PROTOCOL: MRX-503

TITLE: An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)

DRUG: Maralixibat

IND: 119916

EudraCT: 2019-003395-39

SPONSOR: Mirum Pharmaceuticals Inc.
950 Tower Lane
Foster City, CA 94404

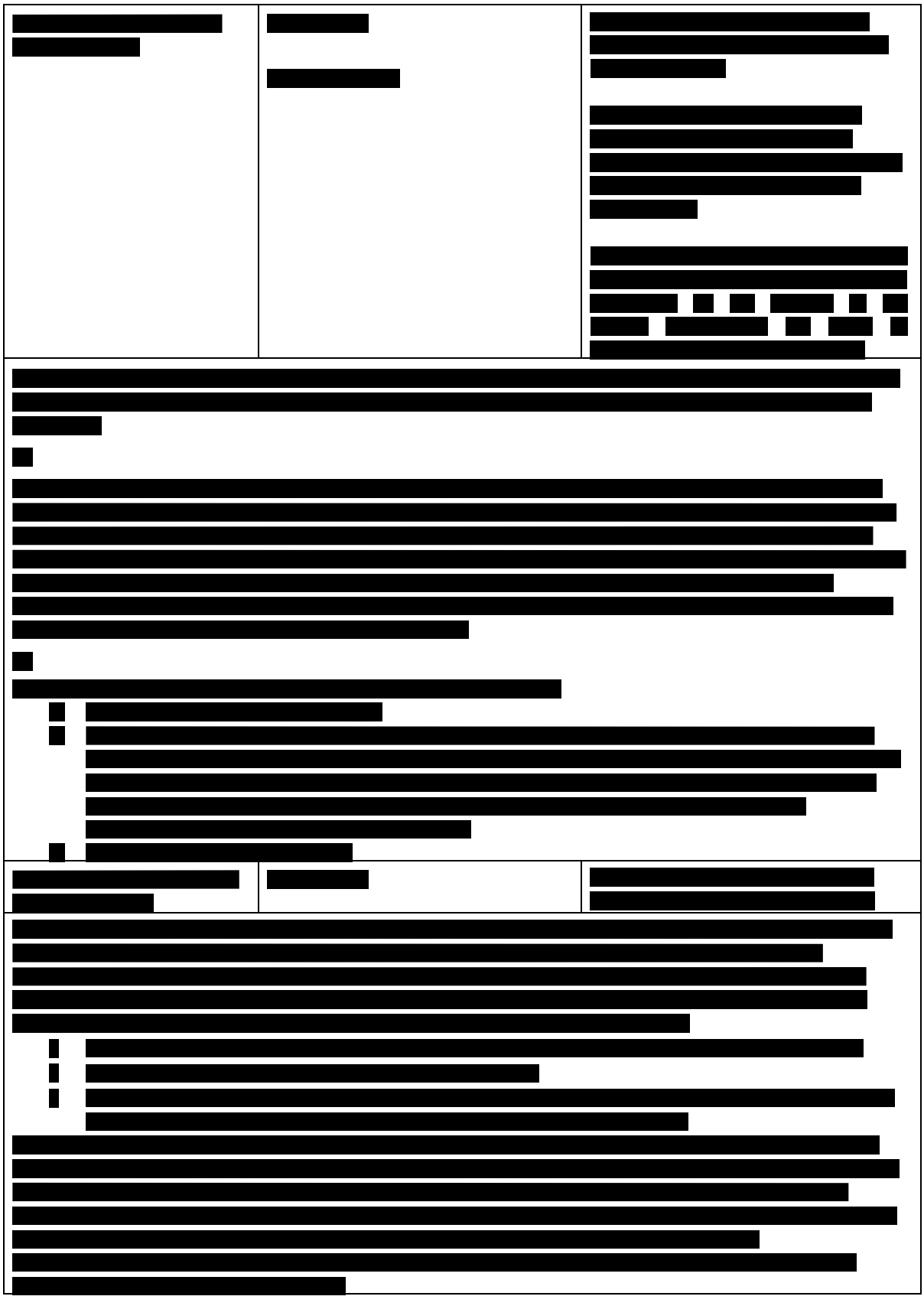
PRINCIPAL/ COORDINATING INVESTIGATOR: [redacted]

PROTOCOL HISTORY: Amendment 2: 18 November 2021
Amendment 1: 15 June 2020
Version 1: 23 September 2019

SUMMARY OF CHANGES FROM PREVIOUS VERSION

[redacted]

[redacted]



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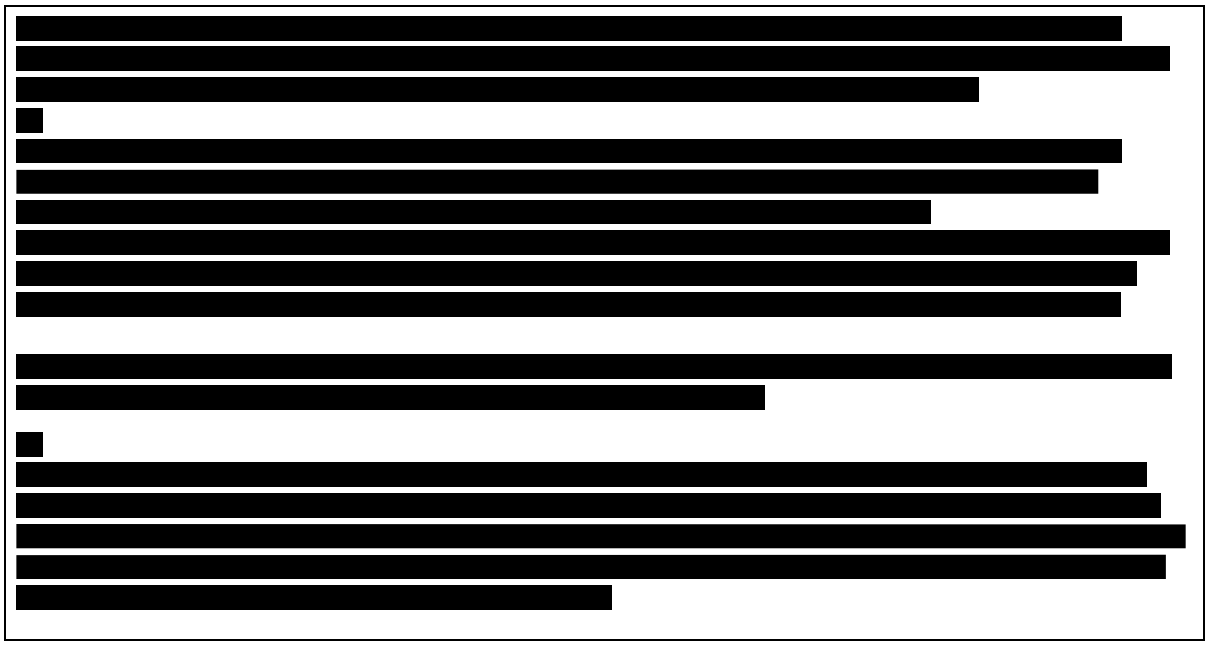

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STUDY SYNOPSIS

PRODUCT NAME/NUMBER	Maralixibat
PROTOCOL NUMBER	MRX-503
EUDRACT NUMBER	2019-003395-39
DEVELOPMENT PHASE	3
PROTOCOL TITLE	An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)
INDICATION	Progressive familial intrahepatic cholestasis (PFIC)
OBJECTIVES	Primary objective: The primary objective of the study is to evaluate the long-term safety and tolerability of maralixibat. Secondary objectives: To evaluate the long-term efficacy of maralixibat, including the maintenance of severity and frequency of pruritus as well as serum bile acids (sBA) over time and growth in the primary cohort Exploratory objectives: [redacted]
ENDPOINTS	***Safety endpoints:*** The evaluation of long-term safety and tolerability of maralixibat is the primary objective of the study. The primary endpoints related to safety and tolerability include: • Incidence of treatment-emergent adverse events during the study by System Organ Class and Preferred Term (serious, nonserious, related, and non-related) • Safety laboratory parameters (clinical laboratory tests [hematology, chemistry, urinalysis, lipid-soluble vitamins, and related measures)] over time Additional safety and tolerability endpoints include the following: • Change from baseline in physical examination findings (including body weight, height, and body mass index) • Change from baseline in vital signs • Concomitant treatment usage

	The evaluation of efficacy is the secondary objective of the study. The secondary efficacy endpoints include the following: • Mean change from maralixibat baseline in the average morning Observer-Reported Itch Reported Outcome Instrument (ItchRO[Obs]) severity score over time • Maintenance of treatment effect based on the average morning ItchRO(Obs) severity scores over time • Mean change from maralixibat baseline over time in sBA levels • Mean change from maralixibat baseline over time in the average morning ItchRO(Obs) frequency score • Proportion of subjects who experience an sBA control over time (sBA control definition is detailed in the statistical analysis plan [SAP]) • Proportion of responders over time (responder definitions are detailed in the SAP) • Mean change from maralixibat baseline over time in height and weight z-scores • Time from maralixibat baseline to liver-associated events The exploratory endpoints include the following: • [redacted]
RATIONALE	There is currently only one approved pharmacological treatment for PFIC. Preliminary data from the Phase 2 Study LUM001-501 (an open-label study of the efficacy and long-term safety of maralixibat in the treatment of cholestatic liver disease in pediatric subjects with PFIC) report that a subgroup of subjects with PFIC2 experienced significant clinical benefit as manifested by a large reduction or normalization of sBA, reduction in pruritus (assessed using the ItchRO(Obs)]), and normalization of elevated total serum bilirubin and ALT for those subjects with elevated baseline values. Also, twice-daily (BID) dosing led to a higher response rate compared with once-daily dosing. The primary objective of the present study is to evaluate the long-term safety and tolerability of maralixibat. The safety assessments used in this study are standard and widely used in clinical studies. Evaluation of efficacy is a secondary objective of the present study.

	By enrolling subjects from the antecedent study (MRX-502), this study is designed to evaluate the long-term safety of maralixibat. In addition, treatment effect and the maintenance of treatment effect on pruritus and sBA as well as the long-term benefit on other parameters such as growth and the time to liver-associated events will be evaluated.
STUDY DESIGN	This is an international, open-label, multicenter, Phase 3 study to evaluate the long-term safety and efficacy of maralixibat in the treatment of pediatric subjects with PFIC who have previously participated in and completed [redacted] End-of-Treatment [EOT] visit) of Study MRX-502. All subjects will receive maralixibat in Study MRX-503. It is recommended that the option to participate in the MRX-503 study is presented well in advance of the subjects' EOT Visit ([redacted] in MRX-502 to allow the subjects and caregivers sufficient time for an informed decision about study MRX-503 participation. The study MRX-503 baseline visit (Day 0) will occur on the same day as the Study MRX-502 EOT visit. Subjects who do not complete the Study MRX-503 baseline visit (Day 0) on the same day as the Study MRX-502 EOT visit will be considered for participation in Study MRX-503 only after discussion with the medical monitor. Study MRX-503 will be divided into a [redacted] (maximum [redacted]) Dose Escalation period and a long-term Stable Dosing period at 600 µg/kg BID maralixibat (or the maximum tolerated dose) until the study is terminated by the sponsor or the subject discontinues the study or transitions to commercial product. During the Stable Dosing period, subjects will continue to receive maralixibat with safety and efficacy assessments occurring every [redacted] until termination of the study or transition to commercial supply of maralixibat, at the discretion of the sponsor. Subjects will be contacted by telephone or email for safety follow-up [redacted] days after the last dose of maralixibat. At the EOT/early termination visit, subjects who discontinue from the study will be provided an option to participate in a long-term follow-up period for liver disease. Subjects who consent to this follow-up will be contacted by study staff to complete a disease-related event questionnaire at least once a year (from the end of treatment/early termination visit) until disease progression or an event occurs (whichever comes first). The Dose Escalation period will consist of the following weekly steps: [redacted] [redacted] [redacted] • [redacted] 600 µg/kg maralixibat BID for the remaining duration of the study All subjects will initiate dose escalation at [redacted] regardless of the subject's treatment arm in Study MRX-502, to maintain the treatment blind while Study MRX-502 is still ongoing. Dose escalation should occur in the absence of major safety (e.g., liver parameters) or tolerability concerns (e.g., gastrointestinal [GI]-related TEAEs) related or possibly related to maralixibat. Subjects with such safety concerns can be down-titrated to a lower, previously tolerated dose level for 1 week before continuing dose escalation. The minimum dose to continue in the study will be [redacted] µg/kg maralixibat BID; subjects who cannot tolerate this dose will be discontinued from the study. Investigators have until Week 6 to determine the maximum tolerated dose; if re-challenges or further dose escalations fail, the subject will remain on the

	maximum tolerated dose level for the remainder of the Stable Dosing period. Dose reductions are allowed for the above-mentioned safety or tolerability reasons down to a minimum level of [redacted] µg/kg BID. Subjects who cannot tolerate this dose ([redacted] µg/kg BID) will be discontinued from the study. After a dose interruption, subjects should reinitiate dosing at their maximum tolerated dose.
PLANNED NUMBER OF SUBJECTS	Up to 90 subjects are estimated to be eligible for enrollment in this extension study by completing Study MRX-502.
STUDY ENTRY CRITERIA	**Inclusion criteria:** 1. Provide informed consent and assent (as applicable) per Institutional Review Board/Ethics Committee 2. Completion of Study MRX-502; treatment interruption between MRX-502 and MRX-503 should be avoided. Subjects who do not complete the Study MRX-503 baseline visit (Day 0) on the same day as the Study MRX-502 EOT visit will be considered for participation in Study MRX-503 only after discussion with the medical monitor. 3. Males and females of nonchildbearing potential. Males and nonpregnant, nonlactating females of childbearing potential who are sexually active must agree to use acceptable methods of contraception during the study through 30 days after the last dose of maralixibat. 4. Females of childbearing potential must have a negative urine pregnancy test result at the baseline visit (Day 0). 5. Access to email or telephone for scheduled remote visits. 6. Ability to read and understand the questionnaires (both caregivers and subjects above the age of assent). 7. Access to consistent caregiver(s) during the study 8. Subject and caregiver willingness to comply with all study visits and requirements

	Exclusion criteria: 1. Any female who is pregnant or lactating or who is planning to become pregnant 2. Administration of prohibited medication between the MRX-502 EOT visit and the MRX-503 baseline visit (Day 0) 3. History of noncompliance in study MRX-502, nonadherence to medical regimens, unreliability, mental instability, or incompetence that could compromise the validity of informed consent or lead to nonadherence with the study protocol based on investigator judgment 4. Experienced an adverse event (AE) or serious adverse event (SAE) related to maralixibat during the MRX-502 study that led to permanent discontinuation of the subject from maralixibat 5. Any other conditions (including decompensated liver disease) or laboratory abnormalities that, in the opinion of the investigator or sponsor medical monitor, may compromise the safety of the subject or interfere with the subject participating in or completing the study 6. Cognitive impairment of the subject or caregiver that would, in the opinion of the investigator, preclude appropriate understanding of study information and compliance with study procedures
TEST PRODUCT	Name: maralixibat. Dose, route, frequency: Subjects will receive ready-to-use maralixibat oral solution based on individual body weight, up to 600 µg/kg BID. Fixed concentrations of maralixibat oral solutions (i.e., [redacted] mg/mL) will be used. To accurately measure the required volume, 0.5-, 1.0-, and 3.0-mL sized oral dosing dispensers will be provided. Maralixibat requires refrigerated storage conditions (2°C–8°C).
CONTROL PRODUCT(S)	Not applicable
TREATMENT REGIMENS	The morning dose should be administered approximately 30 minutes before breakfast and 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.
COORDINATING/ PRINCIPAL INVESTIGATOR	[redacted]
PLANNED STUDY SITES	The study will be conducted at multiple sites in North America, Europe, Asia, and South America. Other regions may be added if that was necessary for enrollment purposes of Study MRX-502. Sites will have participated in the antecedent Study MRX-502. Sites that did not participate in Study MRX-502 but referred subjects to participating sites in MRX-502 may be opened in Study MRX-503.
CRITERIA FOR EVALUATION	Because subjects in MRX-503 will have completed MRX-502, some will be on active treatment at the start of MRX-503. [redacted]

	[redacted]
STATISTICAL METHODS	**Analysis Populations:** The following analysis population are planned for this study: • Safety Population: The Safety Population will consist of all subjects who receive at least 1 dose of maralixibat in MRX-503. • **Intent-To-Treat (ITT) Population**: The ITT Population will consist of all randomized subjects. Additional subgroups of the ITT population will be specified based on the presence/absence of postbaseline efficacy assessments for particular efficacy endpoints. • Per-Protocol (PP) Population: The PP Population will consist of all subjects in the Safety Population who receive at least 1 dose of maralixibat and do not have any major protocol violations or deviations. Major protocol violations/deviations will be identified prior to database lock. Note that subjects who were on placebo in MRX-502 will be receiving maralixibat for the first time in this study, whereas those who were on active treatment in MRX-502 will be continuing treatment. As such, the efficacy analyses will be performed by MRX-502 treatment sequence to account for those differences in exposure. **Statistical Methodology:** A SAP that describes the details of the analyses to be conducted will be written prior to database lock. The SAP will provide the statistical methods and definitions for the analysis of the safety and efficacy data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, medical, disease history, study medication exposure, and prior medications. [redacted]

[redacted]	[redacted]

	[redacted]

	[redacted]
SAMPLE SIZE DETERMINATION	All subjects who complete the core Study MRX-502 are eligible to roll over into Study MRX-503 if they elect to do so and they meet all eligibility criteria. Thus, the sample size is not based on clinical assumptions, clinically meaningful treatment effect, or statistical considerations.
STUDY AND TREATMENT DURATION	The study is planned to start in January 2020 and continue until approximately January 2023. The sequence and maximum duration of the study periods will be as follows: 1. Dose Escalation period: [redacted] 2. Stable Dosing period: until the study is terminated by the sponsor or the subject discontinues the study or transitions to commercial product. During the Stable Dosing period, subjects will continue to receive maralixibat with safety and efficacy assessments occurring every [redacted] until termination of the study or transition to commercial supply of maralixibat, at the discretion of the sponsor 3. Safety follow-up: [redacted]
Date of Synopsis:	Amendment 2, 18 November 2021

ABBREVIATIONS

β-hCG	beta-human chorionic gonadotropin
[redacted]	[redacted]
ABCB11	ATP binding cassette subfamily B member 11
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AFP	α-fetoprotein
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	[redacted]
ASBT	apical sodium-dependent bile acid transporter
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATP8B1	ATPase phospholipid transporting 8B1
BID	twice daily (dosing)
CBC	complete blood count
[redacted]	[redacted]
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
[redacted]	[redacted]
DMC	data monitoring committee
EC	Ethics Committee
EDC	electronic data capture
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
EMA	European Medicines Agency
EOT	end of treatment
ET	early termination
EU	European Union
FDA	Food and Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
GI	gastrointestinal
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IBAT	ileal bile acid transporter

ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
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]
ITT	intention-to-treat
LSV	lipid-soluble vitamin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
[redacted]	[redacted]
PBC	primary biliary cholangitis
PEBD	partial external biliary diversion
PCI	potentially clinically important
PD	pharmacodynamic
[redacted]	[redacted]
PFIC	progressive familial intrahepatic cholestasis
PG	propylene glycol
[redacted]	[redacted]
PK	pharmacokinetics
PP	Per-Protocol
PSC	primary sclerosing cholangitis
QD	once daily
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acids
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent AE
TJP2	tight junction protein 2 gene
TSB	total serum bilirubin
UDCA	ursodesoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
US	United States
[redacted]	[redacted]

Table 1 Schedule of Assessments ([redacted])

Procedure[a]	**Initial Dosing**	**Dose Escalation ([redacted])**					**Stable Dosing[b]**										
Visit/Subject Contact Number	**Bas./ V1[c]**	[redacted]															
Study Week	**0**	[redacted]															
Study Day	**0**	[redacted]															
Window (in days)		[redacted]															
Informed consent/assent	X																
Eligibility assessment	X																
Physical examination and vital signs[d]			X		X		X		X		X		X		X		X
Liver ultrasound																	X
Pregnancy test[e]	U[f]				U		U		U		U		U		U		U
eDiary device provided/returned[g]	P																
ItchRO(Obs), [redacted]	Twice-daily completion of ItchRO [redacted]																
Review eDiary and assess compliance			X		X		X		X		X		X		X		X
[redacted]					X		X		X		X		X		X		X
[redacted]					X		X		X		X		X		X		X
[redacted]					X		X		X		X		X		X		X
[redacted]			X		X		X		X		X		X		X		X
[redacted]											X						X
CBC with Differential			X				X		X		X		X		X		X
Coagulation			X				X		X		X		X		X		X
Chemistry Panel			X				X		X		X		X		X		X
Lipid Panel[j]			X				X		X		X		X		X		X
Urinalysis							X		X				X				X
[redacted]							X		X				X				X
sBA collection[j]			X				X		X		X		X		X		X
Lipid-soluble vitamins[j,k]							X		X		X		X		X		X
AFP sample									X								X
PK sample[l]									X								X
Serum storage sample			X				X		X		X		X		X		X
[redacted]			X				X		X		X		X		X		X
Maralixibat supplied[m]	X		X		X		X		X		X		X		X		X
Maralixibat administration[n]	Twice-daily administration																
Assess AEs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant treatments[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Schedule of Assessments (Continued from [redacted]

Procedure[a]	**Stable Dosing**[b]												
Visit/Subject Contact Number	[redacted]												
Study Week	[redacted]												
Study Day	[redacted]												
Window (in days)	[redacted]												
Physical examination and vital signs[d]		X		X		X		X		X		X	X
Liver ultrasound				X				X					X
Pregnancy test[e]		U		U		U		U		U		U	S
eDiary device provided / returned[g]													R
ItchRO(Obs), [redacted]	Twice-daily completion of ItchRO [redacted] after each scheduled onsite visit												
Review eDiary and assess compliance		X		X		X		X		X		X	X
[redacted]		X		X		X		X		X		X	X
[redacted]		X		X		X		X		X		X	X
[redacted]		X		X		X		X		X		X	X
[redacted]		X		X		X		X		X		X	X
[redacted]													X
CBC with differential		X		X		X		X		X		X	X
Coagulation		X		X		X		X		X		X	X
Chemistry panel		X		X		X		X		X		X	X
Lipid panel[j]		X		X		X		X		X		X	X
Urinalysis		X		X		X		X		X		X	X
[redacted]				X				X					X
sBA collection[j]		X		X		X		X		X		X	X
Lipid-soluble vitamins[j,k]		X		X		X		X		X		X	X
AFP sample													X
Serum storage sample		X		X		X		X		X		X	X
[redacted]		X		X		X		X		X		X	X
Maralixibat supplied [m]		X		X		X		X		X		X	X
Maralixibat administration[n]	Twice-daily administration												
Assess AEs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant treatments[p]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Schedule of Assessments (continued from [redacted]

Procedures[a]	Stable Dosing[b]	End of Treatment or Early Termination[q]	Safety Follow-Up
Visit/Subject Contact	[redacted]	**Visit**	**Subject Contact**
Study Week	[redacted]		
Study Day	[redacted]		[redacted]
Window (in days)	[redacted]	[redacted]	[redacted]
Informed consent/assent		X[s]	
Physical examination & vital signs (including height and weight)[d]	X	X	
Pregnancy test[e]	U	S	
[redacted]	X	X	
CBC with differential	X	X	
Coagulation	X	X	
Chemistry panel	X	X	
Urinalysis	X	X	
Lipid panel[j]	X	X	
sBA collection[j]	X	X	
Lipid-soluble vitamins[j,k]	X	X	
AFP sample	X	X	
Maralixibat supplied[m]	X		
Maralixibat administration[n]	X		
Assess AEs[o]	X	X	X
Prior and concomitant treatments[p]	X	X	X
Liver imaging[t]	X	X	

AE=adverse event; AFP=alpha-fetoprotein; β-hCG=β-human chorionic gonadotropin; Bas.=baseline; [redacted] CBC=complete blood count; [redacted] CRF=Case Report Form; eDiary=electronic diary; [redacted] EOT=end of treatment; ET=early termination; [redacted] ItchRO=Itch Reported Outcome; Obs=observer; P=provided; PEBD=partial external biliary diversion; [redacted] PFIC=progressive familial intrahepatic cholestasis; [redacted]; PK=pharmacokinetic; [redacted] R=returned; S=serum; sBA=serum bile acid; SC=subject contact; U=urine; V=visit; [redacted]: Progressive Familial Intrahepatic Cholestasis V2.0.

[a] See Appendix 9 for management of study procedures during pandemic.

[b] Subjects will continue treatment until the study is terminated by the sponsor or the subject discontinues the study or transitions to commercial maralixibat.

[c] The study MRX-503 baseline visit (Day 0) will occur on the same day as the study MRX-502 EOT visit. Subjects who do not complete the study MRX-503 baseline visit (Day 0) on the same day as the study MRX-502 EOT visit will be considered for participation in study MRX-503 only after discussion with the medical monitor. The evaluations and procedures completed for the study MRX-502 EOT visit will serve as the evaluations for the study MRX-503 baseline visit (Day 0), if MRX-503 baseline visit is performed in the same day as MRX-502 EOT visit or within 30 days.

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

[e] Females of childbearing potential only; result must be reviewed prior to dispensing maralixibat.

[f] If available, the subject's MRX-502 EOT Visit serum β-hCG pregnancy test results will be used for the MRX-503 baseline visit (Day 0). Otherwise, a urine β-hCG pregnancy test will be performed.

[g] Caregivers [redacted] will be instructed to complete their eDiary twice daily (morning and evening). Caregivers will be retrained on the use of the eDiary during the baseline visit (Day 0).

[h] To be completed by caregivers for all subjects.

[i] Subjects will complete the same modules they completed during the MRX-502 study.

[j] Subjects should make every effort to fast at least 6 hours prior to collection. Water intake is permitted if necessary but not recommended.

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

[l] PK samples will be drawn predose and ~2.5 hours after the morning dose.

[m] If needed, maralixibat may be supplied via direct-to-patient shipments in between site visits.

[n] Subjects should take the final Study MRX-502 dose in the morning on the day of the Study MRX-503 baseline visit. Eligible subjects will begin dosing with maralixibat in the evening on the day of the MRX-503 baseline visit (Day 0). Subsequently, as much as possible, the morning dose should be administered ~30 minutes before breakfast and the evening dose ~30 minutes before the main evening meal. During the Dose Escalation period, dose escalation should occur in the absence of major safety (e.g., liver parameters) or tolerability concerns (e.g., gastrointestinal-related treatment-emergent adverse events) related or possibly related to the maralixibat. Subjects with such safety concerns can be down-titrated to a lower, previously tolerated dose level for 1 week before continuing dose escalation.

[o] AEs for study MRX-503 will only be collected from the time informed consent (and assent when appropriate) is signed. AEs ongoing at the end of study MRX-502 will be carried over and followed through until resolution.

[p] Concomitant medications continuing at the end of study MRX-502 will be carried over and followed through until resolution.

[q] Study sites should record dates of any future scheduled procedures related to PFIC (e.g., PEBD, ileal exclusion, liver transplant, or listed for liver transplant), if known at this visit. Assessments listed under the EOT/ET visit do not need to be repeated if the visit occurs within 14 days of a previous clinic visit (unless otherwise specified; e.g., pregnancy test).

[r] [redacted] Repeating Cycle visit will start at [redacted]; visits should continue at [redacted] etc.

[s] Subjects who provide consent (and assent as appropriate) will be followed up at least once a year (from the EOT/ET visit) to check disease progression.

[t] A liver ultrasound/MRI scan will be done starting from [redacted] and every [redacted] thereafter (i.e., [redacted]) and at EOT/ET.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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 (ATP8B1), ATP binding cassette subfamily B member 11 (ABCB11), 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), whereas 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).

PFIC 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). Whereas 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 of 21 patients (62%) 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).

Given the clinical outcomes associated with PFIC, including the negative impact on patients' and caregivers' quality of life, and the fact that there is currently only one approved pharmacological treatment for PFIC, there is a high unmet medical need for therapies for this disease.

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 IBAT). Maralixibat was designed to be minimally absorbed, thereby maximizing the local exposure of the molecule to the receptor, minimizing systemic exposure of the drug, and 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 doses described in this document are of maralixibat chloride but are presented as "maralixibat." For example, 600 µg/kg maralixibat chloride is equivalent to 570 µg/kg maralixibat free base but will be referred to as 600 µg/kg maralixibat throughout this document.

The pharmacokinetics, 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 Alagille syndrome (ALGS) and PFIC.

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 at or below 20 mg in adults and in pediatric patients with ALGS receiving doses up to 280 µg/kg/day (maximum dose 20 mg/day). 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 (maximum observed plasma concentration [C_{max}], terminal elimination half-life [$t_{1/2}$], 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 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. No SAEs related to maralixibat have been reported in these studies and no clinically significant laboratory abnormalities were documented in maralixibat-treated subjects.

Study LUM001-201 was a Phase 2, randomized, double-blind, placebo-controlled study to evaluate maralixibat in combination with ursodeoxycholic acid (UDCA) in subjects with PBC. There was no significant difference between overall maralixibat and placebo with respect to pruritus reduction, as measured by the Adult Itch Reported Outcome Instrument (Adult ItchRO™) score, the primary endpoint, or 5-D Itch score. Treatment-related adverse events were most frequently reported in the gastrointestinal (GI) disorders System Organ Class (SOC; 71.4% vs. 41.7% in the maralixibat and placebo groups, respectively) and included TEAEs of diarrhea, nausea, and abdominal pain upper.

LUM001-401 was a Phase 2, open-label, single-cohort, pilot study to evaluate safety, tolerability, and efficacy in 27 subjects with PSC. Significant reductions from baseline in serum bile acid (sBA) levels, but not other liver function parameters, were observed during the study. There was a nominally statistically significant reduction in pruritus, as measured by the Adult ItchRO score during the study. The majority of TEAEs were mild or moderate GI TEAEs (81.5%): 51.9% diarrhea, 33.3% nausea, 29.6% abdominal pain.

More than 150 subjects have been exposed to maralixibat, some for longer than 6 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 or possibly related SAEs included abdominal pain upper (3 events, 1 subject), abdominal pain, diarrhea, increased blood bilirubin, increased international normalized ratio (INR), pancreatitis, increased alanine aminotransferase (ALT), autoimmune hepatitis, hematochezia, and anemia. No deaths or important new 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 related, 10%–20% probably or possibly related events) of subjects with ALGS, similar to the ALT elevations reported after PEBD surgery in this patient population and within the limits of the variability observed in a natural history cohort of patients with ALGS. No predictors of this treatment response have been identified so far. None of the observed events was 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 or bilirubin or liver enzyme elevations in patients with PFIC.

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 demonstrated significant improvements in a subgroup of 6 out of 19 subjects with nontruncated 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 ≥70% 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. Finally, the treatment responders experienced a significant catch-up growth, as indicated by a positive height and weight z-score change from baseline compared with those subjects who did not respond to maralixibat treatment, who continued to follow the natural history of the disease with further delay in their growth.

1.3 Summary of Potential Risks and Benefits

An important therapeutic advantage of maralixibat is its high selectivity for IBAT, the location of IBAT 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 studies, absorption, distribution, metabolism, and elimination (ADME) studies, and 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 IBAT by maralixibat results in increased fecal bile acid excretion, inhibition of the postprandial rise in sBAs, 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, a few instances of GI-related AEs have resulted in study discontinuations. Preliminary data from the ongoing studies indicate that 1 subject has discontinued due to a GI-related AE (hematochezia).

Related SAEs from the completed studies include abdominal pain, diarrhea, pancreatitis, increased blood bilirubin (which resulted in interruption of treatment with maralixibat), increased INR, cholangitis, and increased ALT. The study medication was restarted for the subject 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 Phase 2 study in subjects with PFIC (LUM001-501) showed a subgroup of 7 out of 19 subjects with nt-PFIC2 that demonstrated multiparameter improvements of normalization or ≥70% decrease in sBA levels, concomitant with an increase in 7αC4 levels, a disappearance or clinically meaningful improvement in pruritus, an increase in quality-of-life scores as well as normalization of liver-related parameters (AST/ALT and TSB) in those subjects with abnormal baseline values. Most importantly, the treatment responders experienced a significant catch-up growth, as indicated by a positive height and weight z-score change from baseline compared with those subjects who did not respond to maralixibat treatment.

The overall safety, tolerability, and preliminary efficacy of maralixibat in ongoing and completed studies indicate that there is a positive benefit-risk profile for the treatment of rare pediatric cholestatic liver diseases. LIVMARLI™ (maralixibat) oral solution is approved in the United States for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older.

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.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

There is currently only one approved pharmacological treatment for PFIC.

Preliminary data from the Phase 2 study LUM001-501 (an open-label study of the efficacy and long-term safety of maralixibat in the treatment of cholestatic liver disease in pediatric subjects with PFIC) report that a subgroup of subjects with PFIC2 experienced significant clinical benefit as manifested by a large reduction or normalization of sBA, reduction in pruritus (assessed using the Observer reported Itch Reported Outcome Instrument [ItchRO(Obs)™]), and normalization of elevated TSB and ALT for those subjects with elevated baseline values. Also, BID dosing led to a higher response rate compared with the previously used QD dosing.

The primary objective of the present study is to evaluate the long-term safety and tolerability of maralixibat. The safety assessments used in this study are standard and widely used in clinical studies. Evaluation of efficacy is a secondary objective of the present study.

By enrolling subjects from the antecedent study (MRX-502), this study is designed to evaluate the long-term safety of maralixibat. In addition, treatment effect and the maintenance of treatment effect on pruritus and sBA as well as the long-term benefit on other parameters such as growth and the time to liver-associated events will be evaluated.

There is a high unmet medical need in patients with PFIC because there is currently only one approved pharmacological therapy, and there are multiple complications with surgical treatment options (liver transplantation and PEBD) with the need for lifelong immunosuppression or stoma care. Maralixibat has demonstrated an overall benign safety profile, as would be expected from the unabsorbed nature of the drug, with the most common AEs being mild to moderate and self-limiting GI events such as diarrhea and abdominal pain. Abnormalities of liver-related laboratory parameters, which occur naturally in patients with PFIC, have not been causally linked to the study drug thus far. Theoretical risks of treatments with an IBAT inhibitor (e.g., lipid-soluble vitamin [LSV] deficiency, nephrolithiasis, growth deficit from fat malabsorption) have not been detected in the clinical development program thus far. Instead, a clinically relevant growth benefit has been observed in maralixibat treatment responders. Taken together, the benefit-risk ratio of maralixibat in patients with PFIC is considered supportive of the present study. Measures to minimize the burden to study subjects including means to limit pain and distress during blood draws (e.g., pediatric staff, minimize number of punctures, use of local anesthetics) are recommended in this protocol.

2.2 Study Objectives

2.2.1 Primary Objective:

- To evaluate the long-term safety and tolerability of maralixibat

2.2.2 Secondary Objectives:

- To evaluate the long-term efficacy of maralixibat, including the maintenance of severity and frequency of pruritus as well as sBA over time and growth in the primary cohort

2.2.3 Exploratory Objectives:

- [redacted]

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is an international, multicenter, open-label, Phase 3, study in subjects diagnosed with PFIC who have previously participated in and completed [redacted] End-of-Treatment [EOT] visit) of Study MRX-502. All subjects will receive maralixibat in Study MRX-503.

It is recommended that the option to participate in Study MRX-503 is presented well in advance of the subjects' Study MRX-502 EOT visit to allow the subjects and caregivers sufficient time for an informed decision about Study MRX-503 participation.

The Study MRX-503 baseline visit (Day 0) will occur on the same day as the Study MRX-502 EOT visit. Subjects who do not complete the Study MRX-503 baseline visit (Day 0) on the same day as the Study MRX-502 EOT visit will be considered for participation in Study MRX-503 only after discussion with the medical monitor. The evaluations and procedures completed for the Study MRX-502 EOT visit will serve as the evaluations for the Study MRX-503 baseline visit, if MRX-503 baseline visit is performed on the same day as MRX-502 EOT visit or within 30 days of the MRX-502 EOT visit. Data from the Study MRX-502 EOT visit will be programmed and included in the Study MRX-503 datasets for analysis. If the period between MRX-502 EOT visit and MRX-503 baseline visit is >30 days or if the subject was on drug interruption at the time of the MRX-502 EOT visit, the full set of assessments done at MRX-502 EOT visit will be repeated for the MRX-503 baseline visit.

At the Study MRX-503 baseline visit, after informed consent (and assent when appropriate) is obtained for Study MRX-503, subjects will be evaluated for study eligibility (see Section 4 [inclusion/exclusion criteria] and Table 1). Subjects should take the final Study MRX-502 dose in the morning on the day of the Study MRX-503 baseline visit. Eligible subjects will begin dosing with maralixibat in the evening on the day of the MRX-503 baseline visit (Day 0). All subjects will receive study treatment on top of standard-of-care therapy, including antipruritic concomitant treatment (for prohibited treatment see Section 5.2.2).

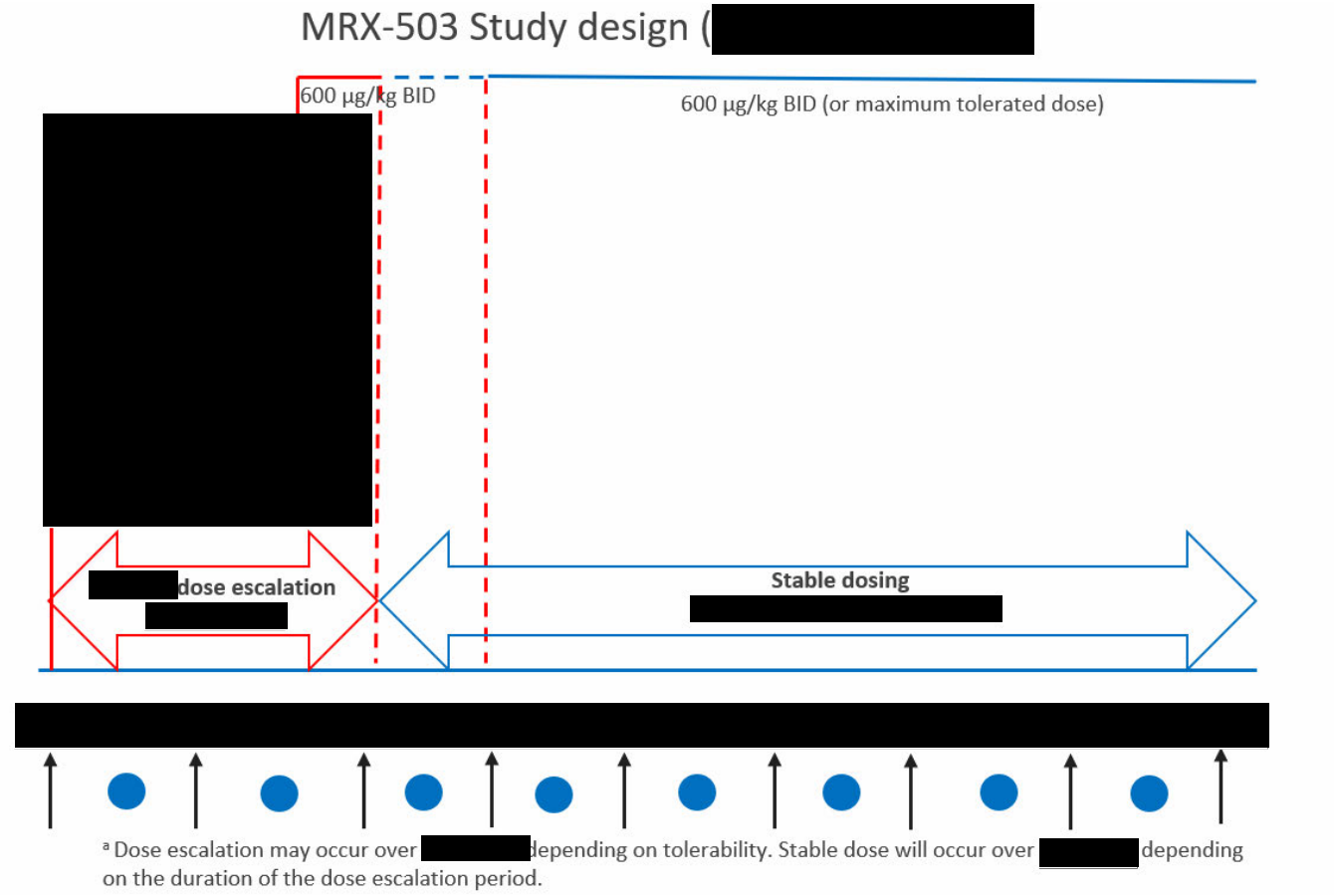
Up to ~90 subjects are expected to complete Study MRX-502 and be eligible for enrollment in extension Study MRX-503.

The study will be divided into the following periods (see Figure 1):

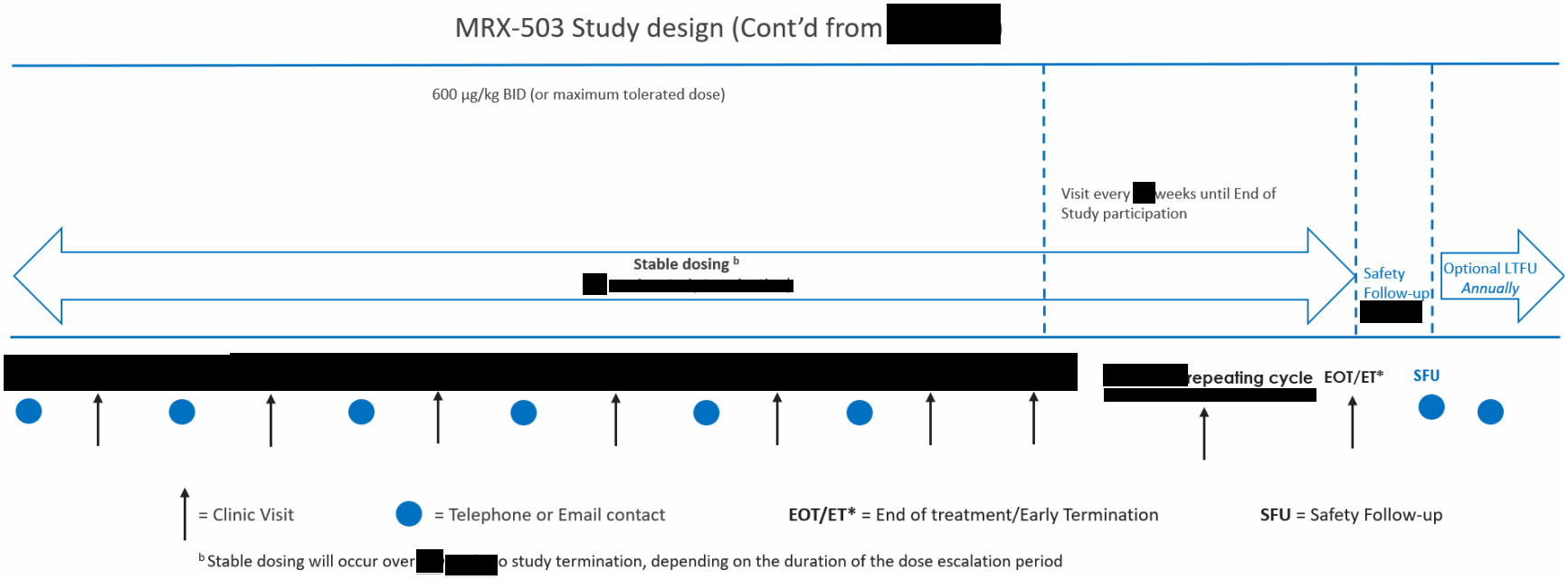
1. Dose-Escalation period ([redacted])
2. Stable Dosing period: until the study is terminated by the sponsor or the subject discontinues the study or transitions to commercial product. During the Stable Dosing period, subjects will continue to receive maralixibat with safety and efficacy assessments occurring every [redacted] until termination of the study or transition to commercial supply of maralixibat, at the discretion of the sponsor.
3. Safety follow-up period [redacted])

The study schedule between [redacted] in MRX-503 matches the study schedule of MRX-502.

Figure 1 Study Design Flow Chart



BID=twice daily; W=week.
Note: Study design (continued from [redacted] is on the next page.



BID=twice daily; LTFU=long-term follow-up; W=week.

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

3.1.1 Rationale for Treatment and Dose Escalation

The lower age limit for enrollment in the antecedent study (MRX-502) was 1 year based on the fact that the GI tract is fully mature at 1 year in humans and higher plasma exposures were observed in rats with immature GI tracts in juvenile toxicokinetic studies. Because subjects entering Study MRX-503 must have already completed at least [redacted] of dosing in Study MRX-502, all subjects will be at least 1.5 years of age at the time they enter Study MRX-503.

The doses used in this study have been 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 healthy, obese/overweight volunteers, there was an almost linear dose-response curve leading to higher fecal bile acid levels with escalating doses of maralixibat up to 100 mg QD (pediatric equivalent doses of 1400 µg/kg QD); BID dosing (50 mg BID or 700 µg/kg BID pediatric equivalent) led to even higher fecal bile acid excretion compared to QD dosing while demonstrating a well-tolerated and acceptable safety profile of maralixibat across the tested dose range. Higher doses of maralixibat, up to 1400 µg/kg daily dose, might therefore be more efficacious, whereas a BID regimen has the potential to allow for more complete coverage of the distal ileum throughout the day. The additional multiparameter responder on higher doses and BID dosing regimen in the PFIC Phase 2 Study LUM001-501 supports this hypothesis.

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.

Table 2 Sample Daily Exposure (mg/day) for Subjects

Weight (kg)	Daily Exposure of Maralixibat (mg)			
	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]

BID=twice daily.

3.1.2 Rationale for Endpoints

The primary objective of the study is to evaluate the long-term safety and tolerability of maralixibat using the following endpoints: AEs (including serious, nonserious, related, and nonrelated AEs) and standard clinical laboratory tests (hematology, chemistry, urinalysis, LSVs, and related measures).

Secondary endpoints include pruritus severity and frequency as measured by the ItchRO, sBA concentrations, height and weight z-scores, and the proportion of responders. The selection of ItchRO(Obs) to evaluate the therapeutic response to maralixibat treatment was based on the clinically significant improvements observed in 7 subjects in the Phase 2 PFIC Study LUM001-501. Initial efficacy data collected from the first interim data analysis demonstrated signals of broad, significant, and sustained efficacy in a subgroup of 7 subjects, all with PFIC2. Among other positive clinical outcomes, these subjects experienced large reductions in pruritus, as measured by improvements in ItchRO(Obs) score of ≥1.0. These clinically significant reductions were sustained through 48 weeks of treatment for most subjects, showed little variability throughout the study, and closely mirrored the results frequently observed after PEBD (Yang et al. 2009; Stapelbroek et al. 2010). Full treatment effect is usually observed by 12 weeks of treatment. A seventh subject was identified as exhibiting a partial response that was characterized by significant improvements in sBA (reduction of 88% from baseline) and in ItchRO(Obs) scores. Both measures of efficacy remained largely sustained for the duration of the study for all of these subjects, except during intercurrent illnesses (e.g., GI or upper respiratory infections). This pattern of consistent, monotonic, and concomitant improvements across multiple parameters in these subjects is consistent with what has previously been described following biliary diversion surgery and inconsistent with the usual natural history of PFIC, which is characterized by progressive deterioration in liver function without periods of normalization of pruritus, bile acids, or liver enzymes. sBA change from baseline will also be analyzed. The underlying pathophysiological driver in PFIC is a specific inability to excrete bile acid, which leads to bile acid accumulation and is believed to be responsible for the pruritus in patients with PFIC and their progressive liver injury. Documenting a decrease in sBA would therefore suggest a reduction in the underlying driver of the disease; this is supported by the Phase 2 data from Study LUM001-501, where subjects with multi-parameter response experienced a normalization of liver enzymes and bilirubin (if elevated at baseline) and improved growth. Height and weight z-score data will be collected to document growth benefits. The proportion of responders will be examined to further evaluate the therapeutic response to maralixibat treatment.

[redacted]

[redacted]

3.1.3 Rationale for Study Population

The safety analysis will be done on the Safety Population, which consists of all subjects who receive at least 1 dose of maralixibat in Study MRX-503.

The efficacy analyses will be performed on the intention-to-treat (ITT) and per-protocol (PP) populations [redacted]:

- [redacted]
- [redacted]
- [redacted]

[redacted]

3.2 Duration and Study Completion Definition

Subjects will continue to receive maralixibat until termination of the study (study completion) or transition to commercial supply of maralixibat at the discretion of the sponsor. Subjects who are administered maralixibat until study completion or until transition to commercial product are considered to have completed the study. 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 contact (see Section 7.1.4 and Table 1) but neither the long-term clinical follow-up of persistent safety findings nor the long-term follow-up for disease progression.

3.3 Sites and Regions

This study will be conducted at multiple sites in North America, Europe, Asia, and South America. Other regions may be added if it was necessary for enrollment purposes of Study MRX-502. Sites will have participated in the antecedent Study MRX-502. Sites that did not participate in Study MRX-502 but referred subjects to participating sites in Study MRX-502 may be opened in Study MRX-503.

4 STUDY POPULATION

4.1 Inclusion Criteria

A subject will not be considered eligible for the study without meeting all of the criteria below.

1. Provide informed consent and assent (as applicable) per Institutional Review Board/Ethics Committee (IRB/EC)
2. Completion of Study MRX-502; treatment interruption between MRX-502 and MRX-503 should be avoided. Subjects who do not complete the Study MRX-503 baseline visit (Day 0) on the same day as the Study MRX-502 EOT visit will be considered for participation in Study MRX-503 only after discussion with the medical monitor.
3. Males and females of nonchildbearing potential. Males and nonpregnant, nonlactating females of childbearing potential who are sexually active must agree to use acceptable methods of contraception during the study and through 30 days after the last dose of the maralixibat.
4. Females of childbearing potential must have a negative urine pregnancy test result at the baseline visit (Day 0).
5. Access to email or telephone for scheduled remote visits
6. Ability to read and understand the questionnaires (both caregivers and subjects above the age of assent)
7. Access to consistent caregiver(s) during the study
8. 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. Any female who is pregnant or lactating or who is planning to become pregnant
2. Administration of prohibited medication between the MRX-502 EOT visit and the MRX-503 baseline visit (Day 0)
3. History of noncompliance in Study MRX-502, nonadherence to medical regimens, unreliability, mental instability, or incompetence that could compromise the validity of informed consent or lead to nonadherence with the study protocol based on investigator judgment
4. Experienced an AE or SAE related to maralixibat during the MRX-502 study that led to permanent discontinuation of the subject from maralixibat

5. Any other conditions (including decompensated liver disease) or laboratory abnormalities that, in the opinion of the investigator or sponsor medical monitor, may compromise the safety of the subject or interfere with the subject participating in or completing the study
6. Cognitive impairment of the subject or caregiver that would, in the opinion of the investigator, preclude appropriate understanding of study information and compliance with 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 nonchildbearing potential if they are premenarchal and either Tanner Stage 1 or younger than age 9 years.
- Females of childbearing potential must have a negative β-human chorionic gonadotropin (β-hCG) pregnancy test as outlined in Table 1. If available, the subject's MRX-502 EOT visit serum β-hCG pregnancy test results will be used for the MRX-503 baseline visit (Day 0). Otherwise, a urine β-hCG pregnancy test will be performed. Results of the pregnancy test must be reviewed prior to dispensing maralixibat.
- 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 30 days following the last dose of maralixibat. 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). Double-barrier methods are not considered as highly effective (failure rate <1%) and are only permitted if all highly effective methods are contraindicated for medical reasons.
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the Baseline Visit (Day 0), plus condoms. Note: If subject becomes sexually active during the study, she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days. The contraceptive efficacy of oral contraceptives may be

compromised by the investigational product (IP) and/or the permitted concomitant medication. Therefore, additional barrier methods should be used.

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 30 days following the last dose of maralixibat:

- 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 days in which blood samples are collected for the lipid panel and/or cholestasis biomarkers, subjects will be encouraged to fast for at least 6 hours (water intake is permitted if necessary but not recommended) before blood sample collection (see Table 1). On these visit days, maralixibat 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

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may discontinue the subject from the study at any time (refer to Section 4.5.1). The investigator is encouraged to discuss discontinuation of a subject with the medical monitor when possible. The reason for termination and the date of stopping maralixibat must be recorded in source documents. The evaluations listed for EOT/Early Termination [ET] visit are to be performed as completely as possible for any subject who discontinues early (see Table 1 and Section 7.1.3.4).

The investigator or sponsor may discontinue a 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 8.3.4).

AEs or disease progression 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 and outcome must be recorded in 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 with disease progression, listing for liver transplant, or undergoing PEBD may continue in the study unless, in the investigator's opinion, it would compromise the subject's ability to safely continue in the study.

Subjects undergoing PEBD who choose to remain in the study will interrupt study medication on the day before the procedure and will remain without study medication pending evaluation of clinical response to PEBD (maximum of 90 days of study medication interruption). Criteria to determine PEBD response (total, partial, or no response) will follow each study site's clinical practice. If the subject is considered to have partial or no response to PEBD, study medication administration can be resumed after discussion and approval by the medical monitor. All study visits and procedures should continue during study medication interruption.

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

Subjects who discontinue from the study for safety reasons will be followed until resolution of the event or until a final outcome (i.e., no further improvement is anticipated), according to the investigator's discretion.

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 7.1.3.5).

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 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 recorded.

The follow-up will be performed and documented at least annually (from the date of the EOT/ET visit), until disease progression or an event occurs (whichever comes first).

4.5.1 Reasons for Discontinuation from Study

Reasons subjects must discontinue the study include but are not limited to:

- Death
- Withdrawal by subject/parent/guardian
- Investigator's opinion that the subject may be severely harmed if he/she continues study participation, namely by the treatment and procedures according to the study protocol
- Loss to follow-up
- Pregnancy
- Liver transplant

Reasons that may require study discontinuation include but are not limited to:

- Occurrence of a disease that interferes with the study treatment or represents an exclusion criterion
- Noncompliance with study procedures as judged by the investigator or the medical monitor
- AE
- PEBD surgery or listing for liver transplant, if, in the opinion of the investigator, it would compromise subject's ability to safely continue in the study
- Disease progression, that in the opinion of the investigator would compromise the subject's ability to safely continue in the study
- Other

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

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact. At least 1 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 he or she return to the site for final safety evaluations and return any used/empty packaging and unused maralixibat.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 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.

5.2 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 between the dates of the first dose of maralixibat in Study MRX-503 and the Study MRX-503 EOT/ET visit, inclusive. Concomitant treatment information must be recorded in the subject's source document. Investigators must ensure that subjects receive LSV supplements, as needed, for the duration of the study.

During the study, subjects should take their concomitant medication at a similar time interval to maralixibat. There is a possibility that maralixibat may reduce the absorption of UDCA. Other potential drug-drug interactions with medication relevant to this patient population are not known at this time. It is recommended that the intake of any concomitant medication always occur at a similar time interval to the administration of study medication throughout the study. Physicians must check the corresponding current Summaries of Product Characteristics (SmPC).

5.2.1 Permitted Treatment

Concomitant medications are allowed during the study, with the exception of the prohibited therapies and time restriction periods described in Section 5.2.2.

Dose adaptations to body-weight changes are allowed.

5.2.2 Prohibited Treatment

Table 3 details the prohibited treatments and the time restriction period at any time before or during the study. None of the medications listed in Table 3 are allowed during the conduct of the study.

Table 3 Prohibited Treatments and Time Restriction Prior to the Baseline Visit

Prohibited Treatment	Time Restriction prior to the Baseline Visit (Day 0)
Any investigational drug, biologic, or medical device	Any time between the MRX-502 EOT visit and the MRX-503 baseline visit or 5 half-lives of the study agent, whichever is longer
Another IBATi other than maralixibat	Any time before the study

EOT=end of treatment; IBATi=ileal bile acid transporter inhibitor.

6 STUDY MEDICATION

6.1 Identity of Investigational Product

The IP is maralixibat chloride (maralixibat; formerly SHP625, LUM001), which will be provided as a fixed-concentration, oral solution (i.e., [redacted] and 20 mg/mL). The study medication, maralixibat, is presented in 30-mL volumes packaged in 30-mL size amber colored polyethylene terephthalate (PET) bottles and requires refrigerated storage conditions (2°C–8°C). All subjects will receive maralixibat in Study MRX-503.

Subjects will receive ready-to-use maralixibat oral solution based on individual body weight, up to 600 µg/kg BID. To accurately measure the required volume, 0.5-, 1.0-, and 3.0-mL sized oral dosing dispensers will be provided.

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 ≤26 mg/kg/day 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.

6.2 Administration of Study Medication

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

6.2.1 Interactive Response Technology for Study Medication Management

An interactive response technology (IRT) will be used for management of study visits and maralixibat. 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 maralixibat management, will be provided to the site.

6.2.2 Allocation of Treatment to Subjects

All subjects will receive maralixibat.

6.2.3 Dosing

Subjects will be administered (or will self-administer) ready-to-use maralixibat oral solution based on their individual body weight, up to 600 µg/kg BID. The dosing volume will be determined based on the individual body weight, the dose level according to the dose escalation plan ([redacted] 600 µg/kg), and the strength of solution being administered

[redacted] 20 mg/mL). To accurately measure the required volume, 0.5-, 1.0-, and 3.0-mL sized oral dosing dispensers will be provided.

Subjects should take the final Study MRX-502 dose in the morning on the day of the Study MRX-503 baseline visit. Eligible subjects will begin dosing with maralixibat in the evening on the day of the MRX-503 baseline visit (Day 0).

Maralixibat administration will take place during the Dose Escalation and Stable Dosing periods of the study based on a BID regimen. As much as possible, the morning dose should be administered approximately 30 minutes before breakfast and 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. Maralixibat and concomitant medication should be administered approximately at the same time each day throughout the study. The interval between administration of maralixibat and any concomitant treatment used should not change during the study. The morning doses administered at the site during the site visits should be taken from the new bottles allocated during that respective visit and not from the bottles returned by the subject.

All subjects will initiate dose escalation at Dose Level 1 ([redacted] µg/kg BID for 1 week), regardless of the subject's treatment arm in Study MRX-502, to maintain the treatment blind while Study MRX-502 is still ongoing.

The Dose Escalation period will consist of the following [redacted]:

- [redacted]
- [redacted]
- [redacted]
- [redacted] 600 µg/kg maralixibat BID for the remaining duration of the study

Dose escalation should occur in the absence of major safety concerns (e.g., liver parameters) or tolerability concerns (e.g., GI-related TEAEs) considered to be related or possibly related to maralixibat. Subjects with such safety concerns can be down-titrated to a lower, previously tolerated dose level for 1 week before continuing dose escalation. The minimum dose to continue in the study will be [redacted] µg/kg maralixibat BID; subjects who cannot tolerate this dose will be discontinued from the study. Investigators should also review maralixibat compliance during the Dose Escalation period to ensure that subjects have adequate exposure to maralixibat to assess safety and tolerability. Any concerns with compliance should be discussed with the medical monitor.

Investigators have until [redacted] to determine the maximum tolerated dose; if re-challenges or further dose escalations fail, the subject will remain on the maximum tolerated dose level for the remainder of the Stable Dosing period. Dose reductions are allowed for the above-mentioned safety or tolerability reasons down to a minimum level of [redacted] µg/kg BID. Subjects who cannot tolerate this dose ([redacted] µg/kg BID) will be discontinued from the study.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

All maralixibat bottles are 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.

6.3.2 Packaging

Study medication is packaged in the following labeled containers:

- [redacted]
- Ready-to-use oral solution of maralixibat 20 mg/mL

The sponsor or designee will provide 0.5-, 1.0-, and 3.0-mL sized oral dosing dispenser(s). Bottle adapters are used to facilitate withdrawal of the solution from the bottle using an oral dosing dispenser. Therefore, bottle adapter(s) may be provided separately if not already included. Changes to sponsor-supplied packaging may not occur without full agreement in advance by the sponsor.

6.3.3 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.

6.4 Drug Accountability

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

The investigator or his/her designee will dispense the maralixibat only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the maralixibat assigned. All dispensed maralixibat 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 maralixibat bottles 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 maralixibat 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 maralixibat, and empty/used maralixibat packaging are to be returned or destroyed. Maralixibat volume must be accounted for 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 maralixibat must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile maralixibat delivered with those used and returned. All accountability discrepancies must be investigated and documented to the sponsor’s satisfaction.

6.5 Subject Compliance

Subject compliance with study procedures and treatment dosing will be assessed and recorded at each visit by the investigator or designee. Subjects and/or caregivers will be asked to complete a diary indicating that the maralixibat dose was taken in the morning and in the evening. Any concerns with compliance should be discussed with the medical monitor.

During the Dose Escalation period, subject compliance will be reviewed as part of the dose escalation assessment. Any concerns with compliance should be discussed with the medical monitor.

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 and re-challenge with a higher dose (applicable for subjects whose doses have been down titrated) 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.

During the Stable Dosing period (i.e., [redacted] to EOT/ET), subjects will be allowed a maximum of 90 days of cumulative dose interruption. A dose interruption is defined as missing both the morning and the evening dose. Any dose interruption longer than the maximum allowed will be documented as a protocol deviation.

Any subject who has over 90 days of cumulative dose interruption during the stable dosing period should be discussed with and reviewed by the medical monitor to determine if the subject may remain in the study.

Subjects who interrupt dosing for safety/tolerability or other reasons may reinitiate dosing, but only after discussion with the medical monitor.

After a dose interruption, subjects should reinitiate dosing at their maximum tolerated dose.

Procedures outlined in Section 7.1.3.4 should be followed for any subject who is discontinued early from the study due to treatment noncompliance.

7 STUDY PROCEDURES

See Appendix 9 for management of study procedures during pandemic.

7.1 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 7.2. Where possible and permitted, study visits can be organized at the subject's home (or other agreed upon location) with qualified health care professionals, once approved by the Principal Investigator and medical monitor.

Prior to performing any study-related procedures, the investigator or his/her designee must obtain written informed consent (and assent when appropriate) from the subject (as per local requirements). Participation in Study MRX-503 starts when the informed consent (and assent when appropriate) is signed. For information about informed consent process see Section 10.3.1.

On the same day as the subject's Study MRX-502 EOT visit, after the subject has completed the EOT visit, the subject will be presented with the option to provide informed consent (and assent when appropriate) to participate in Study MRX-503. Subjects will complete the MRX-503 baseline visit (Day 0) assessments on the same day as the MRX-502 EOT visit.

7.1.1 Baseline Visit (Day 0)

The investigator or designee will register the baseline visit (Day 0) in the IRT system. The subjects' unique 6-digit identification number from Study MRX-502 will be referenced in their MRX-503 study identification number. The subject's identification number must remain constant and must be used on all study documentation related to that subject.

Evaluations and procedures completed for the Study MRX-502 EOT visit will serve as the evaluations for the Study MRX-503 baseline visit (Day 0). Therefore, data and assessment results will be pulled by data management from the Study MRX-502 EOT visit to the Study MRX-503 baseline visit (Day 0) accordingly.

For females of childbearing potential, the Study MRX-502 EOT visit serum β-hCG pregnancy test results will be used, if available. Otherwise, a urine pregnancy test will be performed (see Section 7.2.4.5).

Adverse events for Study MRX-503 will be collected from the time informed consent (and assent when appropriate) is signed (see Section 8).

If the subject does not meet eligibility criteria, the early termination of the subject will be recorded by the investigator or designee.

7.1.2 Dose-Escalation Period: Visit 1 (Week 0) to [redacted]

Subjects will return to the site to attend study visits, and assessments and procedures will be performed as outlined in Table 1.

The Dose Escalation period will comprise [redacted] All assessments and procedures listed for [redacted] and interim contacts ([redacted] Dose Escalation) or [redacted] and interim contacts ([redacted] Dose Escalation) in Table 1 should be completed during this period. Subject contacts may be by phone or email.

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

Additional details regarding dose escalation are provided in Section 6.2.3.

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

7.1.3 Stable Dosing Period

Subjects will return to the site to attend study visits, and assessments and procedures will be performed as outlined in Table 1.

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

7.1.3.1 [redacted] (Weeks [redacted])

Subjects will return to the site for [redacted] (for subjects with [redacted] dose escalations), or [redacted] (for subjects requiring [redacted] dose escalations). Assessments and procedures will be performed as outlined in Table 1.

For [redacted] a [redacted] visit window will be permitted. For [redacted] a [redacted] visit window will be permitted. Visit dates and acceptable windows are calculated from the baseline visit (Day 0).

7.1.3.2 [redacted] (Weeks [redacted])

Subjects will return to the site for [redacted]. Assessments and procedures will be performed as outlined in Table 1.

For [redacted], a [redacted] visit window will be permitted. Visit dates and acceptable windows are calculated from the baseline visit (Day 0).

7.1.3.3 Subject Contact ([redacted])

Subjects/caregivers will receive an email or a telephone call on [redacted] during which the use of concomitant treatments and AEs will be reviewed as outlined in Table 1. For subjects requiring [redacted] of dose escalation, the first subject contact during the Stable Dosing period will occur at [redacted]

For subject contacts through [redacted] a [redacted] visit window will be permitted. For subject contacts from [redacted] a [redacted] visit window will be permitted. For subject contacts from [redacted], a [redacted] visit window will be permitted. Visit dates and acceptable windows are calculated from the baseline visit (Day 0).

7.1.3.4 [redacted] to [redacted] Repeating Cycle Period

Subjects will return to the site every [redacted] after [redacted] Assessments and procedures will be performed as outlined in Table 1.

7.1.3.5 End-of-Treatment/ Early Termination Visit

Subjects will return to the site for the EOT visit, or for the ET visit upon early termination, and the procedures and assessments outlined in Table 1 will be performed.

If maralixibat 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 maralixibat was discontinued, or the subject should be scheduled for an additional ET visit as soon as possible if maralixibat was discontinued in between visits.

Subjects who discontinue prematurely at any time during the study will also have a final safety follow-up email or phone call [redacted] after the last dose of maralixibat (see Section 7.1.4).

For the optional long-term follow-up, please refer to Section 7.1.5.

The investigator or designee will register the EOT/ET visit in the IRT system accordingly.

7.1.4 Safety Follow-Up ([redacted] Post-Treatment)

The safety follow-up period for this protocol is [redacted] from the last dose of maralixibat. Subjects/caregivers will have a final safety follow-up email or phone call at [redacted]

Subjects who discontinue prematurely at any time during the study will have a final safety follow-up email or phone call [redacted] after the last dose of maralixibat. Subjects who discontinue from the study for safety reasons are also followed-up as long as clinically indicated or until no further improvement with an adverse outcome is expected. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure by the site (see Section 8.1).

7.1.5 Disease-Related Event Questionnaire (Long-Term Follow-Up on Liver Disease)

At the EOT/ET Visit, subjects who discontinue from the study will have the option to participate in the long-term follow-up period. Subjects who provided informed consent and assent (as appropriate) to participate in the long-term follow-up will be contacted at least once a year (from the EOT/ET visit) regardless of study completion, to provide information on clinical outcome. The long-term follow-up is to allow the study doctors to continue to follow subjects and for the investigator and/or designee to contact them, their caregivers, and/or their primary care physician to obtain information on disease progression and/or clinical outcomes for the subject. The disease progression questionnaire should be kept in the subject's source records and will collect information on the following:

- How their disease has progressed
- If they have had PEBD surgery (date)
- If they have been listed for or have had a liver transplant (date)
- If they have had any other procedure relevant to the management of their cholestatic liver disease (i.e., PEBD, cholecystostomy tube, ileal exclusion, or other) (dates)
- Death and date of death

The follow-up will be done at least annually (from the date of the EOT/ET visit) and documented accordingly until disease progression or an event occurs (whichever comes first).

7.1.6 Additional Care of Subjects After the Study

No aftercare is planned for subjects.

7.2 Study Evaluations and Procedures

7.2.1 Efficacy

7.2.1.1 Itch Reported Outcome (ItchRO)

Pruritus will be assessed using the Itch caregiver/patient reported outcome measure (ItchRO) (see Table 1). Caregivers for all subjects will complete the Observer instrument: ItchRO(Obs) (see Appendix 2). 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 [redacted] will complete the ItchRO questionnaire administered as a diary BID from Day 0 through [redacted] and for [redacted] after every study visit, starting from [redacted] and onward as described in Table 1, Appendix 2, and Appendix 3.

Throughout Study MRX-503, [redacted] caregivers will continue to complete the same ItchRO modules they completed during Study MRX-502. [redacted]

If needed, [redacted] caregivers will be retrained 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) on Day 0.

ItchRO(Obs)

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]

[redacted]

[redacted]

7.2.1.2 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, [redacted] Subjects will be encouraged to fast at least 6 hours prior to collection (water intake is permitted if necessary but not recommended). Fasting times will be recorded on the CRF.

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

7.2.2 Medical History, Disease History, and Medication History

All clinically or medically relevant information, including PFIC disease history, regardless of how much time has elapsed since the date of any diagnosis that was collected in Study MRX-502, will be pulled for Study MRX-503 (see Section 5.1).

7.2.3 Demographics

Where collection is permitted, the subject's data on race and ethnicity from Study MRX-502 demographic information will be pulled into the MRX-503 study.

Information, including sex, age (year and months) will be entered in the Study MRX-503 CRF by the site personnel. The full date of birth will be collected in the central laboratory database because variance in pediatric age-related reference ranges is significant, and the full date of birth is required to ensure correct interpretation of the laboratory report. Local, country-specific guidelines should be followed where there is regional variation for collection of demographic information.

7.2.4 Safety

7.2.4.1 Physical Examination

A symptom-directed physical examination will be completed at clinic visits according to Table 1.

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 the baseline visit (Day 0) should be assessed as potential AEs. Refer to Section 8 for additional details.

7.2.4.2 Adverse Event Collection

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?"). AEs will be collected from the time informed consent (and assent when appropriate) is signed (refer to Section 8).

7.2.4.3 Vital Signs (including height and weight)

Vital signs include blood pressure, temperature, respiration rate, and pulse rate. 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 subjects who can stand on their own (generally ≥2 years) or not (usually <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 (subjects who can stand on their own, generally ≥2 years of age) or infant scale (children <2 years).

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

7.2.4.4 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 subinvestigator 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 4. Routine monitoring of urea/creatinine will be performed. Glomerular filtration rate (GFR) monitoring will only be estimated if clinically indicated by the investigator, using the age-specific Schwartz formula.

Unscheduled safety laboratory sampling should be conducted as required in case of any clinical safety concerns throughout the study. Unscheduled 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 4 List of Laboratory Analytes

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

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; CBC=complete blood count; EOT=end of treatment; ET=early termination; [redacted] 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] Bicarbonate only collected at sites in North and South America region.

[b] 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 ~6 hours 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.

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

[d] Oxalate will be assessed at [redacted] and EOT/ET.

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

Measures to minimize the pain and distress to study subjects during blood draws (e.g., pediatric staff, minimize number of punctures, use of local anesthetics) are recommended.

7.2.4.5 Pregnancy Test

A β-HCG pregnancy test will be performed on all female subjects of childbearing potential as outlined in Table 1 or if pregnancy is suspected.

7.2.4.6 Ultrasound Liver Imaging

A liver ultrasound or magnetic resonance imaging (MRI) will be performed as outlined in Table 1.

7.2.5 Others

7.2.5.1 Liver Biochemistry

Blood samples will be collected as described in Table 1 to evaluate liver biochemistry. A list of all laboratory analytes measured during the study (including liver biochemistry assessments) is provided in Table 4. Details describing liver biochemistry (e.g., TSB, ALT) along with definitions of elevated liver biochemistry levels and analyses methods will be provided in the statistical analysis plan (SAP).

7.2.5.2 Liver-associated Events

Liver-associated events include PEBD surgery, listing for liver transplantation, liver decompensation events (hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis), hepatocellular carcinoma, and death from liver-associated event. Detailed definitions of the events will be included in the SAP.

7.2.5.3 [redacted]

[redacted]

7.2.5.3.1 [redacted]

[redacted]

7.2.5.3.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.5.3.5 [redacted]

[redacted]

7.2.5.4 Responder Biomarkers

Blood samples will be collected as described in Table 1 to measure levels of cholestasis biomarkers including total sBA, [redacted] Detailed descriptions of the responder analysis of biomarkers will be provided in the SAP.

7.2.5.5 [redacted]

[redacted]

[redacted]

[redacted]

Measures to minimize the pain and distress to study subjects during blood draws (e.g., pediatric staff, minimize number of punctures, use of local anesthetics) are recommended.

7.2.5.7 [redacted]

[redacted]

7.2.5.8 Pharmacokinetic Assessments

To assess the plasma level of maralixibat, blood samples will be drawn predose and ~2.5 hours after the morning dose at [redacted] and [redacted]

Actual PK blood sample collection time versus time of dosing will be recorded. The investigator should ensure that every effort will be made to collect all PK blood samples at the precise protocol-scheduled time point. The PK blood collection must not deviate from the nominal collection time set forth in the protocol by more than the allowable window (-30 minutes). Where possible and permitted, homecare can be organized through qualified health care professionals to collect samples at the subject's home (or other agreed upon location). Samples drawn outside the window will be considered a protocol deviation.

The results from the most recent PK assessments from the subjects' MRX-502 study will be used as the baseline for Study MRX-503, if said results are not available at the Study MRX-502 EOT visit.

7.2.6 Volume of Blood to be Drawn from Each Subject

According to the Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors, 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, 2017). 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 the applicable laboratory manual 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.

As detailed in Table 5, approximately 10.5–21.5 mL of blood will be drawn during a clinic visit depending on the tests to be performed (Table 1). During the entire study, provided that the subject will have all scheduled blood draws, the total maximal estimated volume of blood to be drawn is approximately 222 mL up to Visit 16. For the [redacted] cycle visits (starting at [redacted] the estimated volume of blood to be drawn per visit is ~10 mL. Please refer to the applicable laboratory manual for details.

Table 5 Blood Sample Prioritization and Approximate Volume of Blood to be Drawn from Each Subject

Order of Priority	Assessment		Minimal Sample Volume Required (mL) US (North/South America region)	UK (Europe region)	SG (APAC region)
1	Safety	Chemistry panel (including lipid panel), β-hCG[b], AFP[a], serum osmolality	3.5	2.5	2.5
		Coagulation	2	2	2
		CBC with differential	1	1	1
		Lipid-soluble vitamins	2.5	2.5	2.5
2	Total serum bile acids (tSBA)		1	1	1
3	Pharmacokinetic samples (2 time points per visit)		2.0 + 2.0	2.0 + 2.0	2.0 + 2.0
4	[redacted]		2	2	2
5	Cholestasis biomarkers[c]		3.5	3.5	3.5
6	Serum storage sample		2	2	2
			Total=21.5	**Total=20.5**	**Total=20.5**

β-hCG=beta-human chorionic gonadotropin; [redacted] AFP=α-fetoprotein; CBC=complete blood count; eCRF-electronic case report form; [redacted] sBA=serum bile acid.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be ~222 mL.

[a] Results from local AFP drawn as standard of care may be entered in the eCRF instead of taking additional samples.

[b] β-hCG testing for females of childbearing potential only.

[c] [redacted]

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 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 (International Council for Harmonisation [ICH] Guidance E2A 1995).

All AEs are collected from the time the informed consent (and assent when appropriate) is signed until the defined follow-up period stated in Section 7.1.4. This includes events occurring at the Baseline Visit (Day 0), regardless of whether or not maralixibat is administered. AEs ongoing at the end of Study MRX-502 will be carried over and followed through until resolution.

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.

8.1.1 Treatment-Emergent Adverse Event (TEAE)

A 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, TEAEs are defined as AEs that start or deteriorate on or after the first dose of maralixibat in MRX-503 and no later than 14 days following the last dose of maralixibat. Any AE that started before the first dose (i.e., in the MRX-502 study) and worsens in severity or changes from nonserious to serious on or after the first dose date will also be designated as a TEAE.

8.1.2 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.

8.1.3 Suspected Unexpected Serious Adverse Reaction

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

All SUSARs must be reported as described in Section 8.2.7.

8.1.4 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 pretreatment 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 medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.5 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.

8.1.6 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.

8.1.7 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.

8.1.8 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.

All laboratory abnormalities that are clinically relevant should be documented as AEs and included in the final analysis. All AEs observed throughout the course of the study will be documented in the final analysis. 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 value(s) which were not present at 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.

8.1.9 Pregnancy

All pregnancies are to be reported from the time informed consent (and assent when appropriate) is signed until the defined follow-up period stated in Section 7.1.4.

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 postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion due to a congenital abnormality, or a complication of pregnancy or a congenital abnormality diagnosed any time during the pregnancy or postpartum, are considered SAEs and must be reported using the SAE form. 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 SAE form, as well as the pregnancy report form.

8.1.10 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 8.2. 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 nonmedical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of 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 the 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.

8.2 Serious Adverse Event Reporting Procedures

8.2.1 Reference Safety Information

The RSI for this study is included in the Maralixibat Chloride IB that the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All SAEs that meet the criteria defined in the study protocol must be reported within 24 hours of awareness via the electronic data capture (EDC) system. The Safety Report Form may be used and sent via email (Safety@catalystcr.com) in instances when the EDC system is unavailable. The SAE should still be reported in the EDC as soon as the EDC is operational again.

In situations where internet or email is unavailable, contact the local Clinical Research Associate (CRA) for further assistance. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.10) unless they result in an SAE.

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 SAE 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.

8.2.3 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 preexisting 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.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent (and assent when appropriate) until the defined follow-up period stated in Section 7.1.4 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.

8.2.5 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 (ICF) (and 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.

8.2.6 Fatal Outcome

Death in itself is not an SAE but an outcome arising from an 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.

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

The sponsor is responsible for notifying the relevant regulatory authorities (US central IRBs/European Union (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:

(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.

8.3 Safety Monitoring Rules

8.3.1 General Guidelines

The following guidelines are provided for the monitoring of selected laboratory parameters.

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

Retest collection should take place within 48 to 72 hours of the availability of the initial findings of potential concern. The results from the retest must be available prior to the next scheduled study visit or subject contact.

Retests should be conducted by the central laboratory. It may be difficult for some subjects who live far from the study site to return to the study site promptly. In this case, subjects

should be retested locally, but normal laboratory ranges should be recorded, results should be made available to study investigators and the medical monitor immediately, and the data should be included in the case reports.

The baseline values for the purpose of the safety monitoring are the same values as in the preceding Study MRX-502 (MRX-502 protocol, Section 8.3.1).

8.3.2 Close Monitoring Criteria for Liver Parameters

Table 6 provides the criteria for close monitoring of liver parameters.

Table 6 Close Monitoring Criteria for Treatment-Emergent Elevated ALT and TSB

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

[redacted]

Frequency of repeat measurements: If at any time during the study, an ALT or TSB result meets the close monitoring criteria, the measurement(s) must be reconfirmed. Subjects with a confirmed ALT or TSB level that is continuing to rise after meeting the close monitoring criteria should have their liver chemistry (ALT, ALP, INR, and TSB) retested as clinically indicated, until levels stabilize or begin to recover.

Further investigation into liver chemistry elevations: For subjects with a confirmed increase in ALT or TSB level, meeting the close monitoring criteria, the following investigations should be considered, 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, recover, or the study medication has been interrupted or discontinued and the subject has no symptomatic manifestations of hepatitis or immunological reaction.
- Symptoms as well as prior, current, and intercurrent diseases/illnesses
- Use of or recent change in use of concomitant treatment (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- History for exposure to environmental chemical agents and travel

- Serology for viral hepatitis (hepatitis A antibody IgM [HAV IgM], hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody, HCVRNA, cytomegalovirus IgM [CMV IgM], and Epstein-Barr virus [EBV] antibody panel)
- Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])
- AST, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH)
- Complete blood count (CBC) with differential blood count (eosinophils)
- Reticulocyte count, prothrombin time (PT)/INR

Additional investigations of liver parameters, including gastroenterology/hepatology consultations, and/or hepatic imaging, may be performed at the discretion of the investigator, in consultation with the medical monitor.

8.3.3 Guidelines for Interruption of Study Medication for Specific Liver Parameters

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), **as discussed with the medical monitor**, interruption of study medication should be considered:

- [redacted]
- [redacted]
- [redacted]

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

[redacted]

Frequency of repeat measurements: Subjects with a confirmed ALT or TSB level meeting interruption criteria should have their liver chemistry tests retested every 72 hours or as

clinically indicated, until levels stabilize or begin to recover. It may be difficult for some subjects who live far from the study site to return to the study site promptly. In this case, 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.

Further investigation for increased liver chemistry results: For subjects with a confirmed increase in ALT or TSB level above the threshold, the investigations outlined in Section 8.3.2 should be considered, as clinically indicated.

Study medication may be restarted as long as the subject does not meet the dosing interruption criteria based on retest, does not meet criteria outlined in Section 8.3.4, liver parameters have returned to or near maralixibat baseline, and an alternative explanation was found for the increased liver parameter (i.e., intercurrent illness, disease progression, or natural history of the underlying disease). The investigator and the medical monitor or qualified designee should confer as to whether additional close monitoring is needed.

8.3.4 Rules for Study Medication Discontinuation Following Abnormalities of Liver Parameters

Study medication should **not** be restarted:

- If the subject had a probable Drug-induced Livery Injury (DILI) in the opinion of the investigator and medical monitor; in case of disagreement, cases may be subject to independent expert adjudication
- If the subject reports signs/symptoms of acute hepatitis, liver decompensation (i.e., variceal hemorrhage, ascites, hepatic encephalopathy) or hypersensitivity reaction
- If the subject had liver parameters elevations meeting criteria in Section 8.3.3 without alternative explanations or that are inconsistent with the natural history of the disease
- After meeting stopping criteria subsequent to a re-challenge (i.e., meeting stopping criteria after re-introduction of study medication) that is likely related to study medication
- After [redacted] previous interruptions for safety reasons, unless there is a compelling reason why the subject should continue with dosing (i.e., interruptions were due to disease progression, natural history, intercurrent illness) and provided that the subject is still compliant with the study protocol as per Section 6.5.

If study medication is permanently discontinued, the subject will be discontinued from the study and will be expected to complete the ET study procedures ([redacted]/ET).

8.3.5 Safety Monitoring for Lipid-Soluble Vitamins

LSV status will be assessed at every study visit per the schedule of assessments (Table 1); blood samples will be obtained at the study visit before the daily dose of vitamins is administered.

In subjects with LSV deficiency, study medication must be interrupted if clinical symptoms of deficiency occur. Clinical symptoms include but are not limited to:

- Vitamin A: Night blindness, degeneration of the retina, xerophthalmia, follicular hyperkeratosis, keratomalacia, or Bitot's spots
- Vitamin D: Rickets, osteomalacia, costochondral beading, epiphyseal enlargement, cranial bossing, bowed legs
- Vitamin E: Numbness/tingling, decreased deep tendon reflexes, hemolytic anemia, limited extraocular movements, especially upward gaze

Subjects may restart dosing once clinical symptoms resolve and LSV levels begin to improve unless the subject has been previously discontinued for the same symptomatic LSV deficiency. Each subject may be re-challenged after symptomatic LSV deficiency only [redacted].

In the event of a confirmed level that falls either below the subject's maralixibat baseline or below the lower limit of normal (refer to central laboratory manual), whichever is lower, for a vitamin (25-hydroxy vitamin D, retinol, retinol binding protein, α-tocopherol), or INR (as a proxy for vitamin K status), without clinical symptoms of deficiency, the investigator should make the appropriate modification to the subject's vitamin supplementation regimen (see also Section 8.3.6 for INR monitoring).

Appropriate starting doses and vitamins formulations should be used for new cases of LSV deficiency (see Table 7, adapted from Shneider et al. 2012). Doses should be increased, as clinically indicated, to optimize the LSV levels. Parenteral formulations should be used (where available) if enteral supplements are unsuccessful at improving LSV deficiency.

Table 7 Recommended Starting Doses for Lipid-Soluble Vitamins

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

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

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

Figure 2 provides a flow diagram representing the protocol recommendations for treatment of and discontinuation due to worsening of LSV deficiency.

Figure 2 Flow Diagram for Treatment of Worsening of Lipid-Soluble Vitamin Deficiency

8.3.6 Safety Monitoring for Coagulation Panel Results

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

8.3.7 Study Medication Discontinuation Rules for Diarrhea

Maralixibat should be discontinued if a subject has severe diarrhea that requires hospitalization and/or an IV or nutritional supplementation or leads to severe electrolyte disturbances.

8.3.8 Dose Adjustment

GI 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 drug-related GI toxicity, study medication dose may be lowered to a previously well tolerated dose; later attempts to escalate the dose are permitted after discussion and approval by the medical monitor. Dose reduction and escalation decisions should be made in consultation with the medical monitor. Dose lowering should first be attempted with the afternoon dose. A requirement for IV 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.

After approval by the medical monitor, study dose may be adjusted or interrupted in case of a temporary occurrence related to a disease-related event or surgical procedure, including PEBD, that interfere with the study treatment or during which the study medication would not be required or would compromise the safety of the subjects. Treatment re-introduction or new attempt at dose escalation in such subjects will be performed at the discretion of the investigator after approval by the medical monitor.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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.

The study will be monitored according to ICH Good Clinical Practice (GCP) guidelines.

9.2 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.

9.3 Data Monitoring Committee

A data monitoring committee (DMC) will be involved in the management of this study. DMC meetings will be held periodically for the duration of the 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 will pay particular attention to the safety profile of the highest dose level (600 µg/kg BID). Should the DMC review determine that this 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 dose escalation period if this is considered necessary based on their review of safety data.

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. [redacted] The DMC will review these cases and provide recommendations to the sponsor regarding the continuation of specific dose levels, or the study overall. Maralixibat 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.

Further details regarding the DMC can be found in the DMC charter, which will be available prior to the enrollment of the first subject.

9.4 Sample Size Calculation and Power Considerations

All subjects who complete the core Study MRX-502 are eligible to roll over into Study MRX-503 if they elect to do so and if they meet all eligibility criteria. [redacted]

[redacted]

9.5 Statistical Analysis

This section presents a summary of the planned statistical analyses. A SAP that describes the details of the analyses to be conducted will be written prior to database lock. [redacted]

[redacted]

9.5.1 Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population:** The Safety Population will consist of all subjects who receive at least 1 dose of maralixibat in MRX-503.
- **Intent-To-Treat (ITT) Population**: The ITT Population will consist of all randomized subjects. Additional subgroups of the ITT population will be specified based on the presence/absence of post-baseline efficacy assessments for particular efficacy endpoints.
- **Per-Protocol (PP) Population**: The PP Population will consist of all subjects in the Safety Population who receive at least 1 dose of maralixibat and do not have any major protocol violations or deviations. Major protocol violations/deviations will be identified prior to database lock.

[redacted]

9.5.2 Study Subjects and Demographics

9.5.2.1 Disposition and Withdrawals

[redacted]

9.5.2.2 Protocol Deviations

[redacted]

9.5.2.3 Demographics and Other Baseline Characteristics

[redacted]

9.5.3 Exposure and Compliance

[redacted]

9.5.4 Endpoints

Safety endpoints:

The evaluation of long-term safety and tolerability of maralixibat is the primary objective of the study.

The primary endpoints related to safety and tolerability include:

- Incidence of TEAEs during the study by SOC and Preferred Term (serious, nonserious, related, and nonrelated)
- Safety laboratory parameters (clinical laboratory tests [hematology, chemistry, urinalysis, LSVs, and related measures)] over time

Additional safety and tolerability endpoints include the following:

- Change from baseline in physical examination findings (including body weight, height, and BMI)
- Change from baseline in vital signs
- Concomitant treatment usage

9.5.4.1 Efficacy endpoints

The evaluation of efficacy is the secondary objective of the study. The secondary efficacy endpoints include the following:

- Mean change from maralixibat baseline in the average morning ItchRO(Obs) severity score over time
- Maintenance of treatment effect based on the average morning ItchRO(Obs) severity scores over time
- Mean change from maralixibat baseline over time in sBA levels
- Mean change from maralixibat baseline over time in the average morning ItchRO(Obs) frequency score
- Proportion of subjects who experience an sBA control over time (sBA control definition is detailed in the SAP)
- Proportion of responders over time (responder definitions are detailed in the SAP)
- Mean change from maralixibat baseline over time in height and weight z-scores
- Time from maralixibat baseline to liver-associated events

The exploratory endpoints include the following:

- [redacted]

9.5.5 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 9.5.1). Safety variables include TEAEs and clinical laboratory values. No formal inferential analyses will be conducted for safety variables, unless otherwise noted. Analyses will be conducted separately on the primary cohort and all cohorts combined.

All safety and tolerability data will be presented in subject listings.

9.5.5.1 Adverse Events

[redacted]

9.5.5.2 Clinical Laboratory Evaluations

[redacted]

9.5.5.3 Other Safety Assessments

9.5.5.3.1 [redacted]

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9.5.7 [redacted]

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10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH GCP guidelines, 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.

10.1 Sponsor's Responsibilities

10.1.1 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 guidelines, 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.

10.1.2 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.

10.1.3 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.

10.1.4 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate.

The study may be terminated because of the following: the manifestation of an unjustifiable risk, a relevant toxicity with an unfavorable change to the benefit-risk ratio, a change in scientific knowledge (e.g., another toxicological or clinical study) with a negative impact on the evaluation of the benefit-risk ratio, a request or order from the competent authorities, the inability to complete recruitment within the prescribed timeframe, or the withdrawal of the authorization to manufacture or import the investigative product. In addition, interruption or premature termination of a clinical study can result if a study site is deemed unsuitable (by the sponsor, authority, or Ethics Committee) or deviations from the approved statistical analysis plan or the achievement or nonachievement of statistical objectives occur.

Should the study be temporarily suspended due to safety concerns, re-initiation will follow local laws and regulations (see Section 9.3).

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP guidelines, 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 subinvestigators 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 assent when appropriate), inform the primary care physician of the subject's participation in the study.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any subinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those 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 his or her 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.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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, etc.), will have separate source documentation.

The 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.

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

Original 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 investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

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. Nonstudy 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 United States [US] Food and Drug Administration (FDA), European Medicines Agency (EMA), United Kingdom (UK) Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and in accordance with local country-specific regulations and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

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.

10.2.3.4 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).

10.3 Ethical Considerations

10.3.1 Informed Consent/Assent

It is the responsibility of the investigator to obtain written informed consent (and assent when appropriate) from all study subjects prior to any study-related procedures. 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 ICF (and 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 ICF (and 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 Principal Investigator (PI) provides the sponsor with a copy of the consent form (and 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.

10.3.2 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.

10.4 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 assented 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 transferred 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.

10.5 Study Results/Publication Policy

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.

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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12 APPENDICES

Appendix 1 Clinical Outcomes Assessments

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

Clinical Outcomes Assessment	Completed by*
ItchRO(Obs)	Caregivers
[redacted]	[redacted]
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[redacted]

ItchRO(Obs)=Itch Reported Outcome observer instrument; [redacted] Progressive Familial Intrahepatic Cholestasis.

* Throughout the MRX-503 study, subjects and caregivers will continue to complete the same ItchRO, [redacted] modules they completed during the MRX-502 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

Appendix 3 [redacted]

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Appendix 4 [redacted]

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Appendix 5 [redacted]

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Appendix 6 [redacted]

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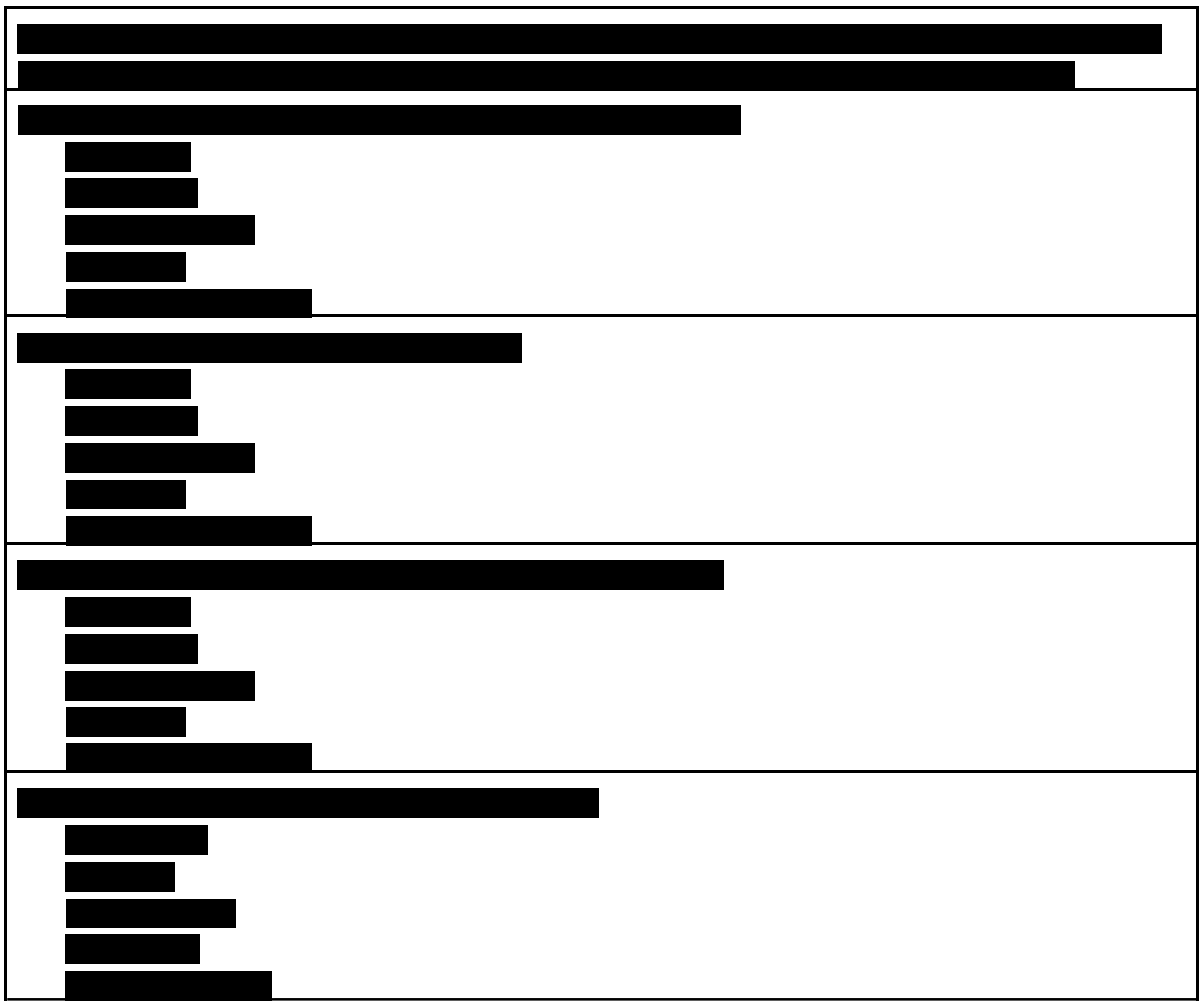

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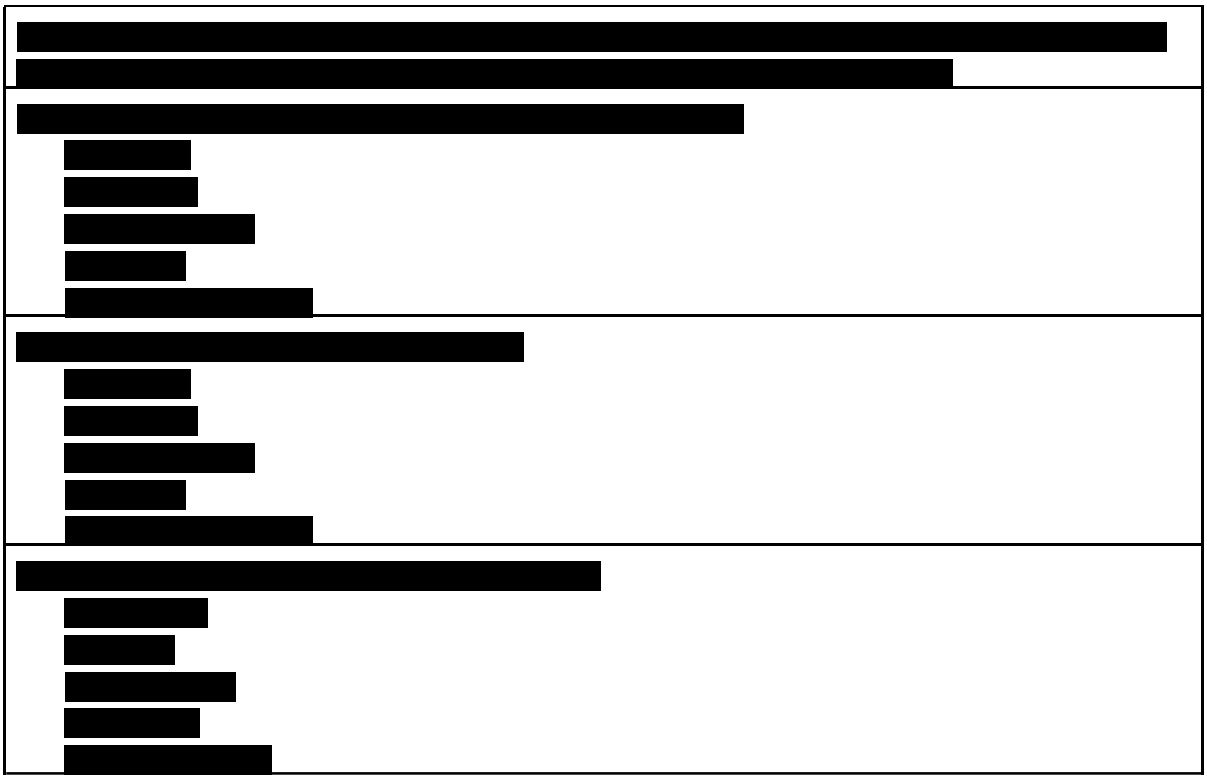

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Appendix 7 [redacted]

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Appendix 9 Management of Clinical Study Procedures during COVID-19 Pandemic or Other Force Majeure

This appendix provides guidance for participant 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 participants and the safety of clinical study staff.

The measures detailed here are 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 participants at the study site during the pandemic (EMA 2020; FDA 2020). Logistical requirements should also be considered, such as the ability of participants to travel to the study site, accessibility of public transportation, site restrictions on clinical studies, etc.

The safety of the study participants 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 study participants and society.

Study Participation

Study sites may continue to recruit new participants (for Study MRX-503 rollover participants from Study MRX-502), 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 studies and participants effectively and in compliance with the protocol and this appendix.
- Upon discussion with the sponsor, medical monitor or designee, 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 electronic Case Report Form (eCRF) and queries resolved in a timely manner.
- The site monitor is able to access the study site to perform onsite 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 participant visit commitments can be fulfilled. If a participant or caregiver is unable or unwilling to attend a study visit or a study site is unable to permit onsite visits by participants and caregivers, adaptation of the onsite 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 participant 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 participant must miss more than one onsite visit in succession, because multiple incomplete visits may have the potential to impact evaluation of study endpoints as well the participant's safety.

The decision to accept protocol deviations for missed assessments is based on the risk to the participant of discontinuing study participation versus missed assessments, such as safety laboratory assessments. Where possible, a homecare visit should be organized to avoid missing visits or assessments.

Alternative Blood Sample Collection:

Where possible and permitted, homecare can be organized through qualified health care professionals, trained on the study protocol, to collect samples at the participant's home (or other agreed upon location). It is preferred that this alternative blood sample collection is 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 participant 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 participants. Due to the potential impact of COVID-19 on multiple organ systems, the sponsor recommends the following dose modification and management plan for participants 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 eCRF 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 participant'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.

Guidance Regarding Vaccination against COVID-19:

- Participants should be requested to contact the site upon planned vaccination against COVID-19. The vaccine should be entered in the eCRF as a concomitant medication and any new or worsened symptom or sign recorded as an adverse event and assessed for seriousness. Maralixibat is taken orally, is minimally absorbed with systemic levels below the lower limit of quantification and binds with and inhibits the ileal bile acid transporter (IBAT) in the distal ileum. The vaccine is administered and acts systemically; hence, no drug-drug interaction is expected, and no need for unblinding is foreseen.

Documenting Alternative Contacts with Participants:

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

- If the visit is listed as onsite 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-Participant Drug Shipment Instructions during Pandemic Containment

If a participant 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 participant (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 participant will be the responsibility of the study site.
- The participant 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., contact information) 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 as directed in the Pharmacy Manual. Shipments that are expected to be completed within 48 hours from pickup to delivery do not generally require any specific temperature monitoring.
- To respect participant confidentiality, the carrier should be given only the contact information of the recipient. The sponsor should not receive any personal information about the participant.
- 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 participant about the next steps.
- The investigator or designee completes the drug accountability forms with each shipment made directly to a participant.
- All documentation (originals/copies, as applicable) related to the site-to-participant 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 study participant.
- Participants 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 participant 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 participants 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 participants and the written agreement of the Principal Investigator (PI)/PI's 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.

REFERENCES

United States Food and Drug Administration. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. March 2020 (updated 30

August 2021). Available online at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency.

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