the CRF except for those that are directly relevant to the monitoring of an AE/SAE, or if a protocol-scheduled blood test has been performed at the local laboratory and not at the central laboratory; collection of other values may be requested by the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records that support the information recorded into the CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. CRFs must be completed by the investigator or designee as stated in the site delegation log.

All data submitted in the electronic CRF must be reviewed, approved, and signed by the investigator. All data, except data entered directly into another platform (e.g., electronic, etc.), will have separate source documentation.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries will be sent for corrections or verification of data.

9.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Information recorded in the CRF should be supported by corresponding source documentation. Source data to be reviewed during this study will include but are not limited to the participant's medical file, daily dosing records, and clinical laboratory reports.

The ICF includes a statement by which the participant agrees to the sponsor's monitor/auditor or its representatives, national or local regulatory authorities, or the IRB/IEC, having access to source data. Non-study site personnel will not disclose any personal information or personal medical information.

The study participant's contact information will be securely stored at each site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Records must be made available within reasonable times for inspection and duplication, if required, by an authorized representative of any regulatory agency (e.g., the United States Food and Drug Administration [FDA], European Medicines Agency [EMA], United Kingdom Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

9.2.3.3 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor, subsidiaries, or development partners such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria, any proprietary interest in intellectual property, and any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations (CFR) 54 2(b) (1998).

9.3 Clinical Data Management

A clinical database will be designed to collect data as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an auditable manner.

9.4 Monitoring Procedures

The sponsor and/or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned CRA/study monitor will visit the investigator and site at periodic intervals, maintain periodic communication, and review the CRF data against the source data for completeness and accuracy as defined in the monitoring plan.

The investigator agrees to allow the CRAs and other authorized personnel access as needed to perform monitoring and other site visits. By signing the investigator's acknowledgement, the investigator agrees to meet with the CRA(s) during study visits, to ensure that study staff are available to the CRA(s) as needed, to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area, and to assist the monitors in their activities, if requested.

9.5 Quality Assurance/Audit

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the UK Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/IEC for each site. The investigator must permit these abovementioned parties to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

9.6 Record Retention

Records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP, applicable requirements and may not be destroyed without written permission from the sponsor. The sponsor must retain all records for 25 years.

9.7 Sample Retention

Any samples remaining after completing the specified tests may be used for purposes related to this research. The samples will be stored in a central archive until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples need to be reanalyzed and will eventually be destroyed. Only the sponsor, the CRO/laboratory, and other authorized designee will have access to the stored samples.

These remaining samples could be used to further liver disease research, its complications and other conditions for which individuals with liver disease are at increased risk, and to improve treatment.

Data collected for this study will be analyzed and stored centrally. The blinding of the identity of the participants will be maintained. After the study is completed, the de-identified, archived data will be transmitted to and stored at a central repository. Data may be used by other researchers, including those outside of the study. Permission for any data transmission and other pertinent details will be included in the ICF.

Identifiable samples can be destroyed at any time at the request of the participant. During the conduct of the study, a participant can choose to withdraw consent to have specimens stored for future research. However, withdrawal of consent regarding sample storage may not be possible after the study is completed.

9.8 Ethical Considerations

9.8.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from the caregivers of all study participants prior to initiation of any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and ICH GCP requirements. Each participant's legally authorized representative (caregiver), as applicable, is requested to sign and date the participant ICF, after the caregiver has received and read (or been read) the written participant information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the participant's rights and responsibilities. A copy of the ICF (i.e., a complete set of participant information sheets and fully executed signature pages) must be given to the participant's caregiver, as applicable.

The ICF also includes a statement by which the participant's caregiver agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/IEC, to access applicable source data. Signed ICFs must remain in each participant's study file and must be available for verification at any time.

The PI provides the sponsor with a copy of the ICF that was reviewed by the IRB/IEC and received their favorable opinion/approval. A copy of the IRB/IEC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating PI) is responsible for this action.

9.8.2 Institutional Review Board or Ethics Committee

This protocol, the ICF (approved by the sponsor or their designee), relevant supporting information, and all types of participant recruitment information will be submitted to the IRB/IEC for review, and all must be approved prior to site initiation. Study medication supplies will not be released until written IRB/IEC approval has been received.

The protocol cannot be altered or changed except through a protocol amendment. Prior to implementing changes in the study, the sponsor and the IRB/IEC must approve any amendments to the protocol and revisions of all ICFs, unless there is a participant safety issue. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

The IRB/IEC will be kept apprised of the progress of the study and of any changes made to the protocol. The IRB/IEC will also be informed of any serious and significant AEs.

9.9 Study Site Initiation

The investigator and any site personnel may not screen or enroll participants into the study until receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received appropriate approvals (health/competent authorities, IRB/IEC) for the protocol and the appropriate ICF.
2. All regulatory, GCP, and other appropriate documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.

9.10 Study Site Closure

At the end of the study, all study sites will be closed. The sponsor may terminate participation of a study site at any time. Examples of conditions that may require premature

termination of a study site include but are not limited to noncompliance with the protocol and/or applicable regulations and guidelines.

9.11 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by the act must provide documentation of this fact.

The confidentiality of participant records in EU countries will be protected in accordance to the General Data Protection Regulation guideline.

The confidentiality of records that may be able to identify participants will be protected in accordance with applicable laws, regulations, and guidelines.

After a participant's caregiver has consented for him or her to participate in the study, the sponsor and/or its representatives may review medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market maralixibat; national or local regulatory authorities; and the IRB/IECs that gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of participants' identities.

Participants are assigned a unique identifying number; however, their initials and dates of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing participants' unique identifying numbers, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be accessed by, and used in, other countries that may not afford the same level of protection that applies within the countries where this study is conducted. Any such transfer would serve to support regulatory submissions, conduct new data analyses to publish or present the study results, or answer questions asked by regulatory or health authorities.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying the study medication may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The site will permit access to such records.

Non-study site personnel will not disclose any personal information or personal medical information.

10 FINAL CLINICAL STUDY REPORT

A final clinical study report (CSR) will be written upon completion of the study. The CSR will include a summary of the study results based on statistical evaluation and clinical assessment of the protocol-defined endpoints.

The sponsor will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

The final CSR may be submitted to the regulatory authorities.

11 PUBLICATION

All publications relating to sponsor products or projects must undergo appropriate technical and intellectual property review, with sponsor agreement to publish prior to release of information.

The term “publication” refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific Web sites, or other disclosure of the study results, in printed, electronic, verbal, or other form.

12 REFERENCES

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.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29–41.

Bull LN, Pawilikowska L, Strautnieks S, et al. Outcomes of surgical management of familial intrahepatic cholestasis 1 and bile salt export protein deficiencies. Hepatol Commun 2018;2:515–28.

Chardot C. Biliary atresia. Orphanet J Rare Dis 2006;1:28.

Chardot C, Carton M, Spire-Bendelac N, et al. Prognosis of biliary atresia in the era of liver transplantation: French national study from 1986 to 1996. Hepatology 1999;30:606–11.

Chen HL, Liu YJ, Chen HL, et al. Expression of hepatocyte transporters and nuclear receptors in children with early and late-stage biliary atresia. Pediatr Res 2008;63(6):667-73.

Chusilp S, Sookpotarom P, Tepmalai K, et al. Prognostic values of serum bilirubin at 7th day post-Kasai for survival with native livers in patients with biliary atresia. Pediatr Surg Int 2016;32(10):927–31.

[redacted]

Davenport M, De Ville De Goyet J, Stinger MD, et al. Seamless management of biliary atresia in England and Wales (1999-2002). Lancet 2004;1354–7.

Davenport M, Parsons C, Tizzard S, Hadzic N. Steroids in biliary atresia: single surgeon, single centre, prospective study. J Hepatol 2013;59:1054–8.

de Vries W, de Langen ZJ, Groen H, et al. Biliary atresia in the Netherlands: outcome of patients diagnosed between 1987 and 2008. J Pediatr 2012;160:638–44.

Emerick KM, Whitington PF. Partial external biliary diversion for intractable pruritus and xanthomas in Alagille Syndrome. Hepatology 2002;35:1501–6.

Ethical considerations for clinical trials on medicinal products conducted with the minors. 2017. Accessed at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf.

European Medicines Agency. Guidance on the management of clinical trials during the COVID19 (coronavirus) pandemic. Version 3, 28 April 2020 (updated Version 4, 4 February 2021). Available online at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

[redacted]

European Medicines Agency. Guideline on Missing Data in Confirmatory Clinical Trials. 2010.

United States Food and Drug Administration. FDA guidance on conduct of clinical Trials of medical products during COVID19 public health emergency. March 2020 (updated updated 30 August 2021). Available online at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency.

Gedulin B, Nikoulina S, Nazarenkov N, Keller B. LUM001, an inhibitor of ASBT, improves liver function and tissue pathology in a rat cholestasis model. Presented at the American Association for the Study of Liver Diseases, November 2013.

Goda T, Kawahara H, Kubota A, et al. The most reliable early predictors of outcome in patients with biliary atresia after Kasai's operation. J Pediatr Surg 2013;48(12):2373–7.

Harpavat S, Heubi JE, Karpen SJ, et al. Prognostic Value of Serum Bile Acids after Kasai Portoenterostomy in Biliary Atresia. AASLD abstract. Hepatology 2019;68:137.

Hartley JL, Davenport M, Kelly DA. Biliary atresia. Lancet 2009;374:1704–13.

Heinrich S, Georgiev P, Weber A, et al. Partical bile duct ligation in mice: A novel model. Surgery 2011;149:445–51.

Hung P-Y, Chen C-C, Chen W-J, et al. Long-term prognosis of patients with biliary atresia: a 25-year summary. J Pediatr Gastroenterol Nutr 2006;42:190–5.

[redacted]

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data, New York: John Wiley & Sons 1980.

Karrer FM, Price MR, Bensard DD, et al. Long-term results with the Kasai operation for biliary atresia. Arch Surg 1996;131(5):493–6.

Kasai M, Mochizuki I, Ohkohchi N, et al. Surgical limitation for biliary atresia: indication for liver transplantation. J Pediatr Surg 1989;24(9):851–4.

[redacted]

Kilgore A, Mack CA. Update on investigations pertaining to the pathogenesis of biliary atresia. Pediatr Surg Int 2017;33(12):1233–41.

[redacted]

Kiriyama S, Kozaka K, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci 2018;25:17-30.

[redacted]

Mack CL, Spino C, Alonso EM, et al. A Phase I/IIa Trial of Intravenous Immunoglobulin Following Portoenterostomy in Biliary Atresia. J Pediatr Gastroenterol Nutr 2019;68:495-501.

[redacted]

McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. Lancet 2000;355:25–9.

Mehl A, Bohorquez H, Serrano, MS, et al. Liver transplantation and the management of progressive familial intrahepatic cholestasis in children. World J Transplant 2016;6:278–90.

[redacted]

Monte MJ, Marin JJ, Antelo A, Vazquez-Tato J. Bile acids: chemistry, physiology, and pathophysiology. World J Gastroenterol 2009;15:804–16.

Neimark E, Chen F, Li X, et al. Bile acid-induced negative feedback regulation of the human ileal bile acid transporter. Hepatology 2004;40:149–56.

[redacted]

Nightingale S, Stormon MO, O'Loughlin EV, et al. Early posthepatoportoenterostomy predictors of native liver survival in biliary atresia. J Pediatr Gastroenterol Nutr 2017;64:203–9.

[redacted]

Pakarinen MP, Johansen LS, Svensson JF, et al. Outcomes of biliary atresia in the Nordic countries - a multicenter study of 158 patients during 2005-2016. J Pediatr Surg 2018;53:1509–15.

Ratitch B, O'Kelly M. Implementation of pattern-mixture models using standard SAS/STAT Procedures. Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group), SP04, Nashville. 2011.

Sanchez-Valle A, Kassira N, Varela VC, et al. Biliary atresia: epidemiology, genetics, clinical update, and public health perspective. Adv Pediatr 2017;64:285–305.

Schafer JL. Analysis of Incomplete Multivariate Data. New York: Chapman & Hall. 1997.

Shneider BL, Magee JC, Karpen SJ, et al. Total serum bilirubin within 3 months of hepatoportoenterostomy predicts short-term outcomes in biliary atresia. J Pediatr 2016;170:211-7.e1–2.

Shneider BL, Magee JC, Bezerra JA, et al. Efficacy of fat-soluble vitamin supplementation in infants with biliary atresia. Pediatrics 2012;130:607–14.

Shneider BL, Brown MB, Haber B, et al. A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000. J Pediatr 2006;148:467–74.

[redacted]

van Wessel DBE, Thompson RJ, Gonzales E, et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. J Hepatol 2020;73:84–93.

[redacted]

[redacted]
.

Verkade HJ, Bezerra JA, Davenport M, et al. Biliary atresia and other cholestatic childhood diseases: Advances and future challenges. J Hepatol 2016;65:631–42.

Wehrman A, Waisbourd-Zinman O, Wells RG. Recent advances in understanding biliary atresia. FICCO Res 2019. https://doi.org/10.12688/f1000research.16732.1.

Whitington PF, Whitington GL. Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. Gastroenterology. 1988;95:130–6.

Wildhaber BE, Majno P, Mayr J, et al. Biliary atresia: Swiss national study, 1994-2004. J Pediatr Gastroenterol Nutr 2008;46:299–307.

[redacted]

Wong ZH, Davenport M. What happens after Kasai for biliary atresia? A European multicenter survey. Eur J Pediatr Surg 2019;29:1–6.

Appendix 1 [redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted]

Appendix 2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 3 List of Potential Laboratory Analytes

CBC with Differential [a]	**Clinical Chemistry** [b]	**Cholestasis Biomarkers** [d, b]	**Urinalysis** [c]
Hematocrit	Albumin	Total serum bile acids	pH
Hemoglobin	ALP	[redacted]	Specific gravity
MCV, MCH, MCHC	Amylase		Protein
Red blood cells	ALT		Glucose
Platelets	AST	**Lipid Soluble Vitamins** [d]	Ketones
White blood cells	Bicarbonate	25-hydroxy vitamin D	Bilirubin
WBC differential (% and absolute)	Bilirubin, indirect (unconjugated)	Retinol/Vitamin A	Occult blood and cells
Neutrophils	Bilirubin, direct (conjugated)	Retinol-binding protein[e]	Nitrite
Eosinophils	Total serum bilirubin	α-Tocopherol/Vitamin E	Urobilinogen
Basophils	Blood urea nitrogen	Vitamin K [f]	Leukocyte esterase
Lymphocytes	Calcium		Microscopic examination
Monocytes	Chloride	**Lipid panel**	Oxalate
Reticulocyte count	Creatinine	Total cholesterol	Creatinine
Red blood cell morphology	GGT	LDL-C (direct)	Microscopy
Coagulation [a]	Glucose	HDL-C	
aPTT	Lipase	Triglycerides	**Maralixibat Levels (PK)**
INR	LDH		Maralixibat in plasma
PT	Phosphate		
	Potassium		**Other** [c]
	Sodium		HAV IgM
	Total protein		HBsAg
	Uric acid		HCV Ab
	Measured serum osmolality [c]		HCV RNA
	[redacted]		CMV IgM
			EBV Ab
			AFP
			CRP

[redacted] AFP=alpha-fetoprotein; ALP=alkaline phosphatase; aPTT=activated partial thromboplastin time; CBC=complete blood count; CMV=cytomegalovirus; CRP=C-reactive protein; GGT=γ-glutamyltransferase; HBsAG=hepatitis B surface antigen; HCV=hepatitis C virus; HDL-C=high-density lipoprotein cholesterol; LDH=lactate dehydrogenase; LDL-C=low-density lipoprotein cholesterol; PT=prothrombin time; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; [redacted] PK=pharmacokinetic; WBC=white blood cell.

[a] CBC and coagulation may be collected from those performed as part of standard of care/local laboratory if blood is drawn within 3 days of the clinic visit. In such case, the investigator or designee will be asked to provide the reference ranges as applicable.

[b] Clinical chemistry and serum bile acid samples must always be sent to the central laboratory.

[c] Performed when clinically indicated.

[d] Blood samples for the analysis of cholestasis biomarkers and lipid soluble vitamins should be drawn prior to administration of vitamin supplementation and as much as is possible, approximately 2 hours after food or formula (water intake is permitted if necessary but not recommended). Other biomarkers (e.g., lysophosphatidic acid) may be measured. At the discretion of the sponsor, samples will be collected and appropriately stored for subsequent analysis, as needed.

[e] Performed when clinically indicated or if clinically significant low serum retinol levels.

[f] Performed when clinically indicated or if clinically significant abnormal INR.

Appendix 4 Management of Clinical Study Procedures and Participants During COVID-19 Pandemic or Other Force Majeure

This appendix provides guidance for participant safety and ongoing access to medical care

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 5 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 6

[redacted]

[redacted]

Document Approvals

Approved Date: 10 May 2023

Approval Task Verdict: Approve	[redacted] 09-May-2023 21:44:55 GMT+0000
Approval Task Verdict: Approve	[redacted] 10-May-2023 12:39:40 GMT+0000

[redacted]