PROTOCOL: MRX-800

TITLE:	MRX-800: A Long-Term Safety Study of Maralixibat, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study
SHORT TITLE:	**MERGE: M**aralixibat **E**xtension Safety Study P**R**ovidin**G** Long-t**E**rm Treatment to Subjects with Cholestatic Liver Disease
DRUG:	Maralixibat (formerly SHP625 or LUM001)
IND:	119916; 119917; 147617
EudraCT:	2019-002755-42
Phase:	2
SPONSOR:	Mirum Pharmaceuticals Inc. 950 Tower Lane Foster City, CA 94404
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted]
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, STE 150 Box 13608 Research Triangle Park, NC 27709
PROTOCOL: HISTORY:	Amendment 3 (Global), 12 Nov 2020 Amendment 2 (Europe), 09 Dec 2019 Amendment 1 (Europe), 18 Nov 2019 Original Protocol, Version 1.0, 13 Sep 2019

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

PROTOCOL SIGNATURE PAGE

Sponsor's (Mirum) Approval

[redacted]	**Date:** November 16 2020
[redacted] Medical Director	

Investigator's Acknowledgement

I have read this protocol for Mirum Pharmaceuticals, Inc. Study MRX-800.

Title: A Long-Term Safety Study of Maralixibat, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study

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 subject to obtain their consent (and/or assent when appropriate) 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 Harmonization 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:** _____

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PROTOCOL SYNOPSIS

PRODUCT NAME/NUMBER	Maralixibat
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PROTOCOL TITLE	A Long-Term Safety Study of Maralixibat, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor, in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study **MERGE: M**aralixibat **E**xtension Safety Study P**R**ovidin**G** Long-t**E**rm Treatment to Subjects with Cholestatic Liver Disease
INDICATION	Subjects with cholestatic liver disease including, but not limited to, Alagille syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), and biliary atresia
OBJECTIVES	The primary objective of the study is to: • Evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS, PFIC, and biliary atresia Secondary objectives of the study are to: • Evaluate the long-term effect of maralixibat on pruritus • Evaluate the long-term effect of maralixibat on serum bile acid (sBA) levels • Evaluate the long-term effect of maralixibat on total serum bilirubin • [redacted] • Evaluate the long-term effects of maralixibat on growth [redacted]

RATIONALE	ALGS is an inherited cholestatic liver disease in children. In patients with ALGS, impairment of the egress of bile acids from the liver leads to cholestasis, hepatocellular injury and damage, and progressive liver disease that may ultimately lead to the need for liver transplantation. Itch (pruritus) is the archetypal symptom of cholestasis, occurring at all stages of cholestatic liver disease, with or without jaundice. Although surgical interruption of the enterohepatic circulation has been successfully employed in the treatment of cholestasis and hypercholesterolemia in ALGS, the management of cholestasis in ALGS remains largely supportive at this time. PFIC is a rare autosomal recessive liver disorder characterized by intrahepatic cholestasis due to canalicular bile transport defects. Progressive familial intrahepatic cholestasis is associated with early mortality, morbidity, and devastating consequences on patients' quality of life. There is currently no treatment approved for PFIC and available medical approaches have limited efficacy. Surgical interruption of the enterohepatic circulation in children with cholestatic liver disease has been shown to be beneficial. However, complications do occur, and many patients and their families are reluctant to accept a permanent external ostomy in spite of the expected benefits. Pharmacological diversion of bile acids to the distal gut with an apical sodium-dependent bile acid transporter inhibitor (ASBTi)/ileal bile acid transporter inhibitor (IBATi) such as maralixibat could be an attractive alternative to surgical intervention in ALGS and PFIC. Biliary atresia 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 biliary atresia 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 extra-hepatic 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, though HPE frequently improves the signs and symptoms of biliary atresia, 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 biliary atresia the leading cause of pediatric liver transplantation worldwide. There is currently no approved pharmacological treatment for biliary atresia, and available medical approaches have limited efficacy. The nonclinical and clinical data provide a strong scientific rationale for the use of maralixibat in biliary atresia, suggesting that a reduction in sBA levels in this patient population may lead to improvements in cholestatic liver disease and ultimately prolonged native liver survival, similar to the treatment benefits observed in other pediatric cholestatic indications. The MRX-800 study is designed to evaluate the long-term safety and effect of maralixibat on relevant serum markers of the disease (ALT, bilirubin, and sBA), pruritus, [redacted], and growth parameters. The current study will also [redacted].

	Based on the high unmet medical need, the current absence of approved pharmacological therapy, the complications with surgical treatment options, the overall benign safety profile, and unabsorbed nature of maralixibat, the positive benefit-risk ratio is considered supportive of the MRX-800 study. The MRX-800 study aims to provide long-term access to maralixibat, particularly to those subjects who benefited from the treatment in previous studies.
STUDY DESIGN	This is a multicenter, open-label study of maralixibat in subjects diagnosed with cholestatic liver disease (including, but not limited to ALGS, PFIC, or biliary atresia) who have previously participated in a maralixibat clinical study. Subjects with other cholestatic liver diseases who have completed a maralixibat study may be enrolled at the discretion of the Sponsor. All subjects will receive maralixibat in this study. All study subjects rolling over into MRX-800 will have been on maralixibat treatment in a prior study. For subjects who enroll in new, placebo-controlled studies with maralixibat, a separate, more closely monitored, open-label study or open-label extension will have to be completed by each study subject prior to enrolling in MRX-800. Previous participation is defined as: • Having completed the End of Treatment (EOT) Visit, for subjects coming from the maralixibat Phase 2 studies (LUM001-303, LUM001-304, and LUM001--305 in ALGS and LUM001-501 in PFIC) • Having completed the entire duration of the study (i.e., core and extension, if applicable), for subjects coming from other maralixibat studies (e.g., MRX-503, MRX-701, and other open-label maralixibat studies) • Previously early terminated from a maralixibat study for reasons other than safety, and received permission from the Medical Monitor to enroll, after completing all screening procedures and confirmation of eligibility • Having reached the stable-dose phase of maralixibat in the open-label extension of a previous study and are ≥1 year of age [redacted] MRX-800 Screening Visit 0/Day 0. It is recommended that the option to participate in the MRX-800 study is presented [redacted]. This will allow the subjects sufficient time to ask questions, arrive at an informed decision on whether or not he/she would like to participate in the MRX-800 study, and prepare for [redacted] MRX-800 Screening Visit 0/Day 0 as per the instructions by the Investigator and site staff. In certain cases where it is not possible [redacted] MRX-800 Screening Visit 0/Day 0 [redacted] is permitted in between these visits. Results from specific assessments done [redacted] for the MRX-800 Screening Visit 0/Day 0. Screening for MRX-800 more than [redacted] since [redacted] can only be considered after discussion with the Medical Monitor. After obtaining informed consent (and/or assent when appropriate), the subjects will enter the MRX-800 study and will be dispensed maralixibat at the dose closest to that of their previous study. Any reduction in dose (or QD dosing, if needed) and re-challenge will be based on safety and/or tolerability and as per the Investigator's discretion. The Medical Monitor should be informed about such dose reductions and

	re-challenges. Subjects that interrupt dosing for safety/tolerability or other reasons may re-initiate dosing, but only after discussion with the Medical Monitor. The Investigator can request to increase the dose for his or her subject(s) to improve the treatment response (e.g., sBA levels or pruritus). After approval by the medical monitor and if study drug supply is available, the Investigator can increase the dose up to a maximum of 450 µg/kg QD for subjects with ALGS [redacted] nd up to 600 µg/kg BID for subjects with PFIC or biliary atresia [redacted] Those subjects with ALGS who started Study MRX-800 on the dose of 450 µg/kg BID can continue with the same dose. The schedule of the dose increase for any subject will be discussed between the Investigator and the Medical Monitor, and the Investigator will contact the subject after the first week on the increased dose to verify safety and tolerability.
Number of Subjects	Subjects who previously participated in a maralixibat study will be enrolled in Study MRX-800.
Study Population	<u>Inclusion and Exclusion Criteria</u> Subjects will need to meet all criteria below to be considered eligible for the study. 1. Provide informed consent and assent (as applicable) per the Institutional Review Board/Ethics Committee (IRB/EC). 2. Previously participated in a maralixibat study and with approval of the Medical Monitor. Previous participation is defined as: • Having completed the EOT Visit, for subjects coming from the maralixibat Phase 2 studies (LUM001-303, LUM001-304, and LUM001-305 in ALGS and LUM001-501 in PFIC). • Having completed the entire duration of the study (i.e., core and extension, if applicable), for subjects coming from other maralixibat studies (e.g., MRX-503, MRX-701, or other open-label maralixibat studies). • Previously early terminated from a maralixibat study for reasons other than safety, and received permission from the Medical Monitor to enroll, after completing all screening procedures and confirmation of eligibility • Having reached the stable-dose phase of maralixibat in the open-label extension of a previous study and are ≥1 year of age 3. At least 1 year of age 4. Males, and females of non-childbearing potential. Males and non-pregnant, non-lactating females of childbearing potential who are sexually active must agree to use acceptable contraception during the study and [redacted] following the last dose of the study medication. Females of childbearing potential must have a negative pregnancy test. 5. Caregivers (and/or age appropriate subjects) must have access to email or phone for scheduled remote visits if applicable. 6. Subject and caregiver willingness to comply with all study visits and requirements.

	Exclusion Criteria A subject will be excluded from the study if any of the following exclusion criteria are met: 1. Experienced an adverse event (AE) or serious adverse event (SAE) related to maralixibat during the lead-in protocol that led to permanent discontinuation of the subject from maralixibat. 2. Any conditions or abnormalities (including laboratory abnormalities) which, in the opinion of the Investigator or Medical Monitor may compromise the safety of the subject or interfere with the subject participating in or completing the study. 3. History of non-adherence to medical regimens, unreliability, medical condition, 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 subject, or lead to nonadherence with the study protocol or inability to conduct the study procedures.
Treatment Groups	The initial MRX-800 dose will be the dose closest to the dose subjects were receiving in their lead-in/previous study, rounded up. The ALGS and PFIC Phase 2 studies had slightly different dose levels than MRX-800. In subject-specific cases, at the discretion of the Investigator, the dose closest to that of the previous study rounded down may be used. The Investigator can request to increase the dose for his or her subject(s) to improve the treatment response (e.g., sBA levels or pruritus). After approval by the medical monitor and if study drug supply is available, the Investigator can increase the dose up to a maximum of 450 µg/kg QD for subjects with ALGS [redacted] and up to 600 µg/kg BID for subjects with PFIC [redacted] Those subjects with ALGS who started Study MRX-800 on the dose of 450 µg/kg BID can continue with the same dose.
Study Drug Dosage and Administration	Subjects will receive ready-to-use maralixibat oral solution based on their individual body weight. Fixed concentrations of maralixibat oral solutions (i.e., [redacted]) will be used. To accurately measure the required volume, 0.5-, 1.0-, and 3.0-mL sized oral dosing dispensers will be provided. The initial dose of maralixibat that will be dispensed to subjects in MRX-800 is the dose closest to the dose subjects were receiving in their lead-in/previous study (rounded up). In subject specific cases, at the discretion of the Investigator, the dose closest to that of the previous study rounded down may be used. The sample daily exposure (mg/day) to maralixibat, [redacted] across the proposed target dose levels for subjects ranging in weight from 5 to 70 kg is provided below. [redacted]. Investigators can increase dosing up to 450 µg/kg QD for subjects with ALGS [redacted] and up to 600 µg/kg BID for subjects with PFIC [redacted] if judged by the Investigator to be beneficial to the subject, and after consultation with the medical monitor. Those subjects with ALGS who started Study MRX-800 on the dose of 450 µg/kg BID can continue with the same dose.

Sample Daily Exposure (mg/day) for Subjects – BID[a]

Weight (kg)	Daily Exposure of Maralixibat (mg)			
	[redacted]	[redacted]	(450 µg/kg - BID)	(600 µg/kg - BID)
5			4.5	6.0
10			9.0	12.0
20			18.0	24.0
30			27.0	36.0
40			36.0	48.0
50			45.0	60.0
60			54.0	72.0
70			63.0	84.0

BID=twice daily dosing; PFIC=progressive familial intrahepatic cholestasis.

[redacted]

[b] Subjects with PFIC [redacted]

The following table shows the recommended dose for the MRX-800 study, based on the dose administered in subjects' lead-in/previous study:

Dosing Table for Study MRX-800

Dose in Previous Study (µg/kg/day)	Frequency	Recommended Dose MRX-800 (µg/kg/day)
[redacted]		
	BID	450/450 (900 total)
	BID	600/600 (1200 total)

BID=twice daily dosing.

Note: For studies that used the commercial maralixibat formulation, subjects will roll over to the same dose they were receiving in the previous study (i.e., up to 600 µg/kg BID).

It is recommended that subjects who were on [redacted] in their previous maralixibat study will be administered (or will self-administer, as appropriate) the first dose of the MRX-800 study medication on [redacted]. For those on [redacted], it is recommended that they be administered (or will self-administer, as appropriate) the first dose of the MRX-800 study medication [redacted].

	The schedule of the dose increase for any subject will be discussed between the Investigator and the Medical Monitor, and the Investigator will contact the subject after the first week on the increased dose to assess for safety and tolerability. A dose may be increased only in the absence of major safety (e.g., liver parameters) or tolerability (e.g., GI-related TEAEs) concerns related or possibly related to study medication. As much as possible, the morning dose should be administered approximately 30 minutes before breakfast and, if applicable, the evening dose approximately 30 minutes before the main evening meal. The doses will be administered prior to meals rather than every 12 hours to better cover the luminal bile acid release associated with meals. The study medication should be administered approximately at the same time each day throughout the study. To accurately measure the required volume, 0.5-, 1.0-, and 3.0-mL sized oral dosing dispensers will be provided. The investigational product requires refrigerated storage conditions (2°C–8°C).
Study Visit Schedule and Procedures	Participation in this study starts when the informed consent (and/or assent when appropriate) is signed. After obtaining informed consent (and/or assent when appropriate), the subject will be screened. The Screening Visit 0/Day 0 will [redacted]. The initial dose of maralixibat that will be dispensed to subjects in MRX-800 is the dose closest to the dose subjects were receiving in their lead-in/previous study (rounded up). In subject-specific cases, at the discretion of the Investigator, the dose closest to that of the previous study rounded down may be used. At [redacted], the Investigator or designee will contact subjects (email or phone call) during which the use of the new maralixibat formulation (for those subjects who entered from the ALGS – PFIC Phase 2 program), the concomitant treatments, and AEs will be reviewed. Subjects will return to the site [redacted] and the following assessments and procedures will be done: symptom directed physical examination and vital signs (including height and weight), blood for clinical laboratory testing, including safety labs, fasting lipid panel, serum bile acids, and determination of fat-soluble vitamins. In addition, subjects and caregivers will be instructed to [redacted] A liver ultrasound/magnetic resonance imaging (MRI) scan will be done starting from [redacted]. For subjects with biliary atresia, the following additional procedures will be performed: [redacted]

	Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing maralixibat. A positive urine pregnancy test result requires a subject to undergo a serum β-HCG pregnancy test. Results of the pregnancy test must be reviewed prior to dispensing study medication. Maralixibat compliance will be assessed, and the study medication will be dispensed upon completion of other study procedures. Information on concomitant treatments/medications, any adverse events, healthcare utilization and caregiver burden will be collected. Subjects, their caregivers, and/or their family doctor/primary care physician will be contacted by the Investigator and/or designee to obtain information on how the subject's disease has progressed and whether the subject has had PEBD surgery or has been listed for, or had a liver transplant or any other procedure relevant to the management of the subject's cholestatic liver disease (i.e., PEBD, cholecystostomy tube, ileal exclusion, liver transplant, or listed for liver transplant, other). Any increase in concomitant medications or introduction of new medication for the treatment of pruritus and/or cholestatic liver disease will also be collected. [redacted] Participation in the study will continue until the study is terminated, at the discretion of the sponsor.
STATISTICAL METHODS	Analysis Population Because this is a long-term safety study there will be only one analysis population. The Safety Population is defined as all subjects who enrolled and received at least 1 dose of maralixibat during the MRX-800 study. Statistical Methodology [redacted] Baseline Study baseline will be defined for this study as Screening Visit 0/Day 0. [redacted] Safety and Tolerability Analyses All safety analyses will be performed on the Safety Population, defined as all subjects who were screened and received at least 1 dose of maralixibat in MRX-800. Analyses will be conducted overall and by disease group. <u>Safety Endpoints</u>

The following safety and tolerability endpoints will be assessed:

- AEs including serious, non-serious, related, non-related AEs
- Clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate)
- Vital signs (temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, weight and height assessments)
- Physical examination
- Concomitant treatment/medication usage
- [redacted]

A Data Monitoring Committee will review safety and study data at specified intervals for the duration of the study.

Efficacy Analyses

All efficacy measures will be analyzed using the Safety Population and summarized by disease group. Change from maralixibat baseline in efficacy measures is of particular interest as the secondary objectives of the study focus on the long-term effect of maralixibat on the outcome measures.

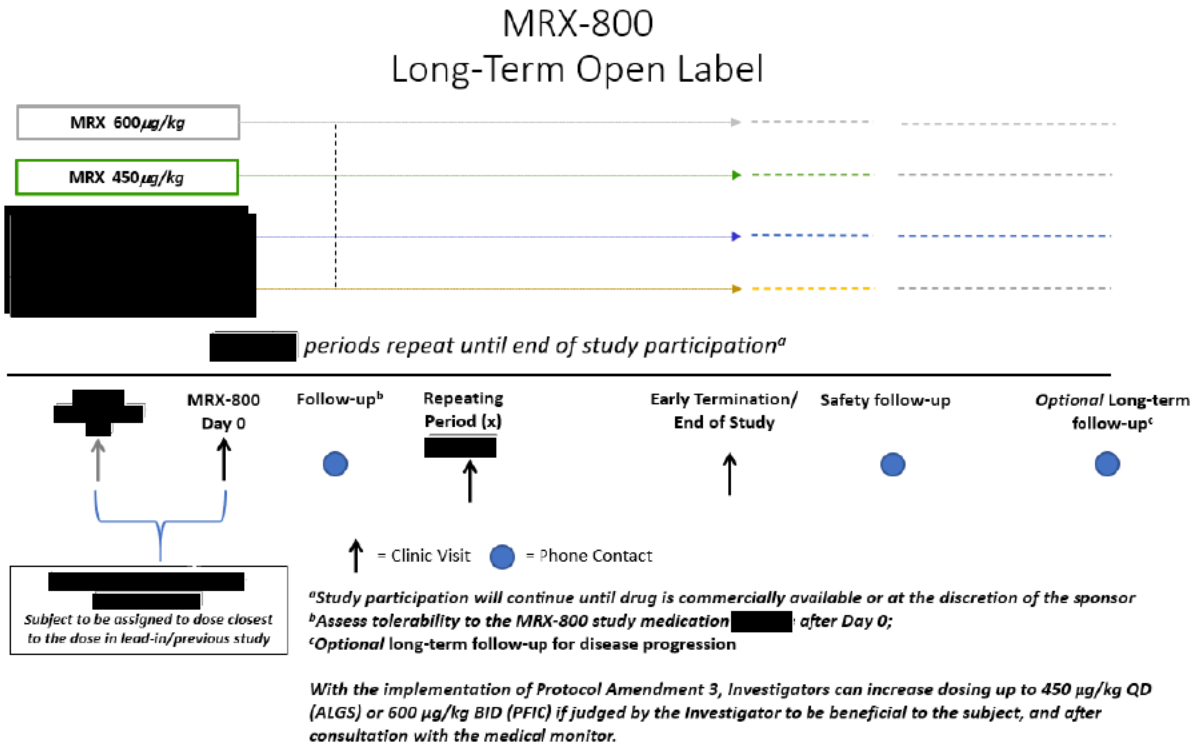
Efficacy Endpoints

The efficacy endpoints are:

- Change from maralixibat baseline over the course of the study in the weekly average morning ItchRO(Obs)™ severity score (ALGS and PFIC)
- [redacted]
- Change from maralixibat baseline over the course of the study in the Clinician Scratch Scale score
- Change from maralixibat baseline over the course of the study in sBA levels
- Change from maralixibat baseline over the course of the study in mean total serum bilirubin

[redacted]

	• Change from maralixibat baseline in height and weight z-score over the course of the study [redacted] [redacted] <u>Additional Analyses</u> Because this is an open-label study, additional analyses may be performed to explore both safety and efficacy measures collected in this study. All such analyses will be interpreted cautiously and not used for formal inference, although inferential statistics may be used as part of the data summary.
SAMPLE SIZE DETERMINATION	Subjects meeting the study's inclusion and exclusion criteria will be enrolled in the study. Because this is an extension study for subjects enrolled under previous protocols, the sample size is not based on statistical considerations.



BID=twice daily; EOT=end of treatement; MRX=maralixibat; MRX-800=Study MRX-800.

ABBREVIATIONS

7αC4	7α-hydroxy-4-cholesten-3-one
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
APRI	AST to platelet ratio index
ASBT	apical sodium-dependent bile acid transporter
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase
ATP	adenosine triphosphate
β-hCG	beta-human chorionic gonadotropin
BID	twice daily (dosing)
CBC	complete blood count
CFMB	change from maralixibat baseline
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CSS	Clinician Scratch Scale
DMC	data monitoring committee
EOT	end of treatment
ET	early termination
FGF-19	fibroblast growth factor-19
FIB-4	fibrosis-4
GI	gastrointestinal
GGT	gamma-glutamyl transferase
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
HPE	hepatoportoenterostomy
IB	Investigator's Brochure
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology

ItchRO™	Itch-Reported Outcome
ItchRO(Obs)™	Observer-reported Itch-Reported Outcome Instrument
[redacted]	[redacted]
LDL-C	low density lipoprotein cholesterol
[redacted]	[redacted]
[redacted]	[redacted]
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PEBD	partial external biliary diversion
[redacted]	[redacted]
PFIC	progressive familial intrahepatic cholestasis
PIS	Patient Impression of Severity
PK	pharmacokinetics
PT	prothrombin time
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acids
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TJP2	tight junction protein 2 gene
TSB	total serum bilirubin
ULN	upper limit of normal

Table 1 Schedule of Assessments

Procedures	Screening [a]	Treatment Period[b]		End of Treatment/ Early Termination	Safety Follow-Up	Long-term Follow Up[c]
Visit/Subject Contact #	**Screening / V0**	**Subject contact**	**[redacted] Repeating Cycle Visit**	**Visit[d]**	**Subject contact**	**Subject contact**
Study Week	[redacted]	[redacted]	[redacted]			
Study Day	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Window (in days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed consent/assent	X			X[c]		
Eligibility assessment	X					
Physical exam & vital signs (including height and weight)[e]	X[f]		X	X		
[redacted]			X	X		
[redacted]			X	X		
Serum and Urine Pregnancy Test[i]	X (urine)		X (urine)	X (serum)		
ItchRO™ questionnaire[j]			X	X		
[redacted]			X	X		
[redacted]			X	X		
[redacted]			X	X		
Clinician Scratch Scale			X	X		
CBC with differential	X[f]		X	X		
Coagulation	X[f]		X	X		
Chemistry panel	X[f]		X	X		
Urinalysis	X[f]		X	X		
Lipid panel[n,o]	X[f]		X	X		
sBA collection[n]	X[f]		X	X		
Lipid-soluble vitamins[o]	X[f]		X	X		

Procedures	Screening [a]	Treatment Period[b]		End of Treatment/ Early Termination	Safety Follow-Up	Long-term Follow Up[c]
Visit/Subject Contact #	**Screening / V0**	**Subject contact**	**Repeating Cycle Visit**	**Visit[d]**	**Subject contact**	**Subject contact**
Study Week	[redacted]	[redacted]	[redacted]			
Study Day	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Window (in days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFP sample	X[f]		X	X		
Serum storage sample[o,p]			X	X		
Healthcare utilization	X[q]		X	X	X	
Study medication supplied[r]	X		X			
Study medication administration[s]	X	X	X			
Assess AEs	X[t]	X[u]	X	X	X	
Prior and concomitant treatments	X[t]	X[u]	X	X	X	
Disease-related event questionnaire						X[c]
Liver imaging[v]			X	X		

AFP=alpha-fetoprotein; ALGS=Alagille syndrome; BID=twice daily dosing; 7αC4=7a-hydroxy-4-cholesten-3-one; CBC=complete blood count; EOT=end of treatment; ET=early termination; FGF- 9=fibroblast growth factor-19; ItchRO™=Itch-Reported Outcome; MRI=magnetic resonance imaging; [redacted] PFIC=progressive familial intrahepatic cholestasis.

[a] Screening Visit 0/Day 0 [redacted] In certain cases where it is not possible for [redacted] MRX-800 Screening Visit 0/Day 0 [redacted]. Screen failure subjects may be re-screened but only after discussing with the Medical Monitor. Re-screening may occur within [redacted].

[b] Subjects will continue treatment until the study is terminated by the sponsor.

[c] Option to participate in the long-term follow-up period will be presented at the EOT/ET Visit. Subjects who provide consent or assent (as appropriate) will be followed up [redacted] to check disease progression.

[d] Assessments listed under the EOT/ET Visit do not need to be repeated if the visit occurs within [redacted] of a previous clinic visit (unless otherwise specified e.g., pregnancy test).

[e] Physical examination includes specific assessments for signs of hepatomegaly, splenomegaly, edema, ascites, jaundice, and scleral icterus. Vital signs include blood pressure, heart rate, temperature, respiration rate. Height and weight will be measured by trained staff using standardized methodology, incl. calibrated stadiometer or headboard and calibrated balance, respectively.

[f] [redacted] MRX-800 Screening Visit 0/Day 0. Retests are needed if results are [redacted] prior to the MRX-800 Screening Visit 0/Day 0. Any missing exams should be performed at [redacted], other than AFP.

[g] [redacted]

[h] [redacted]

[i] Females of childbearing potential only. If available, the subject's [redacted] will be used at Screening Visit 0/Day 0. Otherwise, a urine and serum beta-human chorionic gonadotropin (β-HCG) pregnancy test will be performed. A positive urine pregnancy test result requires a subject to undergo a serum β-HCG pregnancy test. Results of the pregnancy test must be reviewed prior to dispensing study medication.

[j] Caregivers and age-appropriate subjects (only applicable for subjects with ALGS or PFIC) will complete ItchRO™ questionnaires administered as a diary BID for [redacted] after every study visit.

[k] [redacted]

[m] This is only applicable for subjects with ALGS.

[n] Subjects are encouraged to fast at least [redacted] (water intake is permitted if necessary but not recommended) prior to collection.

[o] Blood samples must be drawn before administration of vitamin supplementation.

[p] Possible analysis of FGF-19, autotaxin, 7αC4.

[q] To be done only if not captured at [redacted].

[r] If needed, study medication may be supplied via an unscheduled visit and via direct-to-patient shipments in between visits.

[s] Daily dose to be taken approximately 30 minutes before breakfast. If BID dosing, evening dose should be administered approximately 30 minutes before dinner.

[t] Only new AEs occurring after the subject provides consent or assent (as appropriate) will be collected (see Section 6.1). Ongoing concomitant treatment/medication will be manually entered into the MRX-800 CRF. AEs that were ongoing in the previous study will be copied over by the sites into the MRX-800 CRF.

[u] The Investigator or designee will contact subjects (email or phone call) during which the use of concomitant treatments and AEs will be reviewed.

[v] A liver ultrasound/MRI scan will be done starting from [redacted].

1 INTRODUCTION

1.1 Indication and Current Treatment Options

Alagille syndrome (ALGS) is an inherited cholestatic liver disease in children. In patients with ALGS, impairment of the egress of bile acids from the liver leads to cholestasis, hepatocellular injury and damage, and progressive liver disease that may ultimately lead to the need for liver transplantation. Itch (pruritus) is the archetypal symptom of cholestasis, occurring at all stages of cholestatic liver disease, with or without jaundice.

ALGS is an autosomal dominant multisystem genetic disorder with variable penetration. The clinical diagnosis is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least 3 of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities, and characteristic facial features. Fewer than 200 patients with ALGS are born each year in the United States. The estimated prevalence in the United States is 3 per 100,000. Elevations of serum bilirubin up to 30 times normal and serum bile salts up to 100 times normal are common. Levels of markers of bile duct damage, including gamma-glutamyltransferase (GGTP or GGT) and alkaline phosphatase (ALP), usually are significantly elevated. Cholesterol levels may also be elevated. Multiple xanthomas are common sequelae of severe cholestasis. The pruritus seen in patients with this condition is among the most severe of any chronic liver disease, and it is present in most children by the third year of life. Although surgical interruption of the enterohepatic circulation has been successfully employed in the treatment of cholestasis and hypercholesterolemia in ALGS (Emerick and Whitington, 2002; Modi et al. 2007), the management of cholestasis in ALGS remains largely supportive at this time. As cholestasis tends to improve over the first 5 to 10 years, therapies that ameliorate the complications of cholestasis, without a commitment to liver transplantation, are highly desirable (Emerick et al. 1999).

Progressive familial intrahepatic cholestasis (PFIC) is a rare autosomal recessive liver disorder characterized by intrahepatic cholestasis due to canalicular bile transport defects. There are more than 4 subtypes of PFIC classified based on different mutations. PFIC1, 2, and 3 result from mutations in the adenosine triphosphate (ATP) phospholipid transporting 8B1, ATP binding cassette subfamily B member 11, and ATP binding cassette subfamily B member 4 (*ABCB4*) genes, respectively, and all share the main clinical manifestations of cholestasis and pruritus. PFIC4 is based on mutations in the tight junction protein 2 gene (*TJP2)* and leads to failure of protein localization, disruption of tight-junction structure, and severe cholestatic liver disease (Sambrotta, 2014). In children, PFIC represents 10% to 15% of causes of cholestasis and 10% to 15% of indications for liver transplantation (Davit-Spraul et al. 2009). PFIC2 is the most common subtype and is diagnosed in approximately 50% to 60% of patients with PFIC (Al Mehaidib and Al Shahrani, 2013) while PFIC1 (also known as Byler's disease) and PFIC3 account for approximately 10% to 20% (Alissa et al. 2008; Davit-Spraul et al. 2009) and 30% to 40% of the PFIC population, respectively (Al Mehaidib and Al Shahrani, 2013).

Progressive familial intrahepatic cholestasis is associated with early mortality, morbidity, and devastating consequences on patients' quality of life. In the absence of surgery, PFIC1 and PFIC2 are very aggressive diseases, with only 10% to 15% of PFIC1 and PFIC2 (depending on the variant) patients surviving through the age of 18 (Jericho, 2015). PFIC2 is associated with a continuous progressive course of symptoms (Al Mehaidib and Al Shahrani, 2013). While extrahepatic involvement, such as pancreatitis or diarrhea, can be a feature of PFIC1, the initial presentation and evolution of the disease in PFIC2 tends to be more severe than in PFIC1, with persistent jaundice occurring within the first months of life and rapid progression to cirrhosis and liver failure within the first years of life (Pawlikowska et al. 2010). Interruption of the entero-hepatic circulation of bile acids through partial external biliary diversion (PEBD) surgery can lead to promising results with respect to pruritus, jaundice, and histology, both in patients with PFIC1 and PFIC2. Schukfeh (2012) reported a dramatic 1-year outcome in patients undergoing PEBD with 13/21 (62%) of patients normalizing serum bile acids (sBA) and liver function; however, other groups have reported overall failure rates of PEBD of up to 30%, with 30% to 50% of patients requiring repeat surgery (Halaweish and Chwals 2010). Additionally, PEBD must be performed before liver fibrosis and cirrhosis are established for optimal benefit. For the vast majority of patients who do not undergo PEBD or do not respond, liver transplantation may be the only treatment option (Emerick et al. 2008; Yang et al. 2009; Arnell et al. 2010; Schukfeh et al. 2012).

Biliary atresia 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 biliary atresia 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.

The underlying disease mechanism in biliary atresia involves the mechanical obstruction of the extrahepatic biliary tree and impairment of bile flow, which leads to an ongoing cycle of liver injury due to the accumulation of toxic bile acids and rapidly progressing liver fibrosis, cirrhosis, and portal hypertension. This manifests with increased serum bilirubin and serum bile acids (sBA), as well as increased liver enzymes (Chen et al. 2008; Zhou et al. 2015).

Untreated, the outcome of biliary atresia is uniformly fatal (Karrer et al. 1996). The etiology and pathogenesis of biliary atresia, however, remain largely unknown and are likely multi-factorial (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). Biliary atresia is a recognized orphan disease. Recent biliary atresia 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 biliary atresia 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 extra-hepatic 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 biliary atresia, 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 biliary atresia 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.

Given the clinical outcomes associated with PFIC, ALGS, and biliary atresia, including the negative impact on patients' and caregivers' quality of life and the fact that there are currently no approved treatments, there is a high unmet medical need for a novel treatment for these diseases.

1.2 Product Background and Clinical Information

Maralixibat chloride (formerly SHP625, LUM001) is a potent inhibitor (IC_{50}=0.3 nM) of the apical sodium-dependent bile acid transporter/ileal bile acid transporter/solute carrier family 10 (sodium/bile acid co-transporter family) member 2 (ASBT/IBAT/SLC10A2), a transmembrane protein localized on the luminal surface of ileal enterocytes (hereafter referred to as ASBT). Maralixibat was designed to be minimally absorbed, thereby maximizing the local exposure of the molecule to the receptor, minimizing systemic exposure of the drug, limiting drug-drug interactions, and systemic toxicity. These characteristics include a high molecular weight of 710 Da and the presence of a positively charged quaternary amino moiety that can interact with the negatively charged surface of the enterocyte cell membrane and prevent absorption.

The pharmacokinetics (PK), safety, and efficacy of maralixibat were assessed in a previous clinical development program that evaluated maralixibat as a potential lipid-lowering agent in patients with hypercholesterolemia. The hypercholesterolemia, primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC) programs were terminated by the previous Sponsors for strategic and commercial reasons. Current development efforts are focused on rare pediatric cholestatic liver diseases, including ALGS, PFIC, and biliary atresia.

Maralixibat plasma levels (parent and potential metabolites) after chronic oral administration in adults, adolescents, and children are consistent with a drug that is minimally absorbed. Plasma concentrations, when measured, have been low to undetectable at most time points after oral doses [redacted] These results are consistent with the low absolute bioavailability (≤1%) observed in nonclinical studies with maralixibat and in a clinical study where a dose of 5 mg ^{14}C-maralixibat was administered. These data support the conclusion that maralixibat is minimally absorbed in humans. While the low bioavailability of maralixibat may complicate many classical drug development aspects, such as characterization of PK (C_{max}, $t_{1/2}$, etc.), receptor occupancy, dose ranging and PK-pharmacodynamic (PD) correlation, etc., the potential for systemic adverse interactions with other drugs is expected to be less than for well-absorbed drugs. Drug interaction studies with both lovastatin and simvastatin and with atorvastatin indicated no clinically significant interactions with maralixibat and these statins (both parent and active metabolite).

The previous hypercholesterolemia clinical program comprised 12 studies in which a total of over 1400 adult subjects were exposed to maralixibat. Maralixibat was found to be safe at investigated daily doses up to 100 mg over 28 days and up to 40 mg over 10 weeks. The most commonly reported adverse drug reactions (ADRs) were abdominal cramping/pain and diarrhea/loose stools, which are believed to be mechanism-based due to elevated bile acid concentrations in the colon. The majority of adverse events (AEs) were characterized as mild or moderate in severity, except for severe nausea, diarrhea, or abdominal pain in 6 subjects. Except for a single serious AE (SAE) of cholecystitis reported in 1 study, no other SAEs related to maralixibat have been reported in these studies and no clinically significant laboratory abnormalities were documented in maralixibat-treated subjects.

LUM001-201 was a Phase 2, randomized, double-blind, placebo-controlled study to evaluate maralixibat in combination with UDCA in subjects with PBC. There was no significant difference between overall maralixibat and placebo with respect to change from baseline of Adult Itch-Reported Outcome (ItchRO™) weekly sum score; thus, the primary endpoint was not met. In the analysis of the change from baseline in pruritus (a secondary efficacy endpoint), ItchRO™ weekly sum scores decreased similarly over time in all treatment groups including the placebo treatment group. Mean changes from baseline in Adult ItchRO™ average daily scores at the Week 8, Week 13, and study endpoint were similar in all treatment groups including placebo treatment group. There were no significant changes in 5-D Itch score for overall maralixibat treatment compared to placebo treatment group at any time.

Treatment-related AEs were most frequently reported in the gastrointestinal (GI) disorders System Organ Class (SOC) (30/42 subjects [71.4%] and 10/24 subjects [41.7%] in the overall maralixibat and placebo groups, respectively) and included treatment-emergent adverse events (TEAEs) of diarrhea (23/42 subjects [54.8%]), nausea (7/42 subjects [16.7%]), abdominal pain upper (9/42 subjects [21.4%]), and abdominal pain (7/42 subjects [16.7%]) in the overall maralixibat group.

LUM001-401 was a Phase 2, open-label, single-cohort, pilot study to evaluate safety, tolerability, and efficacy in a population of 27 subjects with PSC of relatively long-standing

(mean [SD] time since original diagnosis was 93.97 months [75.361]). The study endpoint (Week 14/ET) was considered to be the last post-baseline value obtained before or within 7 days of the date of last dose. Analysis of the primary efficacy endpoint was based on the Wilcoxon signed rank test comparing serum bile acid levels at the study endpoint (Week 14/ET) with baseline. Significant reductions from baseline were observed at Week 6 and at study endpoint. However, the study was not powered for determination of statistical significance and further interpretation of these results is limited. The significant reduction in serum bile acid levels were not reflected in improvements in the secondary endpoints of liver function parameters. No significant reductions from baseline ALT, AST, ALP, or total bilirubin were found in paired difference test results; however, an increase in mean direct bilirubin values at study endpoint was noted. The sixth secondary endpoint, reduction in Adult ItchRO™ weekly sum score from baseline values to study endpoint, also was found to be nominally significantly improved from baseline using the paired difference test (p=0.0495).

The majority of TEAEs were mild or moderate in severity (11/27 subjects [40.7%] and 6/27 subjects [22.2%], respectively). Across treatment groups, the most frequently reported TEAEs occurred in the GI disorders SOC (22/27 subjects [81.5%]) and included TEAEs of diarrhea (14/27 subjects [51.9%]), nausea (9/27 subjects [33.3%]), abdominal pain (8/27 subjects [29.6%]), and abdominal distension (4/27 subjects [14.8%]).

More than 119 subjects have been exposed to maralixibat, some for longer than 4 years, in the current pediatric cholestatic liver disease program, which includes completed and ongoing Phase 2 and Phase 3 studies (studies in ALGS, PFIC, and biliary atresia). Consistent with the previous clinical program, the most commonly reported ADRs were abdominal cramping/pain and diarrhea/loose stools, the majority of which were mild or moderate in severity. Related SAEs included abdominal pain, abdominal pain upper, diarrhea, cholangitis, increased blood bilirubin, increased international normalized ratio (INR), pancreatitis, increased alanine aminotransferase (ALT), autoimmune hepatitis, hematochezia, and anemia. No deaths or important new or unexpected risks have been identified to date. A program-wide review of liver safety parameters, including an independent external expert adjudication of selected cases, indicated that maralixibat may cause ALT elevations in a certain percentage (2%–5% probably, 10%–20% probably or possibly related events) of subjects with ALGS, similar to the ALT elevations reported after PEBD surgery in this patient population. No predictors of this treatment response have been identified so far. None of the observed events were serious and none led to liver-related morbidity or mortality. There is no evidence to date that this effect is due to a direct hepatotoxic effect from the minimal amount of maralixibat that is systemically absorbed. The long-term consequences of the observed ALT elevations remain unclear. There is currently no evidence that maralixibat causes bilirubin elevations in patients with ALGS, and there is insufficient evidence of an association between bilirubin or liver enzyme elevations and maralixibat treatment in patients with PFIC.

Clinical data from the Phase 2 study LUM001-304 demonstrated that treatment with 400 µg/kg/day once daily (QD) of maralixibat was associated with a statistically significant improvement in both pruritus scores and reduction of sBA versus placebo at the end of a randomized drug-withdrawal period (Weeks 19 to 22) in which patients were switched to placebo or remained on maralixibat. The protocol-specified primary endpoint of the mean

change from Weeks 18 to 22 of fasting sBA levels in patients who previously responded to maralixibat treatment (defined by a reduction in sBA ≥50% from Baseline to Week 12 or Week 18) showed a statistically significantly difference between the maralixibat group versus the placebo group (p=0.046). In addition, in a pre-specified analysis (referred to as the Week 48 analysis), the change from Week 18 in pruritus as measured by the ItchRO™ weekly morning average scores at Week 22 demonstrated a nominal statistically significant difference between maralixibat vs placebo (p=0.0002), as well as a nominal statistically significant difference in the absolute Week 22 score at the end of the treatment withdrawal period (p=0.0002). Patients treated with placebo experienced a recurrence of their pruritus to near baseline levels, whereas those who continued on maralixibat mostly maintained their reduction in pruritus. A total of 72.4% of subjects experienced an Itch-Reported Outcome Observer (ItchRO[Obs]™) reduction of ≥1.0 point by Week 48, considered to be the threshold for meaningful change.

In the Phase 2 study in subjects with PFIC (LUM001-501), an open-label study of the efficacy and long-term safety of maralixibat in the treatment of cholestatic liver disease in pediatric patients with PFIC, data from the final and posthoc analyses demonstrated significant improvements in a subgroup of 6 out of 19 subjects with non-truncating PFIC2 (nt-PFIC2) at doses of up to 280 µg/kg once daily (QD). A subsequent dose increase to 280 µg/kg twice daily (BID) produced a similar improvement in 1 additional subject with nt-PFIC2 who did not respond to the previous dose regimen. These improvements consisted of normalization or ≥75% decrease in sBA levels, concomitant with an increase in 7α-hydroxy-4-cholesten-3-one (7αC4) levels, a disappearance or clinically meaningful improvement in pruritus, as well as an increase in quality of life scores. Liver-related parameters (aspartate aminotransferase [AST]/ALT and total serum bilirubin [TSB]) were also normalized in those subjects with abnormal baseline values. The treatment responders experienced a significant catch-up growth, as indicated by a positive height and weight z-score change from baseline compared to those subjects who did not respond to maralixibat treatment. The data from Study LUM001-501 demonstrate that all maralixibat participants who achieved the established NAPPED sBA response threshold (defined as sBA threshold of <102 µmol/L or a 75% reduction; van Wessel et al. 2020) remain transplant free, whereas most of those who did not achieve the sBA response criteria eventually received a liver transplantation. The difference between the groups was statistically significant (p=0.0006).

Always refer to the latest version of the Maralixibat Chloride Investigator's Brochure (IB) for the overall benefit-risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of maralixibat.

1.3 Summary of Potential Risks and Benefits

An important therapeutic advantage of maralixibat is its high selectivity for ASBT, the location of ASBT on the luminal surface of the enterocyte, and its limited systemic exposure. In single- and repeat-dose PK studies in rat, rabbit, and dog, the oral bioavailability of maralixibat was < 1% at all doses tested and PK values in clinical studies were at or below the lower level of quantification in the adult and pediatric populations.

The nonclinical safety profile is supported by multiple PD and safety pharmacology, ADME, single-dose toxicity, repeat-dose toxicity, genotoxicity, reproductive toxicity, and juvenile

toxicity studies. Results from PD studies in rats, dogs, and monkeys indicate that selective inhibition of ASBT by maralixibat results in increased fecal bile acid excretion, inhibition of the postprandial rise in serum bile acids, and decrease in serum total cholesterol. No clinically significant changes were observed in rat neurobehavioral, dog cardiovascular, or guinea pig pulmonary function safety pharmacology studies following single oral or IV administration of maralixibat.

The most commonly reported AEs across the previous clinical program of hypercholesterolemia, and the current program of cholestatic liver diseases are in the GI disorders SOC and include abdominal cramping/pain and diarrhea/loose stools. The majority of AEs were mild or moderate in severity. These GI-related AEs are believed to be mechanism-based, due to elevated bile acid concentrations in the colon and therefore are not unexpected. In the completed studies in the cholestatic liver disease clinical program, GI-related AEs have resulted in 3 of the 6 study discontinuations due to AEs to date. Preliminary data from the ongoing studies indicate that 1 subject has discontinued due to a GI-related AE (hematochezia).

To date, a total of 48 subjects across completed and ongoing studies have had an SAE. Related SAEs from the completed studies included abdominal pain and cholangitis. The only related SAEs from the ongoing studies have been blood bilirubin increased, which resulted in withdrawal of the investigational product. The study medication was restarted for the patient with the SAE of blood bilirubin increased. The possibly related SAEs of hematochezia, anemia, and the suspected unexpected serious adverse reaction (SUSAR) of autoimmune hepatitis (preferred term hepatobiliary disease) resulted in withdrawal of the investigational product and study discontinuation. No deaths have been reported.

Results of the LUM001-304 48-week analysis showed a clinically meaningful reduction in pruritus in patients with ALGS. There was a consistent and clearly distinct behavior between the maralixibat and placebo groups, with an increase to near baseline levels in the placebo group when maralixibat was removed, and no material change in ItchRO(Obs)™ in subjects who continued on maralixibat during the randomized drug withdrawal period. Pruritus results corresponded with changes in PD markers such as sBA, 7αC4, and cholesterol. Preliminary data from the long-term extension study LUM001-303 show persistent treatment response over >3 years of treatment.

Results of LUM001-501 final and posthoc analyses showed 6 patients with PFIC2 who demonstrated a resolution or significant reduction of pruritus (ItchRO™ ≥1.0 change from baseline) and serum bile acids (sBA ≥75% change from baseline). A seventh patient was declared a responder after starting BID dosing and doubling the total daily dose. In those responders, bilirubin and aminotransferase levels also normalized in those patients who had elevated values at baseline.

The overall safety, tolerability, and preliminary efficacy of maralixibat in ongoing and completed studies indicate that there is a positive benefit-to-risk profile for the treatment of rare pediatric cholestatic liver diseases.

2 RATIONALE AND OBJECTIVES

2.1 Rationale for the Study

There is currently no approved treatment for PFIC, ALGS, or biliary atresia, and available medical approaches have limited efficacy. Maralixibat is currently being investigated in pediatric patients with ALGS, PFIC, and biliary atresia.

Maralixibat has been studied for the treatment of pruritus in pediatric patients with ALGS, in which lower doses than the planned therapeutic dose of 400 µg/kg/day QD were investigated in 13-week placebo-controlled studies LUM001-301 and LUM001-302. These studies showed trends towards improvement in pruritus and reduction in sBA, as well as an improvement in QoL. Subjects who completed these studies were offered the opportunity to enroll into long-term extension studies, LUM001-305 and LUM001-303, which are both ongoing for >4 years. In study LUM001-304, treatment of ALGS patients with 400 µg/kg/day once daily (QD) of maralixibat was associated with a statistically significant improvement in both pruritus scores and reduction of sBA vs placebo at the end of a randomized drug withdrawal period (Weeks 19 to 22) in which patients were switched to placebo or remained on maralixibat. This study is ongoing in an open-label extension for > 4 years.

Maralixibat was generally safe and well tolerated throughout the clinical development program, including Study LUM001-304. Overall, the safety profile observed for the higher doses of maralixibat (at or above the planned commercial dose of 400 µg/kg/day) has been comparable to that observed at lower doses. Adverse events occurred more commonly in the first 12 months of treatment and reduced with increased duration of exposure over 4 years, which in part may be due to subjects who tolerated the drug and stayed in the study.

Data from the final and post-hoc analyses from the Phase 2 study LUM001-501 in subjects with PFIC show that a subgroup of subjects with PFIC2 experienced clinically significant improvements after maralixibat treatment at 280 µg/kg/day as manifested by a large reduction or normalization of sBA, reduction in pruritus, and normalization of TSB and ALT for those with elevated baseline values. Also, BID dosing (560 µg/kg/day) led to a higher response rate compared with the previously used QD dosing.

There is currently no approved pharmacological treatment for biliary atresia, and available medical approaches (e.g., steroids, immunoglobulins) have limited efficacy. The nonclinical and clinical data outlined above provide a strong scientific rationale for the use of maralixibat in biliary atresia, suggesting that a reduction in sBA levels in this patient population may lead to improvements in cholestatic liver disease and ultimately prolonged native liver survival, similar to the treatment benefits observed in other pediatric cholestatic indications.

Clinical data from ongoing and completed Phase 2 studies in PFIC and ALGS indicate that maralixibat improves signs and symptoms of cholestasis and may improve markers of liver injury and long-term outcome. This includes reductions in sBA, as well as improvements in growth and other measures suggestive of disease modification, such as transplant- or biliary diversion-free survival. In disease states, bile acids have been shown to induce damage and

necrosis in hepatocytes and cholangiocytes. Elevated sBA is associated with increased morbidity and mortality in several cholestatic diseases. A reduction in the levels of serum and hepatic bile acids in patients with biliary atresia is hypothesized to slow liver injury and therefore improve both patient and native liver survival. 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 native liver survival.

Based on the understanding of the mechanism of action of maralixibat 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 biliary atresia. In the short term (<1 year), reductions in both the bile acid pool and markers of liver injury are anticipated, and in the longer term, these may translate into lower total serum bilirubin values. Total serum bilirubin is a prognostic marker for improved longer-term outcomes in patients with biliary atresia, and published data demonstrate that bilirubin levels after HPE are predictive of transplant-free survival (Venkat et al. 2020). Because elevations of bilirubin are associated with worsening of the cholestatic status and liver function, the endpoint will also be assessed in the ALGS and PFIC populations.

The MRX-800 study is designed to evaluate the long-term safety and effect of maralixibat on relevant serum markers of the disease (ALT, bilirubin, and sBA), pruritus, [redacted] and growth parameters. [redacted]

Based on the high unmet medical need, the current absence of approved pharmacological therapy, the complications with surgical treatment options, the overall benign safety profile, and unabsorbed nature of maralixibat, the positive benefit-risk ratio is considered supportive of the MRX-800 study.

The MRX-800 study aims to provide long-term access to maralixibat, particularly to those subjects who benefited from the treatment in previous studies.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is to:

- Evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS, PFIC, and biliary atresia

2.2.2 Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the long-term effect of maralixibat on pruritus
- Evaluate the long-term effect of maralixibat on sBA levels

- Evaluate the long-term effect of maralixibat on total serum bilirubin
- [redacted]
- Evaluate the long-term effects of maralixibat on growth

2.2.3 Exploratory Objectives

The exploratory objectives of the study are to:

- [redacted]

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a multicenter, open-label study of maralixibat in subjects diagnosed with cholestatic liver disease (including, but not limited to ALGS, PFIC, or biliary atresia) who have previously participated in a maralixibat clinical study. Subjects with other cholestatic liver diseases who have completed a maralixibat study may be enrolled at the discretion of the Sponsor. All subjects will receive maralixibat in this study. All study subjects rolling over into MRX-800 will have been on maralixibat treatment in a prior study. For subjects who enroll in new, placebo-controlled studies with maralixibat, a separate, more closely monitored, open-label study or open-label extension will have to be completed by each study subject prior to enrolling in MRX-800.

Previous participation is defined as:

- Having completed the End of Treatment (EOT) Visit, for subjects coming from the maralixibat Phase 2 studies (LUM001-303, LUM001-304, and LUM001-305 in ALGS and LUM001-501 in PFIC)
- Having completed the entire duration of the study (i.e., core and extension, if applicable) for subjects coming from other maralixibat studies (e.g., MRX-503, MRX-701, and other open-label maralixibat studies)
- Previously early terminated from a maralixibat study for reasons other than safety, and received permission from the Medical Monitor to enroll, after completing all screening procedures and confirmation of eligibility

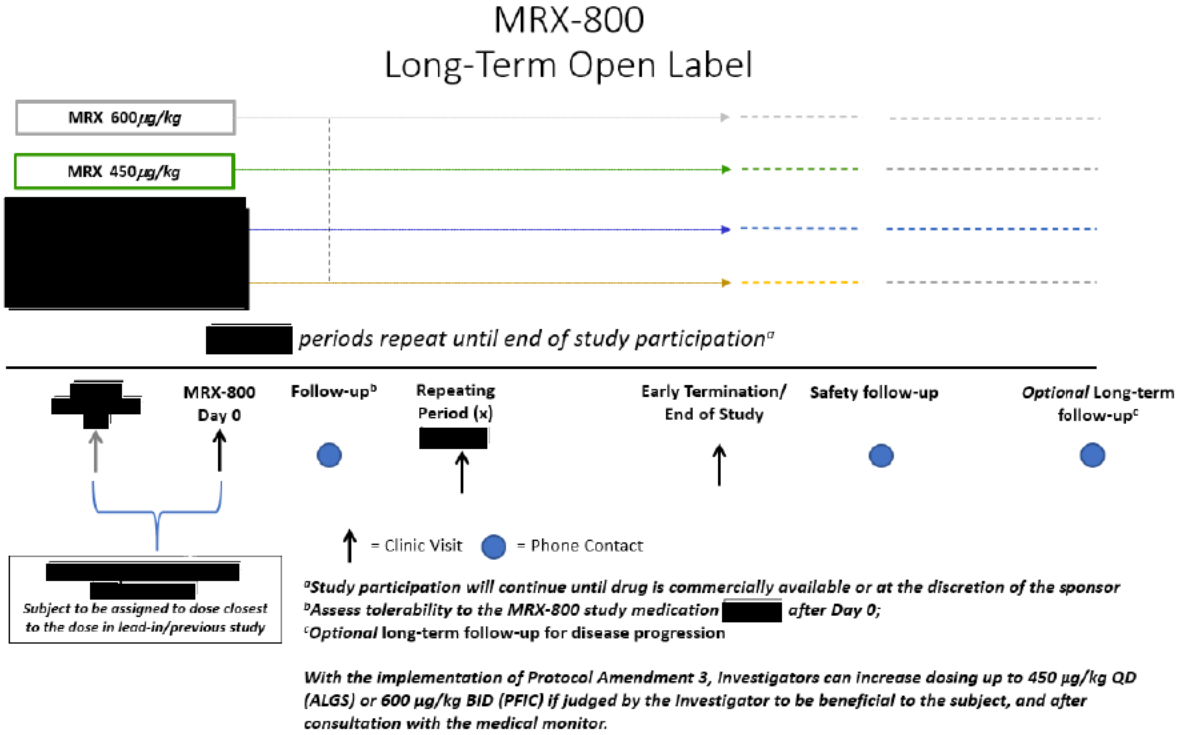
- Having reached the stable-dose phase of maralixibat in the open-label extension of a previous study and are ≥1 year of age

[redacted] MRX-800 Screening Visit 0/Day 0. It is recommended that the option to participate in the MRX-800 study is presented a [redacted]. This will allow the subjects sufficient time to ask questions, arrive at an informed decision on whether or not they would like to participate in the MRX-800 study, and prepare for [redacted] MRX-800 Screening Visit 0/Day 0 as per the instructions by the Investigator and site staff.

In certain cases where it is not possible for [redacted] the MRX-800 Screening Visit 0/Day 0 [redacted]. Results from specific assessments (see Table 1) done [redacted] will be used for the MRX-800 Screening Visit 0/Day 0. Screening for MRX-800 more than [redacted] since [redacted] can only be considered after discussion with the Medical Monitor.

After obtaining informed consent (and/or assent when appropriate), the subjects will enter the MRX-800 study and will be dispensed maralixibat at the dose closest to that of their previous study. Any reduction in dose (or [redacted], if needed) and re-challenge will be based on safety and/or tolerability and as per the Investigator's discretion. The Medical Monitor should be informed about such dose reductions and re-challenges. Subjects who interrupt dosing for safety/tolerability or other reasons may re-initiate dosing, but only after discussion with the Medical Monitor.

Figure 1 Study Design



BID=twice daily; EOT=end of treatement; MRX=maralixibat; MRX-800=Study MRX-800.

3.1.1 Rationale for Treatment

Surgical interruption of the enterohepatic circulation in children with cholestatic liver disease has been shown to be beneficial. However, complications do occur, and many patients and their families are reluctant to accept a permanent external ostomy in spite of the expected benefits. Pharmacological diversion of bile acids to the distal gut with an apical sodium-dependent bile acid transporter inhibitor (ASBTi)/ileal bile acid transporter inhibitor (IBATi) such as maralixibat could be an attractive alternative to surgical intervention in ALGS and PFIC.

There is currently no approved pharmacological treatment for biliary atresia, and available medical approaches have limited efficacy. The nonclinical and clinical data outlined above provide a strong scientific rationale for the use of maralixibat in biliary atresia, suggesting that a reduction in sBA levels in this patient population may lead to improvements in cholestatic liver disease and ultimately prolonged native liver survival, similar to the treatment benefits observed in other pediatric cholestatic indications.

Clinical data from completed Phase 2 studies in PFIC and ALGS indicate that maralixibat improves signs and symptoms of cholestasis and may improve markers of liver injury and long-term outcome. This includes reductions in sBA, as well as improvements in growth and other measures suggestive of disease modification, such as transplant- or biliary diversion-free survival.

The doses used in this study have shown to be generally safe and well tolerated in healthy volunteers, adults and adolescents with hypercholesterolemia, and adults and children with cholestatic liver disease. In Study SHP625-101, a blinded, placebo-controlled, randomized, multiple-dose study in obese adults, bile acid levels in feces increased with escalating doses up to 100 mg QD and 50 mg BID (pediatric equivalent dose of 1400 µg/kg QD and 700 µg/kg BID, respectively) of maralixibat, without any meaningful changes in the safety or tolerability profile. Thus, higher doses of maralixibat might be more efficacious while a BID regimen has the potential to allow for more complete coverage of the distal ileum throughout the day. Therefore, the initial MRX-800 dose will be the dose closest to the dose subjects were receiving in their lead-in/previous study, rounded up. The ALGS and PFIC Phase 2 studies had slightly different dose levels than MRX-800. In subject-specific cases, at the discretion of the Investigator, the dose closest to that of the previous study rounded down may be used.

Investigators can increase dosing up to 450 µg/kg QD for subjects with ALGS [redacted] and up to 600 µg/kg BID for subjects with PFIC [redacted]. Those subjects with ALGS who started Study MRX-800 on the dose of 450 µg/kg BID can continue with the same dose.

The schedule of the dose increase for any subject will be discussed between the Investigator and the medical monitor, and the Investigator will contact the subject after the first week on the increased dose to verify safety and tolerability. A dose may be increased only in the absence of major safety (e.g., liver parameters) or tolerability (e.g., GI-related TEAEs) concerns related or possibly related to study medication (see Section 7.3 for safety monitoring criteria).

Sample daily exposure (mg/day) across proposed target dose levels for subjects ranging in weight from 5 to 70 kg is provided in Table 2. The dosing table for the MRX-800 study is provided in Table 3.

3.1.2 Rationale for Primary Endpoint

The primary endpoint is the long-term safety of maralixibat in subjects with cholestatic liver disease. Subjects who previously participated in a maralixibat study will continue to receive treatment in this study.

These subjects are expected to require life-long treatment and thus, it is considered essential to gather long-term safety data in this vulnerable population. [redacted]

3.1.3 Rationale for Study Population

Subjects who previously participated in a maralixibat study can continue treatment in this study.

3.2 Duration and Study Completion Definition

Subjects will continue to receive maralixibat until termination of the study, at the discretion of the Sponsor. After study completion, each subject will be treated according to standard clinical practice.

The Study Completion Date is defined as the date the final subject, 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 6.1.4 and Table 1), [redacted].

3.3 Sites and Regions

This study will be conducted at globally, at sites in, but not limited to, North America, South America, Australia, Europe, and Asia. Regions may be added as necessary as subjects complete other maralixibat studies. Only sites that have subjects ongoing in a maralixibat Phase 2 or 3 study will be invited to participate.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects will need to meet all criteria below to be considered eligible for the study.

1. Provide informed consent and assent (as applicable) per the Institutional Review Board/Ethics Committee (IRB/EC)

2. Previously participated in a maralixibat study and with approval of the Medical Monitor. Previous participation is defined as:

   - Having completed the EOT Visit, for subjects coming from the maralixibat Phase 2 studies (LUM001-303, LUM001-304, and LUM001-305 in ALGS and LUM001-501 in PFIC)

   - Having completed the entire duration of the study (i.e., core and extension, if applicable), for subjects coming from other maralixibat studies (e.g., MRX-503, MRX-701, or other open-label maralixibat studies)

   - Previously early terminated from a maralixibat study for reasons other than safety, and received permission from the Medical Monitor to enroll, after completing all screening procedures and confirmation of eligibility

   - Having reached the stable-dose phase of maralixibat in the open-label extension of a previous study and are ≥1 year of age

3. At least 1 year of age

4. Males, and females of non-childbearing potential. Males and non-pregnant, non-lactating females of childbearing potential who are sexually active must agree to use acceptable contraception during the study and [redacted] following the last dose of the study medication. Females of childbearing potential must have a negative pregnancy test.

5. Caregivers (and/or age appropriate subjects) must have access to email or phone for scheduled remote visits if applicable

6. Subject and caregiver willingness to comply with all study visits and requirements

4.2 Exclusion Criteria

A subject will be excluded from the study if any of the following exclusion criteria are met:

1. Experienced an AE or SAE related to maralixibat during the lead-in protocol that led to permanent discontinuation of the subject from maralixibat
2. Any conditions or abnormalities (including laboratory abnormalities) which, in the opinion of the Investigator or Medical Monitor may compromise the safety of the subject or interfere with the subject participating in or completing the study
3. History of non-adherence to medical regimens, unreliability, medical condition, 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 subject, or lead to nonadherence with the study protocol or inability to conduct the study procedures

4.3 Reproductive Potential

Local, country-specific guidelines should always be followed where there is regional variation for which methods of contraception are considered acceptable.

4.3.1 Female Contraception

- Females are considered to be of non-childbearing potential if they are premenarchal and either Tanner Stage 1 or less than age 9 years.

- Females of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test [redacted] MRX-800 Screening Visit 0/Day 0), and at every recurring [redacted] clinic visit (see Table 1). If available, the subject's [redacted] β-hCG pregnancy test results will be used for the MRX-800 Screening Visit 0/Day 0. Otherwise, a urine β-hCG pregnancy test will be performed. A positive urine pregnancy test result requires a subject to undergo a serum β-hCG pregnancy test. Results of the pregnancy test must be reviewed prior to dispensing study medication.

- Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or if they are sexually active or become sexually active

during the study, agree to use acceptable methods of contraception, as defined below, throughout the study period and for [redacted] following the last dose of study medication. If hormonal contraceptives are used, they should be administered according to the package insert.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least [redacted] prior to the Screening Visit 0/Day 0, plus condoms. Note: If subject becomes sexually active during the study, he or she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for [redacted].

4.3.2 Male Contraception

Contraception is required for all sexually active male subjects and their partners. All male subjects must agree not to donate sperm, and to use 1 of the following approved methods of contraception until [redacted] following the last dose of study medication:

- Male condom with spermicide
- Intrauterine device with spermicide (use by female sexual partner)
- Female condom with spermicide (use by female sexual partner)
- Contraceptive sponge with spermicide (use by female sexual partner)
- Intravaginal system (e.g., vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide) (use by female sexual partner)
- Oral, implantable, transdermal, or injectable hormonal contraceptive (use by female sexual partner).

4.4 Fasting Requirements

On study visit days at which blood samples are collected for the lipid panel and/or cholestasis biomarkers, subjects are encouraged to fast for [redacted] (water intake is permitted if necessary but not recommended) before blood sample collection (see Table 1). On these visit days, study medication should be administered as usual, in the morning 30 minutes before the normal breakfast time. Only water should be consumed until the scheduled clinic visit.

4.5 Withdrawal/Discontinuation from Study

This is a long-term study, and a subject's participation will continue until the end of the study or at the Sponsor's discretion. Early termination is defined as the discontinuing of any subject's study participation before the end of the study or due to the Sponsor's decision to stop the study.

A subject may withdraw 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. Should a subject decide to withdraw from the study, the Investigator will make every effort to schedule and complete the EOT/ET Visit (Table 1 and Section 6.1.3).

The Investigator or Sponsor may discontinue the subject from the study at any time in case of possibly related or related SAE(s) and may consider discontinuation for poor compliance, AE(s), or other reasons (refer to Section 4.5.1). The Investigator is encouraged to discuss discontinuation of a subject with the Medical Monitor when possible (see Section 7.3.3.2).

Adverse events that in the Investigator's opinion would compromise the subject's ability to safely continue in the study would warrant the subject's discontinuation from the study. The reason for discontinuation must be recorded in the subject's source documents and case report form (CRF). If a subject is discontinued for more than 1 reason, each reason should be documented in the source, and the primary reason for discontinuation should be captured in the CRF.

Subjects who discontinue from the study for safety reasons will be followed-up until resolution of the event or until a final outcome according to the Investigator's discretion.

If subjects discontinue from the study due to disease progression and require PEBD or liver transplant surgery or listing for liver transplant, both the reason for discontinuation and outcome (i.e., PEBD, cholecystostomy tube, ileal exclusion, liver transplant, or listed for liver transplant or other) should be recorded in the subject's source document. If known, the date of the future scheduled procedure should also be recorded. The information regarding PEBD, liver transplant or listing for transplant or other procedure will be collected in the CRF at the time the subject completes/early terminates from the study (EOT/ET) until the completion of their follow-up period. Any dose increase of concomitant medications or introduction of new medication for the treatment of pruritus and/or cholestatic liver disease will also be collected.

The reason for termination and the date of stopping study medication must be recorded in source documents and CRF. The evaluations listed for the EOT/ET Visit are to be performed as completely as possible for any subject who discontinues (See Table 1 and Section 6.1.3).

Subjects, their caregivers, and/or their family doctor/primary care physician will be contacted by the Investigator and/or designee to obtain information on how the subject's disease has progressed and whether the subject has had PEBD surgery or has been listed for, or had a liver transplant or any other procedure relevant to the management of the subject's cholestatic liver disease (i.e., PEBD, cholecystostomy tube, ileal exclusion, liver transplant, or listed for liver

transplant, other). Any increase in concomitant medications or introduction of new medication for the treatment of pruritus and/or cholestatic liver disease will also be collected.

[redacted]

Subjects who discontinue from the study will not be replaced.

4.5.1 Reasons for Discontinuation from Study

Reasons for discontinuation include but are not limited to:

- Death
- Withdrawal of subject/parent/guardian consent or assent (e.g., due to ineffective therapy in case of deterioration)
- Occurrence of a disease that interferes with the study treatment or represents an exclusion criterion
- Non-compliance with study procedures as judged by the Investigator or the Medical Monitor
- Investigator's opinion that the subject may be severely harmed if he/she continues trial participation, namely by the treatment and procedures according to the study protocol
- Adverse event
- Lost to follow-up
- Pregnancy (pregnant subjects will be immediately excluded from the study)
- Need for PEBD surgery, liver transplant, or listing for liver transplant
- Disease progression that in the opinion of the Investigator is due to the disease itself and not due to medications or other factors.

4.5.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of [redacted] documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact. This includes subjects who provided consent or assent (as appropriate) to [redacted]. At least [redacted] of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any used/empty and unused study medication.

5 TREATMENT

5.1 Identity of Investigational Product

The investigational product (IP) is maralixibat chloride (formerly SHP625, LUM001), which will be provided as a fixed, oral solution (i.e., [redacted]) along with either 0.5-, 1.0-, or 3.0-mL sized oral dosing dispensers. The study medication, maralixibat, is presented in 30 mL volumes packaged in 30 mL size amber colored PET bottles and requires refrigerated storage condition (2°C–8°C).

One of the excipients in the maralixibat oral solution is propylene glycol (PG). To limit subject exposure to PG, a specific strength and volume of oral solution will be prescribed to a given subject based on his or her body weight and target dose. The dosing plan will limit PG exposure to [redacted] and, at the same time, will provide appropriate dosing volumes to ensure accurate dosing.

Additional information on maralixibat dosing and PG exposure is provided in the Maralixibat Chloride IB and the pharmacy manual.

5.2 Administration of Study Medication

Details on handling and management of the study medication will be described in the pharmacy manual.

5.2.1 Interactive Response Technology

An interactive response technology (IRT) will be used for screening subjects, management of study visits, and ordering of study medication. The appropriately delegated site personnel will receive training on the use of the IRT system.

The IRT manual, which contains details on applicable modules corresponding to study visits, assessment and/or procedures (see Table 1), including study medication management, will be provided to the site.

5.2.2 Allocation and Dispensing of Study Medication

Eligible subjects will receive study medication at the Screening Visit 0/Day 0 and at subsequent visits ([redacted]) thereafter. If necessary, study medication may be dispensed at an unscheduled clinic visit or via direct from site-to-patient shipment in between visits.

5.2.3 Dosing

Subjects will receive ready-to-use maralixibat oral solution based on their individual body weight. Fixed concentrations of maralixibat oral solutions (i.e., [redacted]) will be used. To accurately measure the required volume, 0.5-, 1.0-, and 3.0-mL sized oral dosing dispensers will be provided.

The initial dose of maralixibat that will be dispensed to subjects in MRX-800 is the dose closest to the dose subjects were receiving in their lead-in/previous study (rounded up). In subject-specific cases, at the discretion of the Investigator, the dose closest to that of the previous study rounded down may be used.

The Investigator can request to increase the dose for his or her subject(s) to improve the treatment response (e.g., sBA levels or pruritus). After approval by the medical monitor and if study drug supply is available, the Investigator can increase the dose up to a maximum of 450 µg/kg QD for subjects with ALGS [redacted] and up to 600 µg/kg BID for subjects with PFIC [redacted]. Those subjects with ALGS who started Study MRX-800 on the dose of 450 µg/kg BID can continue with the same dose.

For further information, please refer to Section 3.1.1, and see Section 7.3 for safety monitoring criteria.

The sample daily exposure (mg/day) to maralixibat, based on BID dosing across the proposed target dose levels for subjects ranging in weight from 5 to 70 kg is provided in Table 2. [redacted]

Table 2 Sample Daily Exposure (mg/day) for Subjects - BID[a]

Weight (kg)	Daily Exposure of Maralixibat (mg)			
	[redacted]	[redacted]	(450 µg/kg - BID)	(600 µg/kg - BID)
5	[redacted]	[redacted]	4.5	6.0
10	[redacted]	[redacted]	9.0	12.0
20	[redacted]	[redacted]	18.0	24.0
30	[redacted]	[redacted]	27.0	36.0
40	[redacted]	[redacted]	36.0	48.0
50	[redacted]	[redacted]	45.0	60.0
60	[redacted]	[redacted]	54.0	72.0
70	[redacted]	[redacted]	63.0	84.0

BID=twice daily dosing; PFIC=progressive familial intrahepatic cholestasis.

[redacted]

[b] Subjects with PFIC [redacted]

Table 3 provides the recommended initial dose for the MRX-800 study, based on the dose administered in subjects' lead-in/previous study.

Table 3 Dosing Table for Study MRX-800

Dose in Previous Study (µg/kg/day)	Frequency	Recommended Dose MRX-800 (µg/kg/day)	Frequency
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	450/450 (900 total)	BID
[redacted]	[redacted]	600/600 (1200 total)	BID

BID=twice daily dosing; [redacted]
Note: For studies that used the commercial maralixibat formulation, subjects will roll over to the same dose they were receiving in the previous study (i.e., up to 600 µg/kg BID).

It is recommended that subjects who were on [redacted] in their previous maralixibat study will be administered (or will self-administer, as appropriate) the first dose of the MRX-800 study medication on [redacted]. For those on [redacted], it is recommended that they be administered (or will self-administer, as appropriate) the first dose of the MRX-800 study medication [redacted]

The schedule of the dose increase for any subject will be discussed between the Investigator and the Medical Monitor, and the Investigator will contact the subject after the first week on the increased dose to assess for safety and tolerability. A dose may be increased only in the absence of major safety (e.g., liver parameters) or tolerability (e.g., GI-related TEAEs) concerns related or possibly related to study medication (see Section 7.3 for safety monitoring criteria).

As much as possible, the [redacted] should be administered approximately 30 minutes before breakfast and, if applicable, the evening dose approximately 30 minutes before the main evening meal. The doses will be administered prior to meals rather than every 12 hours to better cover the

luminal bile acid release associated with meals. Study medication should be administered approximately at the same time each day throughout the study.

5.3 Labeling, Packaging, Storage, and Handling

5.3.1 Labeling

All study medication is labeled according to country-specific requirements. Additional labels may, on a case-by-case basis, be applied to the study medication to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the Sponsor's prior full agreement.

5.3.2 Packaging

Study medication is packaged in the following labeled containers:

- [redacted]
- [redacted]
- [redacted]
- Ready-to-use oral solution of maralixibat [redacted]

The Sponsor or designee will provide 0.5, 1.0, and 3.0 mL sized oral dosing dispensers. Changes to Sponsor-supplied packaging may not occur without full agreement in advance by the Sponsor.

5.3.3 Storage

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 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.

5.4 Drug Accountability

Investigators will be provided with sufficient amounts of the study medication to carry out this protocol for the agreed number of subjects. 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.

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 in the protocol and who works under the direct supervision of the Investigator. Study medication will be dispensed at Screening Visit 0/Day 0 and at each visit occurring every [redacted], in quantities sufficient for dosing until the next scheduled visit (see Table 1). If necessary, direct from site-to-patient shipment of medication is allowed between visits.

The Investigator or his/her designee will dispense the study medication only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the study medication assigned. All dispensed medication will be tracked accordingly.

The Investigator is responsible for ensuring the retrieval of all study supplies from subjects. Subjects 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.

Other than study medication dispensed to subjects, 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 its representatives must be permitted access to review the supplies storage, distribution procedures, and records.

At the end of the study, or as instructed by the Sponsor, all unused stock, subject-returned study medication, and empty/used study medication packaging are to be returned or destroyed. Study medication must be counted and verified by clinical site personnel and the Sponsor (or designated Contract Research Organization (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.

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.

5.5 Subject Compliance

Subject compliance with study procedures and treatment will be assessed at each visit by the Investigator or designee. Compliance with treatment dosing will be monitored and recorded by the site staff. [redacted] Any concerns with compliance should be discussed with the Medical Monitor.

Compliance will be reported on the CRF including dates or periods when doses of study medication were missed or not taken as prescribed. The subject's dosing diary will be used as the source record.

Subjects may remain on study during dose interruptions and should continue to complete all regularly scheduled subject study visits and assessments as outlined in Table 1. Any reduction in dose [redacted] re-challenge with a higher dose, or dose escalation will be based on safety and/or tolerability and as per the Investigator's discretion. Such dose reductions, re-challenges, and dose escalations should be discussed with the medical monitor.

During the entire treatment period (i.e., [redacted]), subjects will be allowed a maximum of [redacted] of cumulative dose interruption. For subjects on BID, a dose interruption is defined as [redacted]. Any dose interruption longer than the maximum allowed will be documented as a protocol deviation.

Any subject who has over [redacted] of cumulative dose interruption during the entire treatment period should be discussed with and reviewed by the Medical Monitor to determine if the subject may remain in the study.

Procedures outlined in Section 6.1.3 should be followed for any subject who is discontinued early from the study due to treatment non-compliance.

Subjects that interrupt dosing for safety/tolerability or other reasons may re-initiate dosing, but only after discussion with the Medical Monitor.

5.6 Prior and Concomitant Treatment

5.6.1 Prior Treatment

Specific prior concomitant treatments/medications and therapies administered for underlying liver disease, treatment of pruritus, or treatment of cholestasis will be collected. Prior treatment information must be recorded in the subject's source document for data collection.

5.6.2 Concomitant Treatment

Concomitant treatment refers to all treatment, including concomitant therapies as well as herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, taken up until the EOT/ET Visit, inclusive. Concomitant treatment information must be recorded in the subject's source document. Investigators must ensure that subjects receive lipid-soluble vitamin supplements, as needed, for the duration of the study.

5.6.3 Permitted Treatment

Medications to treat cholestasis/pruritus are allowed during the study.

Table 4 details the prohibited treatments and the time restriction period at any time before or during the study. None of these medications are allowed during the conduct of the study. If a subject was prescribed growth hormone treatment in the predicate study, this may be continued.

Table 4 Prohibited Treatments and Time Restriction Prior to Visit 0/Day 0

Prohibited Treatment	Time Restriction prior to Visit 0/ Day 0
Any investigational drug, biologic, or medical device	Any time during the screening period
IBATi/ASBTi other than maralixibat	Any time before the study

IBATi=ileal bile acid transporter inhibitor; ASBTi=apical sodium-dependent bile acid transporter inhibitor

6 STUDY PROCEDURES

6.1 Study Schedule

The study procedures and assessments to be performed throughout the study can be found in Table 1. Further instructions about study assessments are provided in this section and in Section 6.2.

Prior to performing any study-related procedures (including those related to screening), the Investigator or his/her designee must obtain written informed consent (and/or assent when appropriate) from the subject (as per local requirements). For information about informed consent process see Section 9.8.1.

6.1.1 Screening Visit 0/Day 0

Participation in this study starts when the informed consent (and/or assent when appropriate) is signed. After obtaining informed consent (and/or assent when appropriate), the subject will be screened. The Investigator or designee will register the Screening Visit 0/Day 0 in the IRT system accordingly. The subjects' unique identification number from their lead-in/previous study will be referenced in their MRX-800 study identification number. The subject's identification number must remain constant and must be used on all study documentation related to that subject.

The Screening Visit 0/Day 0 [redacted]

In certain cases where it is not possible for [redacted] the MRX-800 Screening Visit 0/Day 0 [redacted]. Subjects who terminated early from a previous maralixibat study or for

whom the [redacted] is expired may be considered for entry into MRX-800 after discussion with the medical monitor.

Subjects who meet eligibility criteria will be dispensed enough study medication to last until their next expected clinic visit. Assessments and procedures will be performed as outlined in Table 1.

Evaluations and procedures completed for [redacted] will serve as the evaluations for the MRX-800 Screening Visit 0/Day 0. Therefore, data and assessment results will be pulled by data management from [redacted] to the MRX-800 Screening Visit 0/Day 0 CRF accordingly, including physical examination and vital signs (including height and weight), and laboratory assessments listed in Table 5. Note that laboratory assessments have to be performed if the laboratory samples in [redacted] were collected [redacted] prior to the scheduled MRX-800 Screening Visit 0/Day 0.

For females of childbearing potential, the [redacted] serum β-hCG pregnancy test results will be used, if available. Otherwise, a urine pregnancy test will be performed (see Section 6.2.1.5). A positive urine pregnancy test result requires a subject to undergo a serum β-hCG pregnancy test. Results of the pregnancy test must be reviewed prior to dispensing study medication.

AEs ongoing at the time of the subject's [redacted] should be entered by the site into the MRX-800 Adverse Event CRF.

New AEs for the MRX-800 will only be collected from the time informed consent (and/or assent when appropriate) is signed (see Section 7.1).

The following data (not an exhaustive list) from the previous study will be pulled by data management to the current study: Race and Medical/Disease History.

The following are expected to be entered by the site in the MRX-800 CRF: Date of Birth, Age, Sex, ongoing Concomitant Medication(s). Local, country-specific guidelines should be followed where there is regional variation for collection of demographic information.

If the subject does not meet eligibility criteria following completion of screening assessments, the subject will be considered as a screen failure. A screen failure is a subject who has given informed consent (and/or assent when appropriate) and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been dispensed or administered study medication. The Investigator or designee will register the subject as a screen failure in the IRT system.

In exceptional cases, subjects who initially fail to meet eligibility criteria may be re-screened. All re-screenings should be discussed with the Medical Monitor.

6.1.2 Treatment Period

6.1.2.1 Subject Contact

At [redacted], the Investigator or designee will contact subjects (email or phone call) during which the use of the new maralixibat formulation (for subjects who entered from the ALGS – PFIC Phase 2 program), the concomitant treatments, and AEs will be reviewed as outlined in Table 1.

[redacted]

Subjects will return to the site [redacted] for the following assessments and procedures: symptom-directed physical examination and vital signs (including height and weight), blood for clinical laboratory testing, including safety laboratory tests, fasting lipid panel, serum bile acids, and determination of fat-soluble vitamins. In addition, subjects and caregivers will be instructed to complete [redacted] A liver ultrasound/magnetic resonance imaging (MRI) scan will be done starting from [redacted] as outlined in Table 1.

For subjects with biliary atresia, the following additional procedures will be performed:

- [redacted]
- [redacted]

Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing maralixibat. A positive urine pregnancy test result requires a subject to undergo a serum β-hCG pregnancy test. Results of the pregnancy test must be reviewed prior to dispensing study medication. Maralixibat compliance will be assessed, and the study medication will be dispensed upon completion of other study procedures.

Information on concomitant treatments/medications, any AEs, [redacted]

During this period, [redacted] will be permitted, unless otherwise specified. Visit dates and acceptable windows are calculated from Day 0.

The Investigator or designee will register each visit in the IRT system accordingly.

Subjects can continue treatment until the study is terminated, at the discretion of the Sponsor.

6.1.3 End of Treatment/End of Trial

Subjects will return to the site for the EOT/ET Visit for the following assessments and procedures: symptom-directed physical examination and vital signs (including height and weight), blood for clinical laboratory testing, including safety laboratory tests, fasting lipid panel, serum bile acids, and determination of fat-soluble vitamins, as outlined in Table 1. In addition, subjects and caregivers will be instructed to complete [redacted] A liver ultrasound/MRI scan will also be done.

For subjects with biliary atresia, the following additional procedures will be performed:

- [redacted]
- [redacted]

If study medication is permanently discontinued early, regardless of the reason, the subject will be discontinued from the study (refer to Section 4.5), and the evaluations listed for the EOT Visit are to be performed. The subject should undergo the ET assessments at the visit during which study medication was discontinued, or the subject should be scheduled for an additional ET Visit as soon as possible, if the study medication was discontinued in between visits.

Subjects who discontinue prematurely at any time during the study will also have a final safety follow-up phone call [redacted] after the last dose of study medication.

[redacted]

The Investigator or designee will register the EOT/ET Visit in the IRT system accordingly.

6.1.4 Safety Follow-Up [redacted]

The safety follow-up period for this protocol is [redacted] from the last dose of study medication.

Subjects who discontinue prematurely at any time during the study will have a safety follow-up phone call [redacted] after the last dose of study medication. Subjects who discontinue from the study for safety reasons are also followed-up as long as clinically indicated or until a safety finding has to be considered as permanent. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure by the site (see Section 7).

Subjects may be contacted by the study doctor [redacted], regardless of the subject's completion of the study, to allow the study doctors to continue to follow the subject's condition to check disease progression.

6.2 Study Evaluations and Procedures

6.2.1 Safety

6.2.1.1 Physical Examination and Neurodevelopmental Examination

The physical examination done for [redacted] will serve as the evaluation for the MRX-800 Screening Visit 0/Day 0. Therefore, all physical examination data and assessment results will be pulled by data management and included in the database for the MRX-800 study.

A symptom-directed physical examination will be completed at each subsequent clinic visit ([redacted]) and at the EOT/ET, as appropriate.

Physical examination assessments at each visit should also include specific assessments for signs of hepatomegaly, splenomegaly, edema, ascites, jaundice, and scleral icterus.

Clinically significant changes after Day 0 should be assessed as potential AEs. Refer to Section 7 for details.

[redacted]

6.2.1.2 Adverse Event Collection

AEs ongoing at the time of the subject's previous lead-in study should be entered by the site into the MRX-800 AE CRF. New AEs for the MRX-800 study will only be collected from the time informed consent (and/or assent when appropriate) is signed (see Section 7 and Section 7.2.4).

If, at the end of the treatment phase, there are abnormal clinical laboratory results, vital signs, etc. which were not present at the baseline (Screening Visit 0/Day 0 – see Section 6.1.1), further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

At each study visit and subject contact, subjects or their caregivers will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?").

6.2.1.3 Vital Signs (including height and weight)

Vital signs include blood pressure, heart rate, temperature, and respiration. Blood pressure should be determined by cuff using the same method, the same arm, and the same position, following 5 minutes of rest throughout the study. Any deviations from baseline (Day 0) vital signs that are deemed clinically significant in the opinion of the Investigator are to be recorded as an AE.

Height will be measured by trained site staff in children who can stand on their own (generally ≥ 2 years) using a calibrated stadiometer or headboard, respectively, via 2 independent measurements, recorded to the nearest 0.1 cm (and a third measurement if values differ by > 0.5 cm). The same stadiometer should be used for all study visit measurements.

Weight will be assessed, recorded to the nearest 0.1 kg, using a calibrated balance or electronic scale (children who can stand on their own, generally ≥2 years of age).

Standardized instructions based on regulatory guidance for height and weight measurements will be provided in the study manual.

6.2.1.4 Clinical Laboratory Evaluations

All clinical laboratory evaluations will be performed according to the central laboratory manual. 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 Sub-Investigator must assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are clinically significant or not. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the Investigator or Sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Clinical laboratory assessments will be performed as listed in Table 5.

Unscheduled safety laboratory sampling should be conducted throughout the study as required in case of any clinical safety concerns. The local laboratory values are not required to be collected in the CRF, except for those that are directly relevant to the monitoring of an AE/SAE; collection of other values may be requested by the Sponsor.

Table 5 List of Laboratory Analytes

β-hCG Serum or urine (if indicated) **CBC with Differential** Hematocrit Hemoglobin MCV, MCH, MCHC Red blood cells Platelets White blood cells WBC Differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes **Coagulation** aPTT (sec) INR PT (sec)	**Clinical Chemistry** Albumin ALP Amylase ALT (SGPT) AST (SGOT) Bilirubin, direct (conjugated) Total serum Bilirubin (TSB) Blood urea nitrogen (BUN) Calcium Chloride Creatinine GGT Glucose Lipase Phosphate Potassium Sodium Total protein Uric Acid Measured serum Osmolality Total Lipids	**Lipid Panel**[a] Total cholesterol LDL-C (direct) HDL-C Triglycerides (TG) **Cholestasis Biomarkers**[a] Total serum bile acids (sBA) Serum bile acid subspecies 7α-hydroxy-4-cholesten-3-one FGF-19 Autotaxin **Lipid Soluble Vitamins**[a] 25-hydroxy vitamin D Retinol Retinol binding protein (RBP) α-Tocopherol	**Urinalysis** pH Specific gravity Protein Glucose Ketones Bilirubin Occult blood and cells Nitrite Urobilinogen Leukocyte esterase Microscopic examination[b] Oxalate[c,d] Creatinine[d] **Marker of hepatocellular carcinoma** α-fetoprotein

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; APRI=AST to platelet ratio index; AST=aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; FGF-19=fibroblast growth factor 19; FIB-4=fibrosis-4; GGT=gamma-glutamyl transferase; HDL-C=high density lipoprotein cholesterol; INR=international normalized ratio; LDL-C=low density lipoprotein cholesterol; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time; RBP=Retinol binding protein: SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cell

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

[b] Will be performed on abnormal findings unless otherwise specified.

[c] Oxalate will be assessed at [redacted].

[d] Spot tests on creatinine and oxalate levels will be done to monitor for signs of nephrolithiasis.

A serum storage sample will be collected for the analysis of cholestasis biomarkers as determined by the Sponsor.

6.2.1.5 Pregnancy Test

A urine pregnancy and/or serum β-HCG pregnancy test will be performed on all female subjects of childbearing potential at all visits, or if pregnancy is suspected, as specified in Table 1. A positive urine pregnancy test result requires a subject to undergo a serum β-hCG pregnancy test. Results of the pregnancy test must be reviewed prior to dispensing study medication.

6.2.1.6 Liver Imaging

Subjects will undergo a liver ultrasound/MRI scan starting from [redacted] thereafter (i.e., [redacted] and at EOT/ET.

6.2.2 Efficacy

6.2.2.1 Itch-Reported Outcome (ALGS and PFIC)

Pruritus will be assessed using the Itch caregiver/patient Reported Outcome measure (ItchRO™) (See Table 1). Caregivers for all subjects with ALGS or PFIC will complete the Observer instrument: ItchRO(Obs)™. The ItchRO(Obs)™ should be completed by the same caregiver, for consistency whenever possible. In cases where a caregiver can no longer observe the subject (e.g., no longer living with the subject), the ItchRO(Obs)™ does not need to be completed.

Caregivers and age-appropriate subjects who completed the ItchRO™ assessment in their lead-in/previous study may be asked to continue to complete the ItchRO™ questionnaire, administered as a [redacted], starting from [redacted] and onward as described in Table 1, Appendix 2, and Appendix 3.

[redacted]

Subjects and caregivers will be trained on the proper use of the questionnaires (as per the appropriate platform, i.e., paper, web portal, electronic device, to accommodate cultural restrictions for a limited number of subjects/families) at the [redacted].

ItchRO(Obs)™ (ALGS and PFIC)

The severity of pruritus will be measured by the completion of the first question in the ItchRO(Obs)™ (how severe were your child's itch-related symptoms) (see Appendix 2). The frequency of pruritus will be measured by completion of the third question in the ItchRO(Obs)™ (how much of the time was your child rubbing or scratching). Caregivers will rate the severity and frequency of pruritus using 5 choices to describe their itching condition. The sixth choice, "I don't know" will not count toward their severity or frequency score (categorized as missing data) and is included to account for rare occasions that the designated caregiver cannot observe the child, or the child could not communicate the severity or frequency of their itching condition.

Subjects and caregivers should be made aware that capturing "I don't know" should be kept at an absolute minimum, as this will be considered missing data.

[redacted]

6.2.2.2 Clinician Scratch Scale

The CSS provides an assessment of itch severity (see Appendix 6). The clinician's assessment of the subject's pruritus will focus on scratching and visible damage to the skin as a result of scratching as observed by the physician. The CSS uses a 5-point scale, in which 0 designates no evidence of scratching and 4 designates cutaneous mutilation with bleeding, hemorrhage and scarring. A clinician's assessment of pruritus made by the principal Investigator or sub-Investigator using the CSS will be recorded at each study visit as outlined in Table 1. To the extent possible, assessments should be made by the same individual during study visits.

[redacted]

6.2.2.4 Serum Bile Acids and Other Cholestasis Biomarkers

Blood samples will be collected as described in Table 1 to measure levels of cholestasis biomarkers including total sBA, In addition, serum samples will be collected for potential analysis of sBA subspecies, 7αC4, FGF-19, and autotaxin, as well as liver-related parameters.

Subjects are encouraged to fast [redacted] prior to collection (water intake is permitted if necessary but not recommended).

Total sBA and targeted bile acid subspecies will be quantified with liquid chromatography mass spectrometry methodology for exploratory assessments.

Samples collected for biomarker evaluation may be utilized for additional assessments of related analytical methodology or other exploratory analysis.

6.2.2.5 Assessments to be Performed Additionally in Subjects with Biliary Atresia

For subjects with biliary atresia, the following additional procedures will be performed:

[redacted]

6.2.3 Medical History, Disease History, and Medication History

All clinically or medically relevant information, including PFIC, ALGS, or biliary atresia disease history, regardless of how much time has elapsed since the date of any diagnosis that was collected in the lead-in/previous study will be pulled by data management and included in the data for this study (see Section 6.1.1).

6.2.4 Demographics

Where allowed to collect, the data on race and ethnicity from the subjects' lead-in/previous study demographic information will be pulled by data management to the MRX-800 study.

Information on including gender, age (year and months) and date of birth (as allowed per local regulations), will be entered in the MRX-800 CRF by the site personnel.

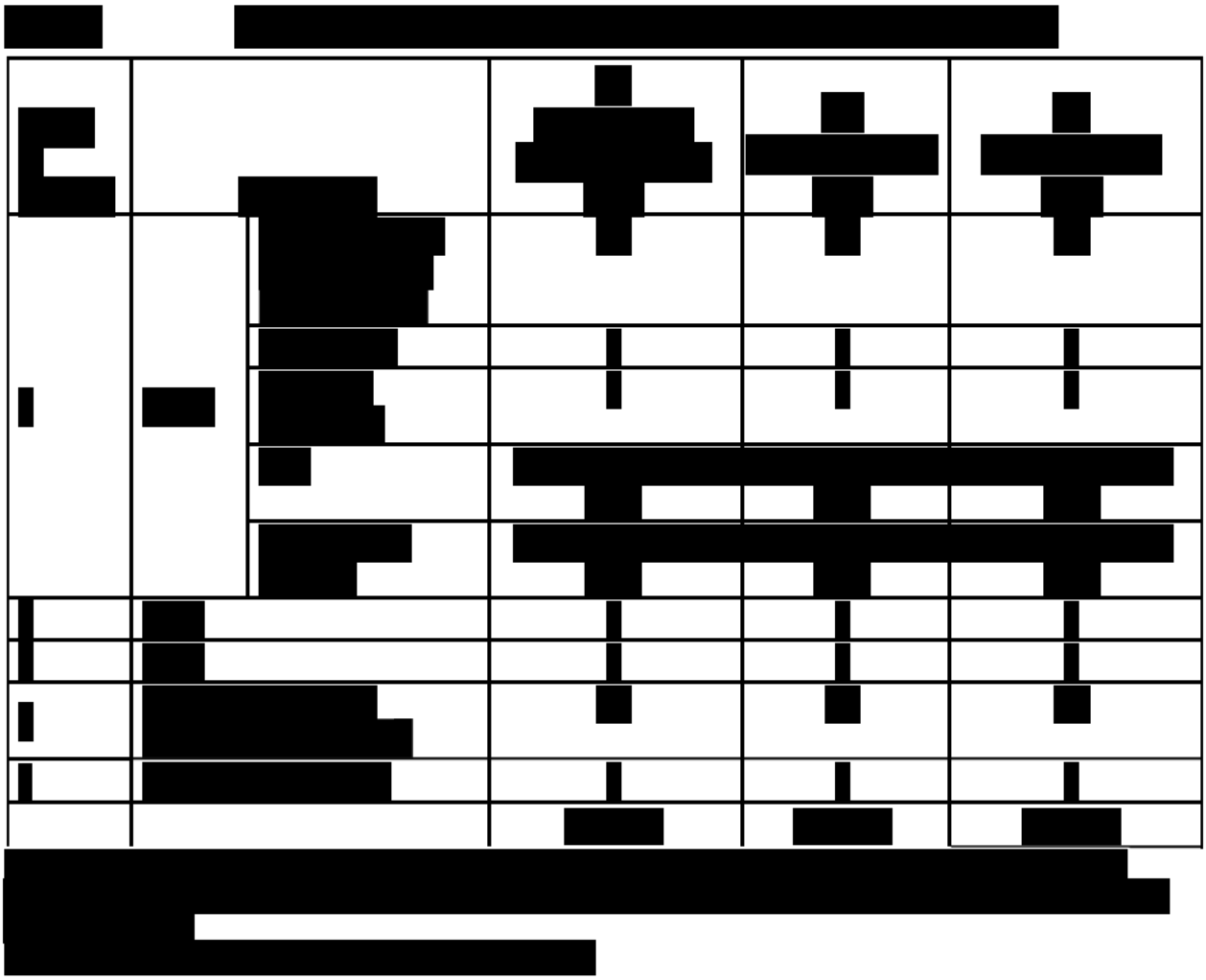
6.2.5 Others

[redacted]

6.2.6 Volume of Blood to be Drawn from Each Subject

As shown in Table 6, a maximum of approximately [redacted] of blood will be drawn during each clinic visit. Please refer to the applicable laboratory manual for details.

According to the Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population, the volume of blood drawn from a subject should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time (Ethical Considerations, 2008). Should the volume of blood required for a single visit or a 30-day period exceed the maximum allowable amount, the Investigator will draw blood in the priority order listed in Table 6 until the maximum amount has been reached. Laboratory draws missing due to the maximum allowable amount being reached will not be considered protocol deviations. Further instructions will be provided in the laboratory manual.



7 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

7.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent (and/or assent when appropriate) is signed until the defined follow-up period stated in Section 6.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not study medication is administered.

AEs that were ongoing at the time of the subject's previous lead-in study should be entered by the site into the MRX-800 CRF for further follow-up.

Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually, and a diagnosis should be provided when the underlying cause is clear. All AEs should be captured on the appropriate AE pages in the CRF and in source documents.

All AEs must be followed to closure, regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

7.1.1 Treatment-Emergent Adverse Event

A treatment-emergent AE (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an IP or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the IP or medicinal product.

In this study, all AEs will be considered TEAEs.

7.1.2 Unexpected Adverse Event

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the medical terms, severity, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the Sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

7.1.3 Suspected Unexpected Serious Adverse Reaction

A SUSAR is defined as any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected

- Assessed as related to study treatment

7.1.4 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of study medication, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of study medication, but the dyspepsia becomes severe and more frequent after first dose of study medication has been administered, a new AE of worsening dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The investigator will make an assessment of the maximum intensity for each AE and SAE according to the NCI CTCAE, version 5.0. Should a subject 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 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. In the absence of meeting any of the seriousness criteria, a severe event does not qualify as being serious. A semicolon indicates “or” within the description of the grade, not “and.”

7.1.5 Relationship Categorization

A physician/Investigator must make the assessment of relationship to study medication for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study medication. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related.” Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the study medication and the occurrence of the AE, then the AE should be considered “related.” The causality assessment must be documented in the source document.

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

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the study medication is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the study medication and the event.

7.1.6 Outcome Categorization

The outcome of AEs must be recorded on the CRF. Outcomes are as follows:

- Fatal
- Not recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

Action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF.

7.1.7 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, disease progression resulting in study discontinuation should be recorded as an AE.

7.1.8 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign can represent an AE if the change is clinically relevant or if, during treatment with the study medication, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the EOT with the study medication, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

Laboratory abnormalities should not be classified as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of laboratory parameters should be recorded as an AE. Laboratory abnormalities related to disease progression that result in interruption of study medication should be captured as AEs.

If, at the end of the treatment phase, there are abnormal clinical laboratory or vital sign which were not present at the Screening Visit 0/Day 0), further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign is clinically significant and therefore represents an AE.

7.1.9 Adverse Events of Special Interest

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

- Lipid soluble vitamin deficiency requiring study drug discontinuation
- Liver parameter disruption requiring study drug interruption and/or dose modification

7.1.10 Pregnancy

All pregnancies are to be reported from the time informed consent (and/or assent when appropriate) is signed until the defined follow-up period stated in Section 6.1.4.

Any report of pregnancy for any female study subject or the partner of a male subject must be reported within 24 hours to the Sponsor or designated Medical Monitor using the pregnancy report form.

The pregnant female study subject must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion due to a congenital abnormality, or a complication or pregnancy or a congenital abnormality diagnosed any time during the pregnancy or post-partum are considered SAEs and must be reported per Section 7.2.2 Reporting Procedures. An elective abortion of a normal pregnancy without complications is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE, using the Pregnancy Report Form.

7.1.11 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Medical Monitor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 7.2. Note: 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 study medication when used for a non-medical 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 study medication other than as directed or indicated at any dose (Note: this includes a situation where the study medication is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of study medication exceeding the protocol-prescribed daily dose
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of a study medication. For studies, medication errors are reportable to the Sponsor only as defined below.

Cases of subjects missing doses of study medication are not considered reportable as medication errors. The administration and/or use of the unassigned or expired study medication is/are always reportable as a medication error.

7.2 Serious Adverse Event Procedures

7.2.1 Reference Safety Information

The RSI for this study is Section 6.8 of the maralixibat chloride IB that the Sponsor has provided under separate cover to all Investigators.

7.2.2 Reporting Procedures

All SAE/AESIs must be reported by the Investigator within 24 hours of becoming aware of the event using the electronic data capture system; the Safety Report Form may be used in instances when the system is not available. Note: The 24-hour reporting requirement for SAE/AESIs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 7.1.11) unless they result in an SAE/AESI.

SAE/AESI Reporting:

SAE/AESIs that meet the criteria defined in the study protocol must be reported within 24 hours of awareness via the electronic data capture system. The Safety Report Form may be used and sent via email (Safety@catalystcr.com) in instances when the electronic data capture system is unavailable. In situations where internet or email is unavailable, contact the local Clinical Research Associate for further assistance.

Safety Report Form and associated documents and communications should be filed in the study binder.

The Safety Report Form could be used for reporting other event types such as medication error, overdose, etc. Pregnancy information should be reported on the Pregnancy Report Form.

For all urgent protocol- or safety-related issues during and outside of business hours, the Investigator must contact the Premier Research Medical Monitor:

North America (US and Canada) sites: Central phone number: +1 512 686 1256 (US)

European and ROW sites: Central phone number: +44 118 936 4096 (United Kingdom)

The Investigator or designee must complete, sign, and date the serious AE form, verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and submit the form following the instructions in the study manual. Follow-up information should be reported as soon as available.

7.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to study medication or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity

- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

7.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study drug) are collected from the time the subject signs the informed consent (and/or assent when appropriate) until the defined follow-up period stated in Section 6.1.4 and must be reported within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the study medication and discovered by the Investigator at any interval after the study has completed must be reported within 24 hours of the first awareness of the event.

7.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form (and/or assent when appropriate) or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

7.2.6 Fatal Outcome

Death in itself is not an SAE but an outcome arising from a SAE. Any SAE that results in the subject's death (e.g., the SAE was noted as the primary cause of death) must be recorded on the CRF with an outcome of "fatal" and the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be recorded as "not resolved," without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another study medication action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the study medication should be recorded as "dose not changed" or "not applicable" (if the subject never received study medication). The study medication action taken of "withdrawn" should not be selected solely as a result of the subject's death.

7.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor is responsible for notifying the relevant regulatory authorities (US central IRBs/EU central ECs and EU competent authorities) of related, unexpected SAEs.

In addition, the Sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the maralixibat program.

The Investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur, as required by local law.

During the course of the study, the sponsor shall inform the regulatory authorities of any SUSARs occurring with maralixibat that occur globally as follows (local reporting requirements may vary):

(a) if it is neither fatal nor life threatening, within 15 days after becoming aware of the information; and

(b) if it is fatal or life threatening, within 7 days after becoming aware of the information.

For fatal and life-threatening events, the sponsor shall, within 8 days after having informed the regulatory authorities, submit a complete report including an assessment of the importance and implication of any findings made.

7.3 Safety Monitoring

7.3.1 General Guidelines

In the evaluation of AEs and the potential relationship to study medication it is important to note that due to their liver disease many patients with ALGS have abnormal liver enzyme levels (e.g., ALT, ALP) and total bilirubin at baseline. If an individual subject exhibits a CTCAE Grade 3 treatment-emergent laboratory abnormality, with the exception of the specific rules outlined below (Section 7.3.2), dosing can be suspended or continued as per the Investigator's judgment and following discussion with the medical monitor. If suspended the Investigator and medical monitor will evaluate the subject's safety data and make a decision to either restart dosing at the same level, restart dosing at a lower dose level, or discontinue dosing.

To ensure subject safety, if 6 or more subjects at a dose level lower suspend or stop study medication or exhibit treatment-emergent toxicity of CTCAE Grade 3 or greater in the same SOC, with the exception of the specific rules outlined in the following sections, further dosing of subjects at that dose level and any higher dose levels will be halted until a safety assessment is completed.

Study visits and completion of ItchRO™ (ALGS and PFIC), for all subjects, will continue during the [redacted] Repeating Treatment Cycle. After review, a decision will be made whether to restart dosing at the same dose level, restart dosing at a lower dose level, or discontinue the subjects

from the study. The Data Monitoring Committee (DMC) will review any SAE as specified in the DMC charter.

7.3.2 Safety Monitoring Guidelines

The following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance:

At any time during the study, the initial clinical laboratory results exceeding the safety monitoring criteria presented below **must be confirmed** by performing measurements on new specimens. Of note: the INR re-test should be conducted by the central laboratory but may also be conducted at a local laboratory on an as needed basis. All new specimen collections should take place as soon as possible, ideally [redacted] of the notification of the laboratory result. It may be difficult for some subjects who live far from the study site to return to the study site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to study Investigators and medical monitors immediately, and the data should be included in the case reports.

Stopping Rule Guidance: Subject dosing must be suspended until the retest results are available. If any of the stopping criteria described below (see Sections 7.3.3 to 7.3.5) is confirmed, the Investigator in consultation with the Medical Monitor (or appropriately qualified designee) will permanently discontinue the subject from further treatment with study medication. The subject will be evaluated as outlined below and will be encouraged to complete the ET study procedures (Table 1). Subjects who do not meet the stopping rules based on retest may continue dosing and the Investigator and the Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. The Investigator should also assess the need to capture an AE, its severity according to the CTCAE directives and potential causality. These assessments should also include an evaluation of whether criteria for an SAE are fulfilled (see Section 7.2.3), in particular whether the event should be considered as an important medical event, i.e., an event that would have met one of the other seriousness criteria in the absence of appropriate medical interventions.

7.3.3 ALGS and PFIC Liver Chemistry

7.3.3.1 Safety Monitoring for Liver Chemistry Tests

Safety monitoring criteria take into consideration the subject's baseline ALT and total bilirubin levels. The baseline will be defined as the [redacted] If the results are more than [redacted] at the time of the MRX-800 Screening Visit 0/Day 0, the re-test values performed at Screening Visit 0/Day 0 will be considered baseline.

If, at any time in the study, an ALT or total bilirubin result meets the criteria shown in the table that follows in relation to the subject's baseline level, the initial measurement(s) should be confirmed within 48 to 72 hours of notification of the laboratory result (Confirmation Guidance as per Section 7.3.2).

Baseline ALT	**ALT**
≤ ULN	> 5 x ULN
> ULN	> 3 x baseline **and** > 5 x ULN

Baseline Total Bilirubin	**Total Bilirubin**
Total Bilirubin ≤ 10 mg/dL	3 mg increases
Total Bilirubin > 10 mg/dL	5 mg increases

Frequency of Repeat Measurements: Subjects with a confirmed ALT or total bilirubin level that is continuing to rise should have their liver chemistry tests (ALT, ALP, INR, and total bilirubin) retested as clinically indicated, until levels stabilize or begin to recover.

Further Investigation into Liver Chemistry Elevations: Based on the inclusion criteria for this study, the population to be enrolled will have pre-existing baseline liver disease and will be monitored closely by the Investigators with experience in the management of pediatric hepatic diseases. For subjects with a confirmed elevation in ALT or total bilirubin level as described above, the following evaluations should be performed as clinically indicated:

- Close and frequent monitoring of liver enzyme and serum bilirubin tests as clinically indicated. Frequency of retesting can decrease if abnormalities stabilize or the study medication has been discontinued and the subject is asymptomatic. If the appropriate frequency of monitoring is not feasible study medication administration will be suspended.

- Obtain a detailed history of symptoms and prior and concurrent diseases.

- Obtain comprehensive history for concomitant drug use (including nonprescription medications, herbal, and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Obtain a history for exposure to environmental chemical agents and travel.

- Serology for viral hepatitis (HAV IgM, HbsAg, hepatitis C virus (HCV) antibody, CMV IgM, and EBV 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, PT/INR

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT, or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Medical Monitor.

7.3.3.2 Stopping Rules for Liver Chemistry Evaluations

In the event of confirmed laboratory results exceeding the following criteria, **and the event is without an alternative explanation as discussed with the Medical Monitor,** discontinuation of dosing of a subject with study medication will be considered if (see also Stopping Rules Guidance in Section 7.3.2):

Baseline Tests	Change Observed
ALT (any level)	ALT ≥ 20 x ULN
Total Bilirubin ≤ 10 mg/dL	5 mg increase **and** a 2 x increase over baseline level
Total Bilirubin > 10 mg/dL	2 x increase over baseline level

7.3.4 Biliary Atresia Liver Chemistry

7.3.4.1 Enhanced Monitoring Criteria for Liver Parameters (Biliary Atresia)

For subjects with biliary atresia, causes of liver injury other than drug-induced 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 judgement.

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.

Table 7 Enhanced Liver Injury Monitoring Criteria

Parameter	Enhanced Monitoring Criteria
ALT	> (2× baseline value AND >50 U/L) OR >500 U/L
Total serum bilirubin	>2× baseline value OR > (baseline value + 2 mg/dL)
INR[a]	INR ≥1.5

INR=international normalized ratio.

Note: Diagnosis of infective cholangitis, as well as other potential causes, should be ruled out (based on the specified cholangitis diagnostic criteria alongside clinician judgement) before judgment regarding liver injury is confirmed.

[a] INR value despite adequate vitamin K supplementation.

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 7.3.5).

7.3.4.2 Guidelines for Interruption of Study Medication for Specific Liver Parameters (Biliary Atresia)

If the confirmed laboratory results meet any of the criteria below and the event is without an alternative explanation (i.e., intercurrent illness, disease progression, natural history of the disease, cholangitis), interruption of study medication should be considered (see Table 8). 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.

Table 8 Treatment Interruption Criteria

Parameter	Treatment Interruption Criteria
ALT	> (3× baseline value AND >100 U/L) OR >600 U/L
Total serum bilirubin	>3× baseline value OR > (baseline value + 3 mg/dL)
INR[a]	> baseline value +0.5

INR=international normalized ratio.

Note: Diagnosis of infective cholangitis, as well as other potential causes, should be ruled out (based on the specified cholangitis diagnostic criteria alongside clinician judgement) before judgment regarding liver injury is confirmed.

[a] INR value despite adequate vitamin K supplementation.

7.3.5 Cholangitis Diagnostic Criteria (Biliary Atresia)

Cholangitis must be considered as a differential diagnosis in subjects showing abnormalities of liver parameters during the treatment period. Investigation for cholangitis should be considered if a subject exceeds bilirubin enhanced liver injury monitoring criteria (Table 7) and must be performed if a subject fulfills 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 previous baseline levels,

    AND
  - Abnormal liver function tests: Increase in 2 or more of AST, ALT, ALP, or GGT to 1.5× ULN or >25% above baseline values 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 subjects with a positive diagnosis of cholangitis, the Enhanced Monitoring and Treatment Interruption criteria during cholangitis episodes will apply (Table 7 and Table 8). This includes the temporary

interruption of study medication until investigator judgment (with potential discussion with the medical monitor) deems the episode has stabilized or resolved. Once the cholangitis episode has improved, use of the Enhanced Monitoring and Treatment Interruption criteria (Table 7 and Table 8) will revert to the standard aforementioned guidelines for monitoring.

7.3.6 Safety Monitoring for Triglycerides

In the event of a confirmed laboratory result for fasting total triglyceride >500 mg/dL, the Investigator and the Medical Monitor may consider a temporary interruption of study medication. Dosing may resume when the triglyceride level returns to <300 mg/dL or to the subject's baseline level.

7.3.7 Safety Monitoring for Fat Soluble Vitamins

Vitamin status will be assessed per the Schedule of Assessments (See Table 1), and blood samples will be obtained at the study visits before the daily dose of vitamins is administered. In the event of a confirmed laboratory result that falls either below or above the normal range for a vitamin (25-hydroxy vitamin D, retinol, retinol binding protein, tocopherol [α]), or for an elevated INR (as a proxy for vitamin K status), the Investigator should make the appropriate modification to the subject's vitamin supplementation regimen.

The response to the change in regimen will be assessed by relevant follow-up blood work 1 month later. Changes will continue to be made until the levels are in the desired range. Adjustments may be discontinued outside of the desired range if there is agreement between the Investigator and Medical Monitor that vitamin sufficiency cannot be reasonably expected.

7.3.8 Monitoring/Stopping Rules for Coagulation Panel Results

In the event of a confirmed laboratory result for INR > 1.5 that is unresponsive to vitamin K therapy, 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 subject's baseline level.

7.4 Adjustment of Dose

Gastrointestinal intolerance, as evidenced by diarrhea/loose stools, abdominal pain/cramping and nausea, is expected to be the most frequent manifestation of a lack of tolerability to study medication. If an individual subject exhibits a treatment emergent CTCAE Grade 2 or greater drug-related GI toxicity, study medication dose may be lowered to a previously well tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose. Dose reduction and escalation decisions should be made in consultation with the Medical Monitor. A requirement for intravenous fluids as treatment for diarrhea will lead to temporary discontinuation of study medication. Re-challenge of treatment with study medication in such patients will be done at the discretion of the Investigator.

7.5 Data Monitoring Committee

A DMC that is assigned to evaluate the currently ongoing Phase 2 and Phase 3 studies with maralixibat will also be involved in the review and evaluation of this study. The purpose of the DMC is to review the progress of the study, particularly with regard to safety, and make recommendations to the Sponsor to stop or modify the study if safety concerns are identified. The DMC meetings will be held approximately [redacted] during the study. Further details regarding the DMC can be found in the DMC charter that will be available prior to the enrolment of the first subject.

In addition to scheduled meetings, the DMC will convene for ad hoc meetings in case of any safety concerns arising during the conduct of the study. In particular, an ad hoc DMC meeting will be held [redacted] The DMC will review these cases and provide recommendations to the Sponsor regarding the continuation of specific dose levels, or the study overall. Study drug would be reduced or stopped in those subjects who experienced these triggering events, as per Investigator judgment; study medication in all other subjects will continue unless Investigators are otherwise advised by the DMC.

Should the DMC review determine that a certain dose is not safe, further dosing at this level must be halted, and the relevant regulatory authority informed.

The DMC will also be able to request that the frequency of safety laboratory tests be increased during the study.

8 STATISTICS

8.1 Statistical Analysis

A statistical analysis plan (SAP) will be written for the study. It will provide [redacted]

Study baseline will be defined for this study as Screening Visit 0/Day 0. [redacted]

8.2 Sample Size Calculation

Subjects meeting the study's inclusion and exclusion criteria will be enrolled in the study. Because this is an extension study for subjects enrolled under previous protocols, the sample size is not based on statistical considerations.

8.3 Analysis Populations

Because this is a long-term safety study, there will be only one analysis population. The Safety Population is defined as all subjects who enrolled and received at least 1 dose of maralixibat during the MRX-800 study.

Siblings will be allowed in this study.

8.4 Subject Disposition, Demographics, and Baseline Characteristics

The number of subjects enrolled, completing and withdrawing from the study, along with the reason for withdrawal will be summarized overall and by disease group.

Demographics and baseline characteristics, relevant disease history, and prior medications, and treatment exposure and compliance will be summarized overall and by disease group. Study completion status and reasons for discontinuation will also be displayed.

8.5 Treatment Exposure and Medical History

Treatment exposure will be summarized as starting dose, average dose, and ending dose across the treatment period. Descriptive statistics for these exposure measures will be provided overall and by disease group. Treatment compliance will also be summarized by examining the percent of doses that are taken as required.

Medical and surgical history and protocol violations/deviations will be presented in subject listings.

8.6 Safety and Tolerability Analyses

All safety analyses will be performed on the Safety Population, defined as all subjects who were screened and received at least 1 dose of maralixibat in MRX-800. Analyses will be conducted overall and by disease group.

All safety and tolerability data will be presented in subject listings

8.6.1 Safety Endpoints

The following safety and tolerability endpoints will be assessed:

- AEs, including serious, nonserious, related, nonrelated AEs
- Clinical laboratory tests (hematology, chemistry, urinalysis; serum pregnancy test, if appropriate)
- Vital signs (temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, weight, and height assessments)
- Physical examination
- Concomitant treatment/medication usage
- [redacted]

8.6.2 Adverse Events

In general, TEAEs are defined as AEs that start or deteriorate on or after the first dose of study medication in MRX-800 and no later than [redacted] following the last dose of study medication or reported through the EOT/ET Visit. In this study, all AEs will be considered TEAEs.

For any subjects who die during the study and the date of death is between the date of first dose of study medication in MRX-800 and the date of study discontinuation (as entered by the site), inclusive, all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries. All summaries of AEs will be based on TEAEs unless specified otherwise.

Adverse events of special interest, particularly GI-related AEs, will be outlined in the SAP and summarized.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and proportion of subjects who experience the event according to MedDRA SOC and preferred term will be presented overall and by disease type. Treatment-emergent AEs will be further summarized by severity and relationship to study medication. Adverse events related to study medication, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized.

Subject listings of AEs will include the dose of study medication at the onset of the event.

8.6.3 Vital Signs

Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate) will be summarized descriptively by study visit and disease as observed and change from baseline values. Potentially clinically important (PCI) values for select vital signs results will be defined in the SAP. The number and proportion of subjects with PCI values will be presented by disease group.

8.6.4 Laboratory Assessments

Safety laboratory test results will be summarized descriptively by study visit and disease group as observed and change from baseline values. The number and proportion of subjects with clinical laboratory values below, within, or above the normal range by time point and in relation to baseline will be tabulated for each safety laboratory analyte by treatment group in a shift table. Potentially clinically important (PCI) laboratory ranges will be defined in the SAP for select laboratory tests. The number and proportion of subjects with PCI laboratory values will be presented by treatment group.

Efficacy laboratory tests (i.e., total sBA, sBA subspecies, ALT, total and conjugated bilirubin, 7αC4, FGF-19, autotaxin, FIB-4, and APRI) will not be included in safety summaries.

Assessments of serum α-fetoprotein will be listed for individual subjects and summarized using descriptive statistics by study visit.

8.6.5 Concomitant Treatments

Prior and concomitant treatments will be summarized descriptively by disease group using the number and proportion of subjects.

Prior medications will be presented separately from concomitant treatments. Medications that started prior to the first dose of maralixibat in MRX-800 will be considered prior medications whether or not they were stopped prior to the first dose of maralixibat in MRX-800. Any medications continuing or starting after the first dose of maralixibat in MRX-800 will be considered to be concomitant. If a medication starts prior to the first dose of maralixibat in MRX-800 and continues after the first dose of maralixibat in MRX-800, it will be considered both prior and concomitant.

Medications will be coded using the World Health Organization Drug Dictionary.

8.6.6 Liver Ultrasound

Liver ultrasound (or MRI) results will be summarized descriptively and presented in listings.

[redacted]

8.7 Efficacy Analyses

All efficacy measures will be analyzed using the Safety Population and summarized by disease group. Change from maralixibat baseline in efficacy measures is of particular interest as the secondary objectives of the study focus on the long-term effect of maralixibat on the outcome measures.

No adjustments for multiplicity will be made.

All efficacy data will be presented in listings.

8.7.1 Efficacy Endpoints

The efficacy endpoints are:

- Change from maralixibat baseline over the course of the study in the weekly average morning ItchRO(Obs)™ severity score (ALGS and PFIC)

[redacted]

- Change from maralixibat baseline over the course of the study in the CSS score
- Change from maralixibat baseline over the course of the study in sBA levels
- Change from maralixibat baseline over the course of the study in mean total serum bilirubin

[redacted]

- Change from maralixibat baseline in height and weight z-score over the course of the study

[redacted]

[redacted]

ItchRO™ (subjects with ALGS or PFIC)

For both the ItchRO(Obs)™ [redacted] severity is item 1 on the instrument and frequency is item 3. The mean change in the average morning ItchRO(Obs)™ severity score between maralixibat baseline and each visit [redacted]

[redacted]

The maralixibat baseline average morning ItchRO(Obs)™ score [redacted] prior to the first dose of maralixibat in the predicate study.

[redacted]

If a caregiver is not compliant with the ItchRO(Obs)™ during the week prior to a study visit, [redacted] On study compliance for the ItchRO(Obs)™ will be defined as [redacted]

Clinician Scratch Scale

Actual and change from maralixibat baseline values will be summarized over time.

[redacted]

Serum Bile Acids

Actual and percent change from maralixibat baseline values will be summarized over time.

[redacted]

[redacted]

Weight and Height Measurements

Weight and height will be summarized descriptively by study visit and disease group as observed and change from maralixibat baseline values. In addition to summarizing observed and change from baseline values in weight and height measurement, weight and height measurements will also be summarized as a z-score for a subject's age and gender.

[redacted]

8.8 Other Analyses

[redacted]

[redacted]

8.8.4 Additional Analyses

Because this is an open-label study, additional analyses may be performed to explore both safety and efficacy measures collected in this study. All such analyses will be interpreted cautiously and not used for formal inference, although inferential statistics may be used as part of the data summary.

9 STUDY CONDUCT

This study is conducted in accordance with current applicable regulations, 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's and Sponsor's files, as appropriate.

9.1 Sponsor's and Investigator's 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 subject 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 sufficient 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 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, subjects' medical records and CRFs in accordance with current GCP and the respective local and (inter)national government 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

This is a long-term study expected to continue until the end of study or until the Sponsor decides otherwise. The Sponsor may suspend or terminate the study, or part of the study, at any time for any reason.

When the study is terminated, the Sponsor will notify all Investigators to schedule EOT/ET visits for subjects who at that time are still receiving treatment with maralixibat.

When the study is suspended or terminated, the Sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate.

Should the study be temporarily suspended due to safety concerns, re-initiation will follow local laws and regulations (see Section 7.5).

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

9.2 Investigator's 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 subjects 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 Sub-Investigators are provided to the study Sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the Investigator should, with the subject's consent (and/or assent when appropriate), inform them of the subject's participation in the study.

9.2.2 Protocol Adherence and Investigator Agreement

The Investigator and any Sub-Investigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those subjects 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/EC and provide them with a detailed written explanation. Upon study completion, the Investigator will provide the Sponsor, IRB/EC, 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 labs) are not required to be collected in the CRF except for those that are directly relevant to the monitoring of an AE/SAE; collection of other values may be requested by the Sponsor.

Electronic CRFs should be handled in accordance with instructions from the Sponsor.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto 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 for by the Investigator. All data, except data entered directly into another platform (e.g., electronic), 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 are 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 subject's medical file, daily dosing records and clinical laboratory reports.

The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data. Non-study site personnel will not disclose any personal information or personal medical information.

The study subject'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 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 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 or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in IP; any significant equity interest in the Sponsor or subsidiaries as defined in 21 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 are 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. 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 Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the Sponsor or its representatives, and the IRB/EC 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

Samples may be used to 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 needs 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.

As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of maralixibat may evolve during the conduct of the trial, the analyses of the stored specimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial.

The 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 subjects 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 informed consent.

Identifiable samples can be destroyed at any time at the request of the subject. During the conduct of the study, a subject 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. Subjects may at any time contact the Investigator if they wish to be informed about results derived from stored specimens.

9.8 Ethical Considerations

9.8.1 Informed Consent/Assent

It is the responsibility of the Investigator to obtain written informed consent (and/or assent when appropriate) from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and ICH GCP requirements. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form (and/or assent when appropriate) or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. The informed consent form (and/or assent when appropriate) also includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, to access applicable source data. Signed consent and assent forms must remain in each subject's study file and must be available for verification at any time.

The PI provides the Sponsor with a copy of the consent form (or assent as applicable) that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC'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 informed consent document (approved by the Sponsor or their designee), relevant supporting information and all types of subject recruitment information will be submitted to the IRB/EC for review, and all must be approved prior to site initiation. Study medication supplies will not be released until written IRB/EC 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/EC must approve any amendments to the protocol and revisions of all informed consent documents, unless there is a subject safety issue. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

The IRB/EC will be kept apprised of the progress of the study and of any changes made to the protocol. The IRB/EC 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 subjects 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 HIPAA must provide documentation of this fact.

The confidentiality of subject 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 subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented (and/or assent when appropriate) to take part 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 following: 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 IRBs/ECs which 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 subjects' identities.

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

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

The study monitor, other authorized representative 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 subjects 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 websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

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13 APPENDICES

Appendix 1 Clinical Outcomes Assessments

The following Clinical Outcomes Assessments will be used in this study:

Clinical Outcomes Assessment	Completed by*
ItchRO(Obs)™	Caregiver
[redacted]	
Clinician Scratch Scale	Clinician
[redacted]	

ItchRO(Obs)™=Itch-Reported Outcome observer instrument; [redacted]

* For the ItchRO™, [redacted]
The same module will be used for the duration of the study, regardless of subsequent birthdays throughout the study.

Appendix 2 Observer Itch-Reported Outcome Instrument ItchRO(Obs)™

ItchRO(Obs): Morning Diary

Based on observations or what your child told you about his/her itching, how severe were your child's itch-related symptoms (rubbing, scratching, skin damage, sleep disturbances or irritability) from when he/she went to bed last night until he/she woke up this morning?

Select one response below.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe
- ☐ I don't know

Below, please select all that contributed to your answer.

- ☐ Child reported itching
- ☐ Observed difficulty falling asleep or staying asleep (sleep disturbance)
- ☐ Observed rubbing or scratching
- ☐ Observed new or worsening marks on the skin due to rubbing or scratching
- ☐ Observed fussiness or irritability

While you were observing your child from when he/she went to bed last night until he/she woke up this morning, how much of the time was your child rubbing or scratching?

Select one response below.

- ☐ None
- ☐ A little bit of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ Almost all of the time/constantly
- ☐ I don't know

ItchRO(Obs): Evening Diary

Based on observations or what your child told you about his/her itching, how severe were your child's itch-related symptoms (rubbing, scratching, skin damage, sleep disturbances or irritability) from the time he/she woke up this morning until he/she went to bed?

Select one response below.

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe
- ☐ I don't know

Below, please select all that contributed to your answer.

- ☐ Child reported itching
- ☐ Observed difficulty falling asleep or staying asleep (sleep disturbance)
- ☐ Observed rubbing or scratching
- ☐ Observed new or worsening marks on the skin due to rubbing or scratching
- ☐ Observed fussiness or irritability

While you were observing your child from the time he/she woke up this morning until he/she went to bed, how much of the time was your child rubbing or scratching?

Select one response below.

- ☐ None
- ☐ A little bit of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ Almost all of the time/constantly
- ☐ I don’t know

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Appendix 6 Clinician Scratch Scale

This scoring scale was originally developed to assess pruritus before and after surgical intervention in children with ALGS and PFIC (Whitington and Whitington, 1988).

The clinician will rate the subject's pruritus, as evidenced by scratching, according to the following scale:

Score	Description
0	None
1	Rubbing or mild scratching when undistracted
2	Active scratching without evident skin abrasions
3	Abrasion evident
4	Cutaneous mutilation, haemorrhage, and scarring evident

[redacted]

[redacted]

Appendix 8 Management of Clinical Study Procedures During Covid-19 Pandemic or Other Force Majeure

This appendix provides guidance for subject safety and ongoing access to medical care and investigational product during the global novel coronavirus 2019-nCoV (COVID-19) pandemic. During this global public health crisis, pragmatic and harmonized actions are required to ensure the necessary flexibility and procedural simplifications that are needed to maintain the integrity of the clinical studies and to ensure the rights, safety, and wellbeing of study subjects and the safety of clinical study staff.

The measures detailed here will be implemented across Mirum studies on a temporary basis until the pandemic is considered resolved by governmental and public health organizations, as applicable.

Regardless of the guidance provided below, consideration should be given to public health advice at the study locations and individual benefit/risk in treatment decisions for subjects at the study site during the pandemic (EMA 2020; FDA 2020). Logistical requirements should also be considered, such as the ability of subjects to travel to the study site, accessibility of public transportation, site restrictions on clinical trials, etc.

The safety of the study subjects is of primary importance, and risks of involvement in the study, in particular with added challenges due to COVID-19, will be weighed against anticipated benefit for the trial subjects and society.

Study Participation

New Subject Enrollment

Study sites may continue to recruit new subjects into ongoing studies, if deemed appropriate on benefit/risk assessment as described and provided that ALL of the following activities to preserve study integrity can be met:

Upon discussion with the site monitor, the study site has confirmed the ability to enroll and manage new subjects effectively and in compliance with the protocol and this appendix.
Upon discussion with the medical monitor, the study site has confirmed that appropriate safety monitoring can take place, in compliance with the protocol and this appendix.
Data will continue to be entered into the Case Report Form (CRF) and queries resolved in a timely manner.
The site monitor is able to access the study site to perform on-site monitoring or is able to perform remote monitoring of data.

Conduct of Telephone/Virtual or Alternative Visits

Due to the current pandemic, it is conceivable that not all subject visit commitments can be fulfilled. If a subject or caregiver is unable or unwilling to attend a study visit or a study site is unable to permit on-site visits by subjects and caregivers, adaptation of the on-site visit to a telephone visit, virtual visit, or use of an alternative location for assessment (including but not limited to local laboratories, family physician, home visit) is recommended to ensure continuity

of subject care during the study (as an interim measure). Priority should be given to maintaining ongoing safety follow-up. Study sites should speak with their site monitor before performing a telephone or virtual visit so he or she may provide guidance regarding logistics that may need consideration. Study sites should contact the medical monitor if the subject must miss more than one on-site visit in succession, because multiple incomplete visits may have the potential to impact evaluation of study endpoints as well the subject's safety. For all remote visits, medical monitor and Mirum medical approval is required. The decision to accept protocol deviations for missed assessments is based on the risk to the subject of discontinuing study participation versus missed assessments, such as safety laboratory assessments. Where possible, a home visit should be organized to avoid missing visits or assessments.

Alternative Blood Sample Collection:

It is preferred that this alternative blood sample collection be performed in a manner to support delivery of samples to the central laboratory, but the analysis of samples may be performed at local laboratories, if necessary. If the analyses are performed at the local laboratories, the site will follow up with the subject to obtain the results and local laboratory reference ranges for data entry into EDC as soon as they are available.

Safety Reporting and Maralixibat Treatment Recommendations for COVID-19

The sponsor recognizes that COVID-19 presents an increased risk for all subjects. Due to the potential impact of COVID-19 on multiple organ systems, the sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected COVID-19 while receiving treatment with maralixibat.

The following safety reporting guidelines are required:

All confirmed or suspected COVID-19–related adverse events (AEs) must be recorded in the CRF and the Serious Adverse Event (SAE) Report Form if the event meets the seriousness criteria. SAEs are reportable to the sponsor within 24 hours of awareness. All study drug interruptions or modifications must be recorded on the AE and drug administration CRFs.

If an event is suspected to be COVID-19 infection, continuation of study drug, and any dose modifications should be assessed on a case-by-case basis, depending on the subject's health status, and discussed with the medical monitor if needed. The COVID-19 infection should be managed as per local treatment guidance and Investigator's clinical judgment.

Drug-Drug Interaction Guidance Regarding Medication Used to Treat COVID-19:

The study protocol and Investigator's Brochure should be referenced for drug-drug interaction information. For further information the medical monitor can be contacted.

Documenting Alternative Contacts with Subjects:

If an on-site visit is replaced by a telephone or virtual study visit, the following are guidelines for data capture:

- If the visit is listed as on-site but is performed remotely, data should be captured as per a normal visit (i.e., document the remote visit in the source documents and complete the relevant CRF pages to capture the visit date, and any possible assessment that can be obtained, such as AEs, study drug administration, and/or concomitant medications and any additional safety or efficacy information). All assessments that cannot be performed should be marked as not done in the CRF. Any protocol deviations related to COVID-19 should be recorded in the clinic notes, prefixed COVID-19.

- Visits that require procedures that cannot be performed remotely should be discussed with the site monitor because this may impact efficacy or safety analyses and should be documented as a protocol deviation due to COVID-19.

Site-to-Subject Drug Shipment Instructions during Pandemic Containment

If a subject is unable to go to the study site because of pandemic containment, the study site may ship the study drug to the home of the subject (or other agreed location) following approval by the sponsor.

For such shipment, the following conditions must be met:

- The sponsor is responsible for delivery of the study drug to the study site. Organization of shipments from the site to the subject will be the responsibility of the study site.

- The subject or caregiver is informed about the shipment method, confirms the address for receipt of the drug, and agrees that his or her personal information (i.e., name and address) may be given to a professional carrier.

- The investigator or designee (e.g., pharmacy) securely packages the drug for shipment.

- A professional carrier is used by the investigator or designee to ship the drug securely and maintain chain of custody, with evidence provided. Maralixibat should be stored and shipped under refrigerated conditions (2°C–8°C) using ice packs. Shipments that are expected to be

completed within 48 hours from pickup to delivery do not generally require any specific temperature monitoring.

- To respect subject confidentiality, the carrier should be given only the name and address of the recipient. The sponsor should not receive any personal information about the subject.

- A procedure is defined with the carrier to immediately upon delivery confirm the receipt of the drug by the recipient and that it is received in good condition.

- The site contacts the recipient to confirm the receipt of the drug and to confirm it is delivered in the expected conditions (e.g., not leaking, not broken) and gives instructions about the drug administration and storage. If the drug is delivered and is not within the expected conditions, the site will give instructions to the subject about the next steps.

- The investigator or designee completes the drug accountability forms with each shipment made directly to a subject.

- All documentation (originals/copies, as applicable) related to the site-to-subject drug shipment should be filed in the investigator site file, including the list of the medication being delivered, the quantity involved, and documentation of receipt by the trial subject.

- Subjects should retain unused study drug and containers and return them to the investigator the next time they visit the investigator site

COVID-19–Specific Remote Source Data Verification

The source documents/source data considered for remote source data verification (rSDV) are those related to the primary endpoint, AEs/SAEs, important medical events, or the reasons for exclusion of a subject from the study.

Remote access to source documents/source data for monitoring purposes may only take place in justified exceptional cases and only to the extent strictly necessary (i.e., only when direct access to study source data is not available due to COVID-19 pandemic restrictions).

The following three options for source data reconciliation without the study monitor being physically present at the study site may be used, based on the site-specific source documentation/source data:

The study site will provide the study monitor, under the responsibility of the investigator, with copies of the source documents/source data in which personal identifying information of the study subjects and information pertaining to their privacy has been obscured or redacted.
Under the responsibility of the investigator, the study site will grant the study monitor direct, controlled, remote access to the systems with which the source documents/source data are managed.

The study site will grant the study monitor, under the responsibility of the investigator, passive access to the source documents/source data via live image transmission (e.g., sharing of the screen or image/sound transmission).

Depending on the option selected for rSDV, the full process to be followed and requirements needed to be met are described in the specific rSDV section of the clinical monitoring plan as well as in a corresponding guideline for the investigators.

In the case of live image transmission, this will take place exclusively via secured systems/environments and systems/servers within European Economic Area/European Union.

In all cases, rSDV will be conducted exclusively by the authorized persons in accordance with the written informed consent of the study subjects and the written agreement of the Principal Investigator (PI)/PIs institution.

Remote source data verification will take place in a protected environment (i.e., providing protection from unauthorized access in any form, including the use of privacy screens to prevent unauthorized viewing of source documents/source data), the source documents/source data reviewed by the study monitor will not be permanently stored by the study monitor, and if necessary, temporarily saved files (including ones automatically generated by the system) are permanently deleted at short notice.

The study monitor will securely destroy any copy of obscured/redacted documents, whether paper or electronic, as soon as they have been used for source data verification.

Appropriate corrective measures will be implemented in the event of technical difficulties or if the security of the transmission is no longer guaranteed.

The information and communication technology used by the sponsor and the study site for rSDV is designed in such a way that secure and General Data Protection Regulation–compliant transmission is guaranteed.

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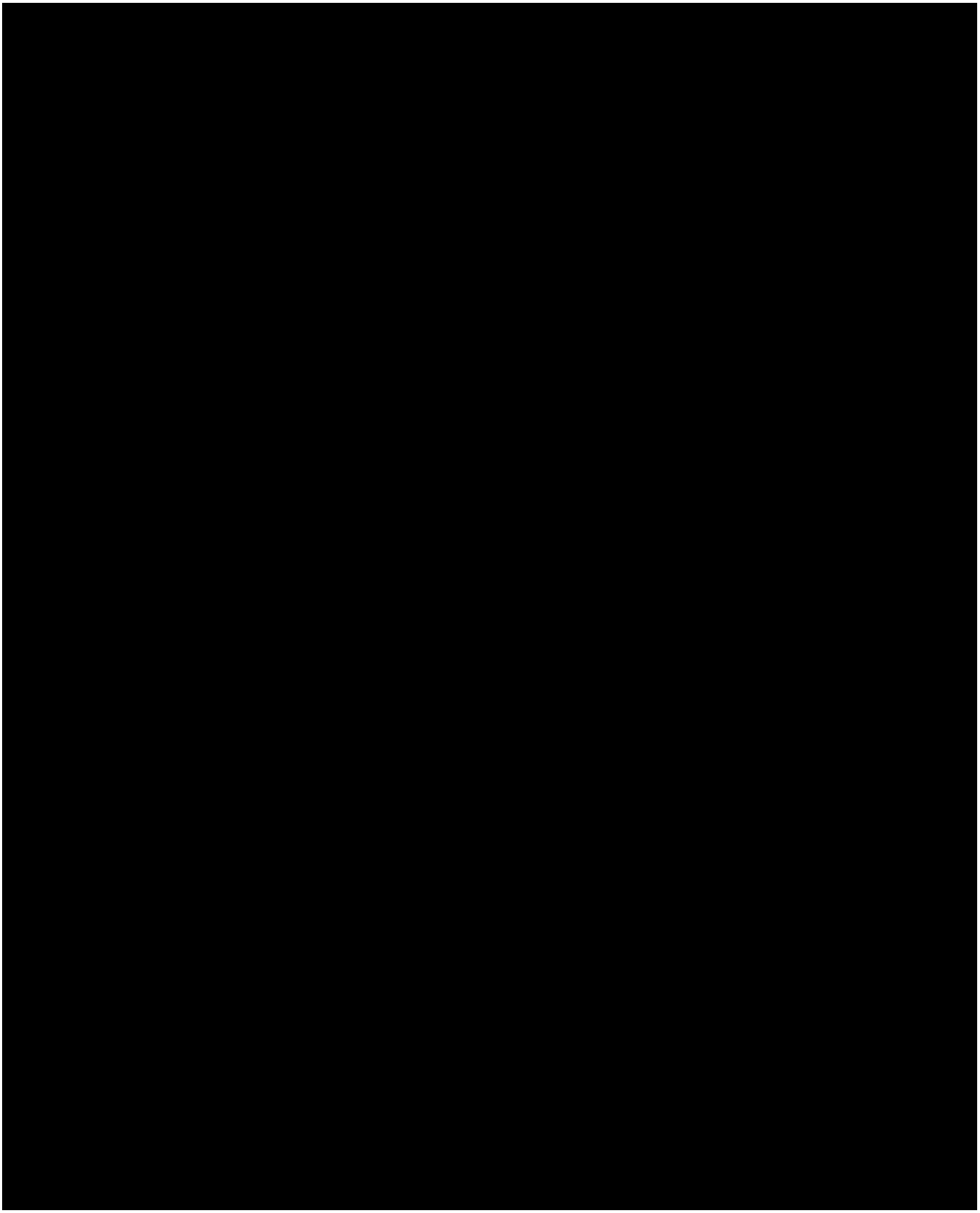

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