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Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
ALGS	Alagille syndrome
[redacted]	[redacted]
ATC	anatomical therapeutic chemical
BID	twice daily
BL	baseline
C4	7α hydroxyl-4-cholesten-3-one
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
DMC	data monitoring committee
ECI	events of clinical interest
[redacted]	[redacted]
EOT	end of treatment
ET	early termination
FGF-19	fibroblast growth factor 19
[redacted]	[redacted]
GGT	gamma-glutamyl transferase
HCC	hepatocellular carcinoma
INR	international normalized ratio
ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Observer-Reported Itch Reported Outcome
[redacted]	[redacted]
IRT	interactive response technology
LLOQ	lower limit of quantitation
LSV	lipid-soluble vitamin
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
PEBD	partial external biliary diversion
[redacted]	[redacted]
[redacted]	[redacted]
PFIC	progressive familial intrahepatic cholestasis
[redacted]	[redacted]
PP	per protocol
PRO	patient reported outcomes
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD	standard deviation
SE	standard error
SI	International System of Units
SOC	system organ class
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSB	total serum bilirubin
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
ULOQ	upper limit of quantitation
WHO	World Health Organization
WHO-DD	World Health Organization - Drug Dictionary

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Mirum Pharmaceuticals, Inc. (Mirum) Study MRX-503 [An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)], based on Amendment 2, dated 18Nov2021.

The study objectives and endpoints as described in protocol MRX-503 are based on the analysis of long-term safety and efficacy data collected during this extension study. The analysis described herein is based on safety and efficacy data collected during both the core study (MRX-502) and the extension study (MRX-503). The MRX-502 SAP, dated 29Sep2022, describes the planned analysis and reporting for the core study, protocol MRX-502: Randomized Double-blind Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC), Amendment 4, dated 10May2022.

The MRX-503 protocol, Amendment 2, specifies the analysis of MRX-503 study data in 2 treatment groups: Placebo-Maralixibat (PBO-MRX) and Maralixibat-Maralixibat (MRX-MRX). The current planned analysis includes 4 treatment groups: PBO (MRX-502 data only), PBO-MRX (MRX-503 data for subjects on Placebo in the MRX-502 study), MRX-MRX (MRX-502 and MRX-503 data for subjects on MRX in the MRX-502 study), and All MRX (PBO-MRX and MRX-MRX data combined).

Reference materials for this SAP include the protocols and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society (RSS, 2014), for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an a priori plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Mirum's MRX-502 or MRX-503 studies.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to evaluate the long-term safety and tolerability of maralixibat in the Safety Population.

2.1.2. Secondary Objective

The secondary objective is to evaluate the long-term efficacy of maralixibat, including the maintenance of improvement in severity and frequency of pruritus as well as serum bile acid (sBA) over time and growth in the primary cohort and PFIC cohort as defined in the MRX-502 SAP.

2.1.3. Exploratory Objectives

2.2. Study Endpoints

2.2.1. Safety Endpoints

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

The primary endpoints related to safety and tolerability include:

- Incidence of TEAEs during the core (MRX-502) and extension (MRX-503) studies by SOC and PT (overall, serious, treatment related, treatment related that led to permanent discontinuation of study drug, events of clinical interest, and deaths)
- Change from baseline in clinical laboratory tests {chemistry, hematology, lipid panel, lipid-soluble vitamins [LSVs], and alpha-fetoprotein [AFP]} over time

Additional safety and tolerability endpoints include the following:

- Change from baseline in body mass index (BMI), weight and height z-scores over time
- Concomitant treatment usage
- Change from baseline in vital signs

- Maralixibat exposure

Safety laboratory tests and associated units of measure that will be used for reporting are listed in Appendix 1. Bilirubin (total and direct), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), fibroblast growth factor 19 (FGF-19), albumin, total serum bile acid (sBA) and changes in BMI, weight and height z-scores over time are considered as both safety and efficacy measurements.

2.2.2. Efficacy Endpoints

The evaluation of efficacy is the secondary objective of the study. Primary, secondary, and exploratory efficacy endpoints are analyzed in the primary cohort and PFIC cohort, individually, in the intent-to-treat (ITT) analysis population.

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoints of this study are defined as the mean change from baseline over time in the average morning ItchRO(Obs) severity score.

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- Maintenance of treatment effect described as the proportion of participants in the MRX-MRX treatment group who obtain ItchRO(Obs) response from [redacted] in Study MRX-503 in the primary cohort and PFIC cohort
- Proportion of ItchRO responders over time at each study visit using the [redacted] study period prior to the visit as per ItchRO(Obs) responder definition (reference Section 6.1.8)
- Mean change from baseline over time in the average morning ItchRO(Obs) frequency score
- Mean change from baseline over time in total sBA levels
- Proportion of subjects who experience an sBA control over time from [redacted] as per sBA responder definition (reference Section 6.1.8)
- Mean change from baseline over time in height and weight z-scores
- Time from baseline to liver-associated events

2.2.2.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- [redacted]

- [redacted]

[redacted]

[redacted]

2.2.3. Other Endpoints

Other endpoints include the following:

- [redacted]

[redacted]

- Plasma levels of maralixibat at predose and approximately 2.5 hours after the morning dose at [redacted]

3. Overall Study Design and Plan

3.1. Overall Design

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

The study MRX-503 baseline visit (Day 0) occurs 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 are considered for participation in Study MRX-503 only after discussion with the medical monitor.

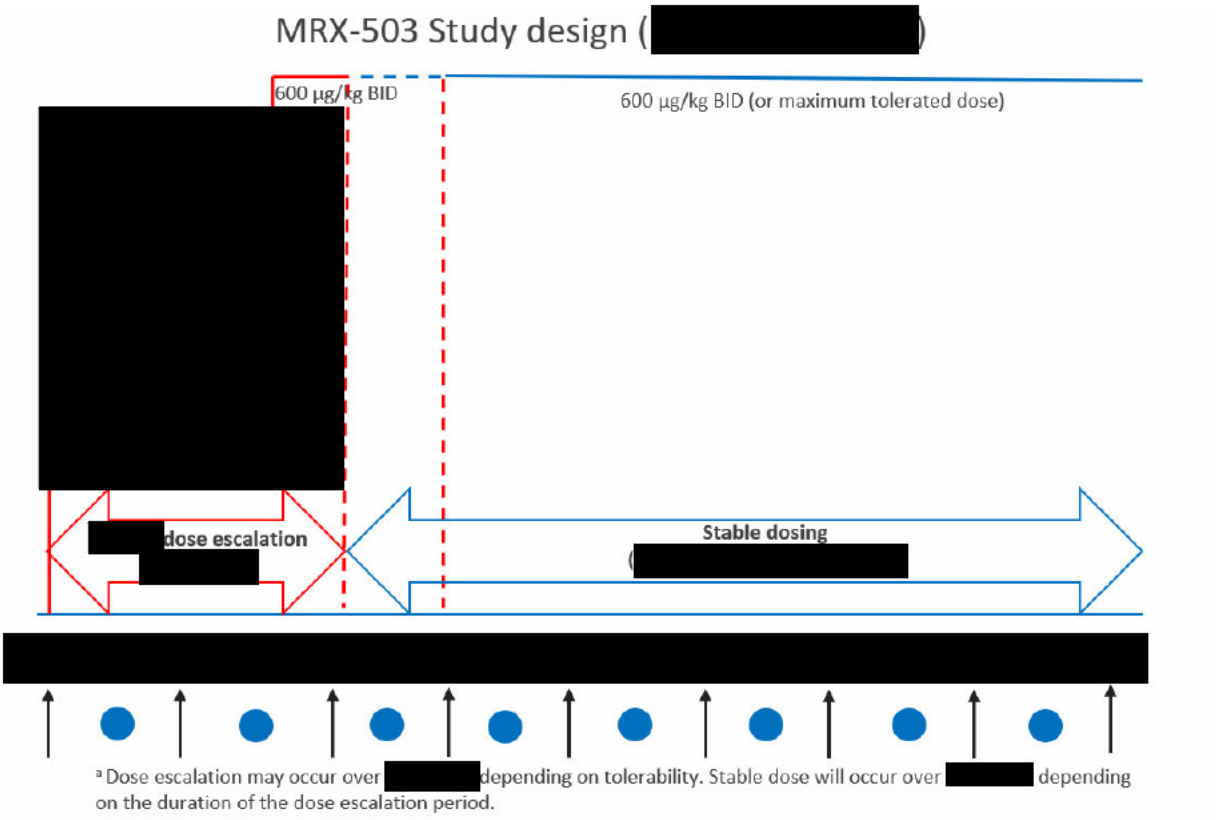
[redacted]

[redacted]

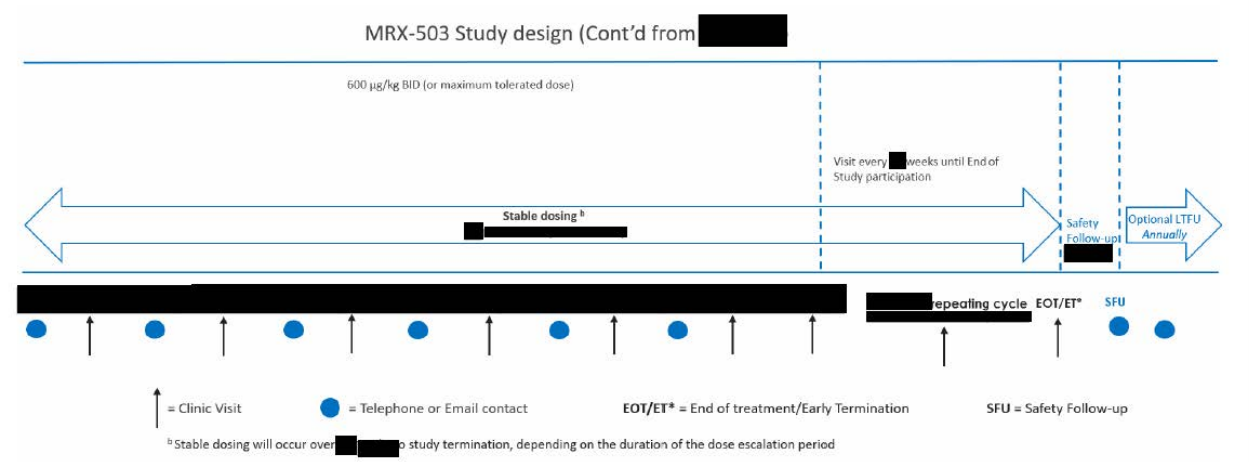
The MRX-503 study will be divided into 3 parts:

1. Dose Escalation period ([redacted])
2. Stable Dosing period ([redacted])
3. Safety Follow-up period ([redacted])

Figure 1. Study Design Flow Chart



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



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

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

[redacted]

600 µg/kg maralixibat BID for the remaining duration of the study

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

Study drug is administered twice daily over the entire treatment period until the study is terminated by the sponsor or the subject discontinues participation.

3.2. Sample Size and Power

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

3.3. Study Population

The study population comprises of male and female participants with a body weight ≥5.0 kg, who are ≥12 months and <18 years of age at time of the MRX-502 study baseline visit, with a confirmed diagnosis of PFIC based on standard-of-care genotyping. Subjects are not considered eligible for the study without having cholestasis [redacted] (upper

limit of normal) (applicable only for the primary cohort) and an average [redacted] leading to the MRX-502 study baseline visit.

Subjects must have completed Study MRX-502 to be eligible for Study MRX-503.

3.4. Treatments Administered

Subjects are assigned to maralixibat in this study, since MRX-503 is an open-label study with a single treatment arm.

Subjects will self-administer (or will be administered) varying volumes of ready-to-use oral solution study drug at each dosing visit, starting with the baseline visit (Visit 1/Day 0). The dosing volume is 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).

Subjects take the first dose of study drug at the baseline visit (Visit 1/Day 0) under the supervision of the Investigator or trained staff.

Study drug administration takes place during the Dose Escalation and Stable Dosing periods of the study based on a BID regimen. 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 q12h to better cover the luminal bile acid release associated with meals. Study drug should be administered approximately at the same time each day throughout the study. The interval between administration of study drug and any concomitant treatment should not change during the study.

3.4.1. Dose Escalation Period

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 (e.g., liver parameters) or tolerability (e.g., GI-related TEAEs) concerns related or possibly related to study medication. Subjects with such safety concerns can be down-titrated to a lower, previously tolerated dose level for [redacted] 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.

3.4.2. Stable Dosing Period

Investigators have until [redacted] to determine the maximum tolerated dose; if re-challenges or further dose escalations fail, the participant will remain on the maximum tolerated dose level for the remainder of the Stable Dosing period to complete a minimum of [redacted] of stable dosing.

During the Stable Dosing period, participants will remain on the maximum tolerated dose level for the remainder of the study. Dose reductions are allowed for safety or tolerability reasons down to a minimum level of [redacted] µg/kg BID. Subjects who cannot tolerate this dose will be discontinued from the study.

3.5. Blinding and Unblinding

There is no blinding of subjects, since this is an open-label study with all participants on maralixibat. However, results from PK sampling, [redacted] sBA testing, [redacted] will be kept blinded to maintain the blinding in the preceding Study MRX-502. The study data will remain blinded in Study MRX-503 until the MRX-502 study database is locked.

3.6. Schedule of Assessments

A detailed schedule of assessments for the MRX-503 study is provided in Table 1.

Table 1: Schedule of Assessments

Procedure[a]	Initial Dosing	Dose Escalation ([redacted])					Stable Dosing[b]										
Visit/Subject Contact Number	Bas./ V1[c]	SC	[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
Healthcare utilization			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

AD-ST-33.06 Effective date: 12-Nov-2020

Procedure[a]	Stable Dosing[b]												
Visit/Subject Contact Number	[redacted]												
Study Week													
Study Day													
Window (in days)													
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
Healthcare utilization		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

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; FGF-19=fibroblast growth factor-19; ItchRO=Itch Reported Outcome; Obs=observer; P=provided; PEBD=partial external biliary diversion; PedsQL=Pediatric Quality of Life Inventory; 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 of study protocol 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 pre-dose 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.

AD-ST-33.06 Effective date: 12-Nov-2020

4. Statistical Analysis and Reporting

4.1. Introduction

[redacted]

4.2. Interim Analysis and Data Monitoring

4.2.1. Interim Analysis

[redacted]

4.2.2. Data Monitoring

A data monitoring committee (DMC) is involved in the management of this study. DMC meetings are held periodically for the duration of the study. The purpose of the DMC is to review the progress of the study, with regard to safety, and make recommendations to the Sponsor to stop or modify the study if safety concerns are identified. 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.

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

5. Analysis Populations

The following analysis populations are planned:

- **Safety Population:** The Safety Population will consist of all participants who receive at least 1 dose of study drug in MRX-503 study.
- **Intent-To-Treat (ITT) Population:** The ITT Population will consist of all participants randomized in Study MRX-502.
- **Per Protocol (PP) Population**: The PP Population will be the same as the PP Population defined in the MRX-502 study. This will facilitate long-term assessment of efficacy in this population.

For the MRX-503 interim analysis, membership in the analysis populations will be determined prior to the MRX-502 study database lock.

[redacted]

5.1. Subject Grouping

The following subject cohorts will be used for the analysis of the various endpoints in this study. Subject cohorts are identified according to the centrally adjudicated PFIC type that is recorded on the Genotype Adjudication file (see Section 6.1.9).

- **Primary cohort**: [redacted].
- **PFIC cohort**: [redacted]
- **Full cohort**: All participants enrolled.

Each of the above-defined cohorts, with the exception of the Full cohort, will exclude any participants with previous documented surgery to address PFIC at baseline of Study MRX-502.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Treatment Groups

All analyses will be conducted for the following 4 treatment groups:

- **MRX-MRX**: Subjects who received maralixibat during participation in study MRX-502. This treatment group will include data from the MRX-502 and MRX-503 studies.

- **PBO**: Subjects who received placebo during participation in Study MRX-502. The PBO treatment group includes data for all subjects during the MRX-502 core study only, including those subjects who did not participate in the MRX-503 extension study.
- **PBO-MRX**: MRX-503 subjects who received placebo during participation in Study MRX-502 and then were switched to maralixibat during participation in the MRX-503 extension study. The PBO-MRX treatment group only includes data for subjects during the MRX-503 extension study.
- **All MRX**: All subjects who received maralixibat during either Study MRX-502 or Study MRX-503. The All MRX treatment group combines MRX-MRX and PBO-MRX treatment groups and includes data from MRX-502 and MRX-503 for the MRX-MRX group, but only data from MRX-503 for the PBO-MRX group.

6.1.2. Baseline Definition

MRX-MRX and PBO Treatment Groups

For the MRX-MRX and PBO treatment groups, baseline values are defined as data measured or collected at the Study MRX-502 baseline visit, Visit 1 (Day 0), before the first dose of MRX-502 study drug is administered. If data are not measured or collected at the baseline visit, then the last non-missing measurement before receiving the first dose of study drug is used as the baseline value.

Baseline and all post-baseline sBA samples collected during Studies MRX-502 and MRX-503 are assayed at Frontage Laboratories. Screening sBA samples, which were collected only during Study MRX-502 study, are assayed at ACM Global Laboratories. Only predose samples assayed at Frontage Laboratories will be used as a baseline sample.

Baseline ItchRO and [redacted] average morning, [redacted] observer [redacted]) are [redacted] before the date of first dose of MRX-502 study drug. The numerator and denominators used in the derivation of weekly average and time period scores are based on the number of non-missing daily and weekly scores, respectively.

For liver-biochemistry laboratory parameters (i.e., ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, and albumin), baseline is defined as [redacted] of Study MRX-502 or the last non-missing measurement before receiving the first dose of MRX-502 study drug if only one value is available. Predose measurements obtained from a local laboratory will be used only if no other data are available. [redacted]

PBO-MRX Treatment Group

For the PBO-MRX treatment group, baseline values are defined as data measured or collected at the MRX-503 baseline visit, Visit 1 (Day 0), before the first dose of maralixibat in Study MRX-503 is administered. If data are not measured or collected at the MRX-503 baseline visit, then the last non-missing MRX-502 assessment closest (on or before) to the MRX-503 first dose date is used as the baseline value for PBO-MRX subjects.

Baseline ItchRO [redacted] average morning, [redacted] scores (observer [redacted]) are constructed as the average of 4 weekly (7-day) average scores in the period consisting of the 28 days immediately before the MRX-502 [redacted] clinic visit date. The numerator and denominators used in the derivation of weekly average and time period scores are based on the number of non-missing daily and weekly scores, respectively.

For liver-biochemistry laboratory parameters (i.e., ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, and albumin), baseline is defined as [redacted] laboratory results before the first dose of MRX-503 study drug. [redacted]

6.1.3. Study Day

For subjects in the MRX-MRX and PBO treatment groups, Study Day 1 is defined as the date of first dose of study drug in Study MRX-502. For subjects in the PBO-MRX treatment group, Study Day 1 is defined as the date of first dose of maralixibat in Study MRX-503.

Study day is calculated relative to the date of Study Day 1.

6.1.4. Adjustments for Covariates

No adjustments will be made for covariates.

6.1.5. Handling of Dropouts or Missing Data

Although all possible efforts will be made to ensure that participants stay in the study and all data are collected as scheduled, the occurrence of missing data cannot be completely eliminated.

Any participant who discontinues early from the study is scheduled to undergo all assessments specified for the end of treatment (EOT)/early termination (ET) visit listed in Table 1. For a participant who discontinues early from the study, his or her ET visit data will be assigned to a protocol-specified visit window as described in Section 6.1.6.

The procedures for handling dropouts or missing data, including the handling of missing individual daily ItchRO [redacted], and adverse event severity and relationship to study drug, are described in the below subsections. Rules for handling missing or partial AE or birth dates are described in Section 6.1.9.

6.1.5.1. [redacted]

[redacted]

6.1.5.2. Missing Adverse Event Severity/Relationship

For analysis purposes, the following rules will be applied for missing AE severity or relationship to study drug. An AE that does not have a recorded relationship to study drug value will be considered as "Related" to study drug. If the severity of an AE is missing, the severity will be reported as "Missing."

6.1.6. Analysis Visit and Time Period Windows

This section is applicable only for post-baseline visit-based assessments/sample collections and ItchRO [redacted] questionnaires completed twice daily during prespecified time periods (as described in Table 4). Analysis visit windows are not applicable for AE, prior or concomitant medication, study drug exposure, or other data that do not fall under the subsections below. Baseline assessments are described in Section 6.1.2.

[redacted]

Visit-Based Assessments/Sample Collections

Analyses of all visit-based efficacy and safety variables will be performed using the analysis visit windows defined by study day relative to the first dose of study drug as outlined below in Table 2 and Table 3: Analysis Visit Windows for PK Samples. Scheduled visits will be selected over unscheduled visits.

Table 2: Analysis Visit Windows for non-PK Samples

Analysis Visit	Analysis Visit Name	Target Day of Analysis Visit	Assessment Window (Study Days[1])
[redacted]			

Table 3: Analysis Visit Windows for PK Samples

Analysis Visit	Analysis Visit Name	Target Day of Analysis Visit	Assessment Window (Study Days[1])
[redacted]			

For those participants who discontinue early from Study MRX-503, Table 2 and Table 3 will also be used to assign the appropriate analysis visit.

[redacted]

[redacted]

[redacted]

Table 4: Analysis Time Period Windows

Analysis Time Period	Analysis Time Period Name	Target Week of Analysis Time Period[1]	Assessment Window (Study Week[2])
[redacted]			

[redacted]

6.1.7. Investigative Sites

An investigative site is defined as a single principal investigator (including subinvestigators) who enroll participants in the study. If an investigator has multiple practice locations, these locations are considered a single investigative site.

There is the potential that a participant could be transferred to a principal investigator who did not enroll the participant. Unless otherwise specified, the investigative site of the enrolling investigator will be used for the unique participant number.

The primary presentations and analyses will be based on data pooled across investigative sites.

6.1.8. Derived Variables

Terms such as "baseline" and "date of first dose" are relative to treatment group: MRX-MRX or PBO versus PBO-MRX (see Sections 6.1.2 and 6.1.3). Select derived variables will be rounded for presentation purposes per Section 4.1.

- **Date of Birth**

  Date of birth, as derived for Study MRX-502, will be used.

- **Age (years) and Age (months) at Baseline**

  Age in years and age in months, as derived for Study MRX-502, will be used for subjects in the MRX-MRX and PBO treatment groups.

  For subjects in the PBO-MRX treatment group, age in years and age in months will be derived based on the date of birth (see above).

- **Age Group at Baseline**: 1 if age (full years) at baseline is 1 to <6 years
  2 if age (full years) at baseline is 6 to <13 years
  3 if age (full years) at baseline is 13 to 18 years

- [redacted]

- [redacted]

- **Time since original diagnosis of PFIC (months)** = (date of first dose – date of original diagnosis of PFIC) / 30.4375
- **Change from baseline** = post-baseline value at time point – value at baseline

  For average ItchRO [redacted] scores, "value" is the average score as defined below.
- **% Change from baseline** = 100 x change from baseline / value at baseline
- [redacted]
- **Baseline ItchRO [redacted] scores:**

  Baseline morning, evening, and highest ItchRO [redacted] scores used for analysis purposes are calculated using the daily scores [redacted] immediately before the date of first dose. [redacted] The "first" 7-day period (immediately before the first dose date) is considered "Week -1," whereas the "last" 7-day period is considered as "Week -4." For each subject and ItchRO [redacted] efficacy variable, a baseline score is derived as the average of the 4 predose weekly average scores.

  The handling of missing daily and weekly average scores is addressed in Section 6.1.5.1. The numerator and denominators used in the derivation of weekly average and time period scores are based on the number of non-missing daily and weekly scores, respectively.
- **Post-baseline ItchRO [redacted] scores:**

  Post-baseline morning, [redacted] ItchRO [redacted] scores used for analysis purposes are calculated using the daily scores from treatment periods immediately after the date of first dose. [redacted]. For each subject and ItchRO [redacted] efficacy variable, post-baseline scores are derived as the average of the [redacted] post-dose weekly average scores for the following time periods: [redacted]

  The handling of missing daily and weekly average scores is addressed in Section 6.1.5.1.

The numerator and denominators used in the derivation of weekly average and time period scores are based on the number of non-missing daily and weekly scores, respectively.

- **ItchRO(Obs) Responder** is defined as a subject having a 4-week average morning ItchRO(Obs) severity change from baseline of ≤-1.0 OR an average severity score of ≤1.0.

  [redacted]

- **sBA Responder** is defined as a subject having an average sBA level of [redacted] change from baseline.

  For the purpose of determining response, the average sBA value from [redacted] of Study MRX-502 (MRX-MRX) or Study MRX-503 (PBO-MRX) will be computed and used.

- [redacted]

- **Ratio of Alpha Tocopherol to the sum of Cholesterol and Triglycerides (mg/g)** = 1000 x alpha tocopherol (mg/dL) / [cholesterol (mg/dL) + triglycerides (mg/dL)]

  For alpha tocopherol concentrations reported as below the minimum quantitation limit, half of the minimum quantitation limit is used in the calculation.

- **Corrected Sodium (mEq/L)** = sodium (mEq/L) + (0.002 x triglycerides [mg/dL])

- **Retinol:RBP Molar Ratio (mol/mol)** = 0.0734 x retinol (µg/dL) / RBP (mg/dL)

- **Anion Gap (mEq/L)** = Sodium (mEq/L) – Chloride (mEq/L) – Bicarbonate (mEq/L)

- **Osmolar Gap (mOsm/kg)** = MO – CO,

  where MO = measured osmolality (mOsm/kg),

  CO = calculated osmolality (mOsm/kg)

  = [2 x (Sodium (mEq/L) + Potassium (mEq/L))] + [Glucose (mg/dL) / 18] + [BUN (mg/dL) / 2.8]

- [redacted]

- **Treatment Duration (days)** =

  Date of last dose of study drug – Date of first dose of study drug + 1 day

  For participants who are missing the date of last dose of study drug, the last known contact date will be used in the calculation of treatment duration.

- **Study Drug Exposure (days)** =

  Treatment duration (days) – Number of days that a participant reported missing both morning and evening doses (between the date of first and last dose)

  For participants who are missing the date of last dose of study drug, the last known contact date will be used in the calculation of study drug exposure.

- **Compliance (%)** = 100 x Study drug exposure (days) / Treatment duration (days)

  Study drug compliance will not be calculated for participants whose date of last study drug is unknown.

- **Total Dose (µg/kg)** = $\sum$ [Number of doses taken$_i$ x Dose received (µg/kg)$_i$]

  where,

  i = 1 to k, (k = number of time periods participant is receiving a constant dose)

- **Average Daily Dose (µg/kg/day)** = Total Dose (µg/kg) / Treatment Duration (days)

  Dose variables (total dose and average daily dose) are not calculated for placebo participants.

- [redacted]

- **Treatment-Emergent Adverse Event (TEAE)** = In general, TEAEs are defined as AEs that start or deteriorate on or after the first dose of study drug and no later than 7 days following the last dose of study drug.

  Any event that started before the first dose and worsens in either intensity or frequency or changes from non-serious to serious on or after the first dose date will also be designated as a TEAE.

  For any participants who die during the study and the date of death is between the date of first dose of study drug and the date of study discontinuation (as entered by the site), inclusive, all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

- **Body Weight, Height and BMI Z-Scores**

  Height, weight, and BMI z-scores are based on a participant's sex and age at each scheduled visit. For participants younger than 24 months of age, the World Health Organization (WHO) growth charts will be used to derive z-scores (WHO 2000). For participants at least 24 months of age, the Center for Disease Control (CDC) growth charts will be used to derive z-scores (CDC 2000).

- **Length of Stay for Hospitalizations (days) =** Date of discharge – Date of admission + 1 day

- **Time to Liver-Associated Event (days)** = Date of liver-associated event – Date of first dose of study drug

6.1.9. Data Adjustments/Handling/Conventions

Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in subject listings for data collected during the MRX-503 extension study.

All p-values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.xxxx). If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

PFIC Type and Subtype

The PFIC type (and BSEP subtype for PFIC2) is centrally assessed by a blinded PFIC genetics expert based on a review of the genotype report. Analyses will be performed according to centrally adjudicated PFIC type, which will be recorded on the Genotype Adjudication file used in MRX-502, and not what is reported within the IRT system or on the eCRF.

Subject Age

The age of a participant during the screening visit of Study MRX-502 will be used to determine the age-specific module or instrument for the appropriate ItchRO [redacted] The same module or instrument will be completed for the duration of Studies MRX-502 and MRX-503, regardless of subsequent birthdays throughout the 2 studies.

[redacted]

Adverse Event and Concomitant Medication Coding

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD Enhanced version September 2019), Anatomical Therapeutic Chemical (ATC) level 2 for ATC class and level 5 (clinical substance) for preferred term.

Prior and Concomitant Treatment Definition and Data Handling

A 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 study drug and the end of the participant's participation in each study, inclusive.

Treatments that started before the first dose of study drug are considered prior treatments regardless of whether they were stopped prior to the first dose of study drug. Any treatment continuing or starting after the first dose of study drug will be considered as concomitant. If a treatment starts prior to the first dose of study drug and continues after the first dose of study drug, the medication will be considered as both prior and concomitant.

Medications that treat pruritus include ATC preferred terms of rifampicin, phenobarbital, alimemazine, brompheniramine maleate, cetirizine hydrochloride, desloratadine, dexchlorpheniramine maleate, dimetindene maleate, ketotifen fumarate, levocetirizine dihydrochloride, loratadine, mequitazine, promethazine, promethazine hydrochloride, ornithine aspartate, ursodeoxycholic acid, colestyramine, naltrexone, naltrexone hydrochloride, and sertraline.

For subjects in the PBO treatment group, all concomitant medications as reported on the MRX-502 study will be included.

For subjects in the MRX-MRX treatment group, concomitant medications that are reported as ongoing at the end of the MRX-502 study, and thus 'duplicated' with the reported end date in the MRX-503 extension study, the concomitant medication as recorded in the MRX-503 database will be used for analysis.

For subjects in the PBO-MRX treatment group, only concomitant medication records in the MRX-503 extension study database will be used for analysis.

TEAE Data Handling

If an event worsens in severity during the study, the lower grade event is marked as "Not recovered/not resolved" on the AE case report form (CRF) and an end date entered. A new event is recorded on the AE CRF with a start date that matches the end date, and the term recorded includes "Worsened" (e.g., "Worsened Headaches"). If an event becomes serious, the date that the event became serious is recorded on the AE CRF as the End Date of that AE and the Start Date of the corresponding serious adverse event (SAE).

For subjects in the PBO treatment group, all AEs as reported on the MRX-502 study will be included.

For subjects in the MRX-MRX treatment group, AEs that are reported as ongoing at the end of the MRX-502 study, and thus 'duplicated' with the reported end date in the MRX-503 extension study, the AE as recorded in the MRX-503 database will be used for analysis.

For subjects in the PBO-MRX treatment group, only AE records in the MRX-503 extension study database will be used for analysis.

Partial Date Imputation

If partial dates occur, the convention for replacing missing dates for the purpose of calculating derived variables is as follows:

Partial PFIC Diagnosis Dates

For partial original PFIC diagnosis dates: (a) if only the day is missing, and the month and year match the first dose date, then the day is assigned the first day of the month (01); otherwise the day assigned is 15; and (b) if both the day and month are missing then the day/month assigned is the first day of July (01JUL), as long as the date is before the first MRX-502 dose date; otherwise, the day/month assigned is the first day of January (01JAN).

Partial AE or Medication Dates

Adverse events or medications with entirely missing start dates will be classified as treatment-emergent or concomitant, as appropriate.

For partial AE or concomitant treatment start dates: (a) if only the day is missing, and the month and year match the first dose date and the end date is on or after the first dose date, then the date is assigned the first dose date thus the event/medication will be considered as treatment-emergent/concomitant; if the month and/or year do not match the first dose date or the end date is prior to the first dose date, then the day is assigned the first day of the month (01); (b) if both the day and month are missing, and the year matches the first dose date and the end date is on or after the first dose date, then the date is assigned the first dose date; if the year does not match the first dose date or the end date is prior to the first dose date, then the day/month are assigned the first day of the year (01JAN).

For partial end dates: (a) if only the day is missing, then the day is assigned the last day of the month; (b) if both day and month are missing, they are assigned the last day of the year (31DEC).

Partial Liver-Associated Event Date

For partial liver-associated event date: (a) if only the day is missing, then the day is assigned the first day of the month (01); (b) if both the day and month are missing, and the year matches the first dose date, then the date is assigned the first dose date; if the year is after the first dose date, then the day/month are assigned the first day of the year (01JAN).

Dates of Birth

Partial or complete dates of birth are not reported by the investigative sites. Complete date of birth is required, however, to derive a participant's weight, height, and BMI z-scores. The convention for imputing missing birth dates for the purpose of statistical analysis will be based

on a subject's age in years and months at the MRX-502 baseline, as defined in the MRX-502 SAP.

Lower and Upper Limit of Quantitation

In general, for quantitative laboratory values reported as "<" or "≤" the lower limit of quantitation (LLOQ), one-half of the reported value (i.e., LLOQ/2) will be used for analysis. The exception to this data treatment is for plasma maralixibat concentrations that are reported as <LLOQ, where a value of zero will be used in calculating summary statistics.

For quantitative laboratory values reported as ">" or "≥" the upper limit of quantitation (ULOQ), the reported value (i.e., ULOQ) will be used for analysis.

Laboratory Test Results

For analysis purposes, repeat laboratory test results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat laboratory value will be used for data analysis.

Local laboratory results are used where central laboratory results are not available.

The International System of Units (SI) will be used in reporting all efficacy and safety laboratory values, unless otherwise specified in Appendix 1.

Treatment Received in Adverse Event Listings

For AE listings reported with the safety table summaries, treatment received at the start of the event will be presented. These select listings will include AE data for each of the treatment groups (i.e., PBO MRX-MRX, and PBO-MRX). For subjects on maralixibat, dose in units of µg/kg/day will be reported. For AEs that started within 7 days after the last dose of study drug, the last treatment received is listed. For AEs that started >7 days after the last dose of study drug, treatment received is blank. For AEs that started prior to the first dose of study drug, NT (Not Treated) will be listed.

Subject listings, presented separate from the table summaries, will only include AEs reported during the MRX-503 extension study.

Treatment Duration and Exposure

For participants who are missing the date of last dose of study drug, for any reason, the last known contact date will be used in the calculation of treatment duration and study drug exposure. Study drug compliance will not be calculated for those participants whose date of last dose of study drug is unknown.

Censoring for Time to First Liver-Associated Event

If a subject does not report a liver-associated event, then the time to first liver-associated event is censored at the last contact date. Last contact date is subject and treatment group specific.

7. Study Subjects and Demographics

Subject disposition, important protocol deviations, demographics, disease history and baseline disease, and study drug compliance will be summarized, unless otherwise noted, by treatment group (MRX-MRX, PBO, PBO-MRX, and All MRX) for the primary cohort, the PFIC cohort, and all cohorts combined (all subjects) in the Safety Population.

7.1. Disposition of Subjects and Withdrawals

Subject disposition will be tabulated in all enrolled subjects.

Subject disposition will include tabulations of the number and proportion of participants in each of the analysis populations, completed study treatment, and discontinued early from the study (along with reasons for withdrawal). Percentages will be based on the number of participants in the Safety Population. The participant disposition tabulation will also include the number of families with siblings enrolled in the study, along with the total number of siblings.

Study drug accountability and compliance listings will be prepared for all participants for data collected during the MRX-503 extension study, showing when the planned dosing schedule was not followed, along with the date and type of dosing deviation. Other MRX-503 subject disposition and study conduct information, including important protocol deviations will be listed.

7.2. Protocol Violations and Deviations

Protocol deviations will be tracked, recorded, and reviewed prior to database lock, following the Protocol Deviation Guidance Plans for the MRX-502 and MRX-503 studies.

Protocol deviations will be classified as “Important” or “Not Important”. An important deviation poses as a relevant operational/study conduction deviation, a possible safety issue to the participant, or it has a potential impact on the statistical analysis of the clinical data. A non-important deviation is identified as any protocol deviation that does not meet the criteria for an important deviation. Potentially important deviations will be reviewed by the Sponsor and Premier to determine the final classification as per the final Protocol Deviation Guidance Plan.

The number and proportion of participants with important protocol violations/deviations will be tabulated by category/type and treatment group in the Safety Population, for the primary cohort, the PFIC cohort, and all cohorts combined (all subjects). These protocol violations/deviations will also be presented in a participant listing by treatment group for data collected during the MRX-503 extension study.

The final decision regarding inclusion and exclusion of participants from the PP populations will be based on a final listing of protocol deviations from Study MRX-502. This will be determined during a (blinded) review meeting before any unblinding occurs or database freeze/lock, with input from the Clinical and Biostatistics team members and approval from the Sponsor.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age at baseline, sex, race, ethnicity, region, height, height z-score, weight, weight z-score, BMI, and BMI z-score will be presented.

Tabulations for age group categories, [redacted], will also be presented. Unless otherwise noted, age is the participant's age at the respective baseline visit for all evaluations and presentations.

Subjects reporting more than 1 race will be counted in a "More than one race" category for purposes of tabulating summary statistics for race.

Disease History and Baseline Disease Characteristics

Summary statistics will also be presented for the following baseline variables:

- PFIC type
- BSEP phenotype
- time since original diagnosis of PFIC (months)
- participants with liver masses detected on ultrasound
- [redacted]
- participants above and below the median baseline sBA level; where the median is calculated separately for the primary cohort, PFIC cohort, and all subjects
- baseline pruritus assessments:
  - [redacted]
  - ItchRO (Obs) 4-week morning average severity score
  - [redacted]

  - [redacted]

- baseline levels of biochemical markers of cholestasis and liver disease and other important baseline laboratory tests:
  - total serum bile acids (sBA)
  - ALT
  - ALP
  - AST
  - GGT
  - bilirubin (total and direct)
  - albumin
  - [redacted]
  - 25-hydroxyvitamin D
  - alpha tocopherol
  - prothrombin intl. normalized ratio
  - vitamin A
  - [redacted]

Subject demographics and baseline characteristics, and medical and surgical history information and prior medications, will be presented in a participant listing by treatment group for data collected during the MRX-503 extension study.

7.4. Prior Medications/Therapies

Prior medications/treatments collected during the MRX-503 extension study will be presented in subject listings by treatment group, subject, PFIC type, ATC Class Level 2 (therapeutic main group) and ATC Class Level 5 (chemical substance).

7.5. Exposure and Compliance

Treatment exposure will be calculated for each participant exposed to maralixibat during the MRX-502 and MRX-503 studies and summarized descriptively by treatment group.

Treatment exposure summaries will include total treatment duration (days), treatment exposure (days), total dose (µg/kg), and average daily dose (µg/kg/day).

Treatment compliance (%) will also be summarized. For a given day, a participant is considered compliant with treatment if any amount of study drug was administered. In addition to the presentation of descriptive statistics on compliance rates, treatment compliance will also be categorized and summarized as <80%, 80-<90%, and 90-100%.

Study drug accountability will be presented in a participant listing by treatment group for data collected during the MRX-503 extension study. Dosing details will be listed separately.

8. Efficacy Analysis

Analyses on the primary and secondary efficacy endpoints will be performed in the ITT and PP populations separately on the primary cohort and the PFIC cohort. Analyses on the exploratory efficacy endpoints will be performed in the ITT population separately on the primary cohort and the PFIC cohort.

For all efficacy analyses, participants will be analyzed by treatment group (MRX-MRX, PBO, PBO-MRX, and All MRX, based on the intent-to-treat principle that asserts that the effect of a treatment can be best assessed by evaluating on the basis of the intention to treat a participant (i.e., the planned treatment regimen) rather than the actual treatment given.

For each of the change from baseline efficacy endpoints, summary statistics on the observed and change from baseline values, including a 95% confidence interval on the mean, will be displayed for each treatment group.

For responder-type endpoints, the number and proportion of participants that are considered a "responder" will be summarized by treatment group for each analysis visit or time period, as appropriate.

For each post-baseline analysis visit, the null hypothesis that the mean change is equal to zero will be tested using the Student's t-test to determine if the mean change is statistically significant. All tests will be performed as 2-sided tests at the 0.05 level of significance.

[redacted]

[redacted]

All efficacy data collected during the MRX-503 extension study will be presented in participant listings.

9. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety Population, defined as all participants who were randomized and received at least 1 dose of study drug. Analyses will be conducted separately on the primary cohort and the PFIC cohort and All Subjects.

Safety measures including AEs, clinical laboratory values, subject BMI z-scores, and concomitant treatment usage will be summarized descriptively by treatment group.

All safety and tolerability data collected during the MRX-503 extension study will be presented in participant listings.

9.1. Adverse Events

All summaries of AEs will be based on TEAEs unless specified otherwise. TEAEs are defined as described in Section 6.1.8 (Derived Variables).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and proportion of participants who experience the event according to MedDRA system organ class (SOC) and preferred term (PT) will be presented by treatment group. Treatment-emergent adverse events related to study drug, AEs leading to withdrawal, and SAEs will be similarly summarized.

A summary of TEAEs will be presented by treatment group. The summary will include the total number and percent of participants reporting:

- Any TEAEs
- Any treatment-related TEAE
- Any severe TEAE
- Any severe treatment-related TEAE
- Any serious TEAE
- Any serious treatment-related TEAE

- Any TEAE leading to permanent study drug discontinuation
- TEAEs resulting in death

A participant reporting multiple cases of the same AE will be counted once within each SOC and similarly counted once within each PT. Treatment-emergent AEs summarized by SOC and PT will be sorted in alphabetical order of the SOC, and by descending frequency order of the PT within each SOC using the All MRX treatment group.

Missing and partially missing AE start and/or stop dates will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.1.9.

Listings of AEs collected during the MRX-503 extension study will be presented in by-participant listings, detailing the participant cohort (primary [redacted], PFIC or other), treatment received at the start of the event (including dose), SOC, PT, verbatim term given by the investigator, onset date and study day, end date and study day, event duration, severity, relationship to study drug, outcome, action taken with study drug, seriousness, and treatment required. Events that are treatment-emergent will be flagged.

9.1.1. Adverse Events Leading to Discontinuation of Study Drug

AEs that lead to permanent discontinuation of study drug will be tabulated by treatment group. Subject listings of AEs that lead to permanent discontinuation of study drug will also be presented for each of the 3 treatment groups (MRX-MRX, PBO, and PBO-MRX).

9.1.2. Deaths and Serious Adverse Events

Treatment-emergent SAEs will be summarized in the same manner as AEs that lead to permanent discontinuation of study drug. Subject listings of all SAEs will also be presented for each of the 3 treatment groups.

Any deaths that occur during the MRX-502 or MRX-503 studies will be presented in a participant listing. The listing will include treatment group, participant ID, participant cohort, study drug and dose received at the time of death (or the last study drug/dose received prior to death), date of death, number of days from the 1st and last dose, MedDRA PT, and relationship to study drug.

9.1.3. [redacted]

[redacted]

[redacted].

9.2. Clinical Laboratory Evaluations

Safety laboratory test results will be summarized descriptively by analysis visit and treatment group as observed and change from baseline values.

All safety laboratory test parameter data collected during the MRX-503 extension study will be presented by panel in participant listings.

Efficacy laboratory tests (i.e., total sBA, ALT, AST, ALP, total and direct bilirubin, GGT, [redacted] will not be included in safety summaries or listings. A separate participant listing for efficacy laboratory data collected during the MRX-503 extension study will be presented.

9.3. Vital Signs and BMI Measurements

BMI z-scores for a participant's age and sex will be summarized descriptively by analysis visit and treatment group as observed and change from baseline values.

Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate), weight, height, and BMI collected during the MRX-503 extension study will be presented by treatment group in participant listings.

9.4. Liver Ultrasound

Liver ultrasound (or MRI) results collected during the MRX-503 extension study will be presented in participant listings.

9.5. Concomitant Medications/Therapies

Concomitant treatments will be summarized descriptively by treatment group using the number and proportion of participants by ATC Class Level 2 (therapeutic main group) and ATC Class Level 5 (chemical substance).

Any treatments continuing or starting after the first dose of study drug will be considered concomitant.

10. Other Planned Analysis

Healthcare utilization and pharmacokinetic analyses will be performed on the Safety Population, conducted separately on the primary cohort, and PFIC cohort.

10.1. [redacted]

[redacted]

11. Changes from Protocol Planned Analysis

[redacted]

[redacted]

12. References

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ICH (1998). ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf

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RSS (2014). The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.

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13. [redacted]

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13.1. [redacted]

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13.1.1. [redacted]

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13.1.4. [redacted]

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13.3. [redacted]

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13.4. [redacted]

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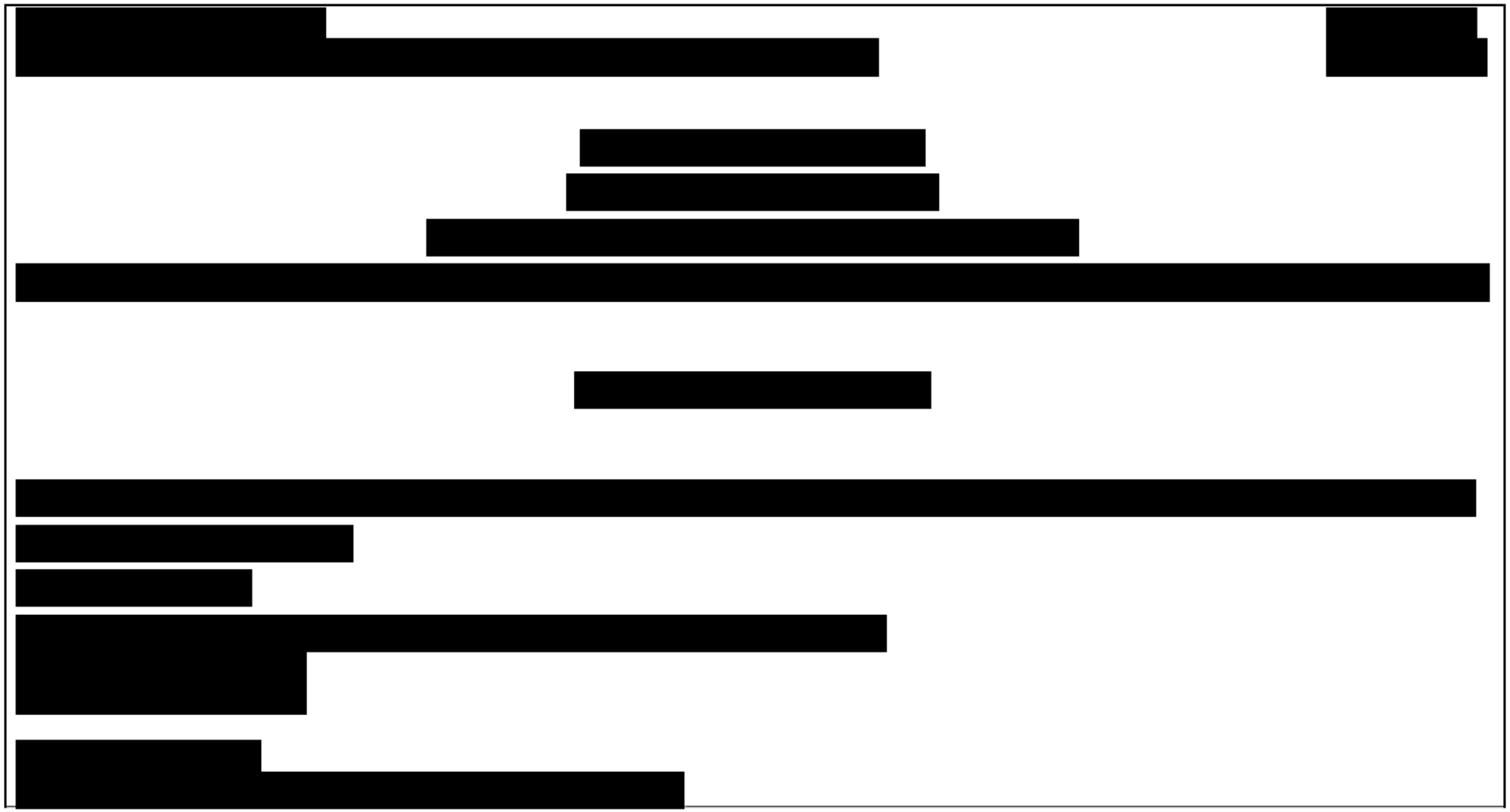

Appendix 1: Listing of Safety and Efficacy Laboratory Analytes

SAFETY LABS

Hematology

Erythrocytes (RBC), $10^6/\mu L$
Hemoglobin, g/dL
Hematocrit, %
MCV, fL
MCH, pg
MCHC, g/dL
Platelets, $10^3/\mu L$
Leukocytes (WBC), $10^3/\mu L$

Differential (% and $10^3/\mu L$)
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Clinical Chemistry

Sodium, mEq/L
Potassium, mEq/L
Chloride, mEq/L
Bicarbonate, mEq/L
Protein, g/dL
Calcium, mg/dL
Phosphate, mg/dL
Glucose, mg/dL
Lipase, U/L
BUN, mg/dL
Creatinine, mg/dL
Urate, mg/dL
Corrected Sodium, mEq/L [3]
Amylase, U/L
Measured Osmolality, mOsm/kg
Calculated Osmolality, mOsm/kg [3]
Osmolar Gap, mOsm/kg [3]
Anion Gap, mEq/L [3]

Lipid Panel

Triglycerides, mg/dL
Cholesterol, mg/dL
LDL-C, mg/dL
HDL-C, mg/dL [1]

Lipid Soluble Vitamins

25-Hydroxy Vitamin D, ng/mL
Vitamin A (retinol), µg/dL
Retinol Binding Protein (RBP), mg/dL
Alpha Tocopherol, mg/dL
INR (surrogate marker for Vitamin K deficiency)
Retinol:RBP Molar Ratio, mol/mol [3]
Ratio of Alpha Tocopherol to the sum of Cholesterol and Triglycerides, mg/g [3]
aPTT, sec (surrogate for LSV)
PT, sec (surrogate for LSV)

Marker of hepatocellular carcinoma

Alpha-Fetoprotein (AFP), ng/mL

Urinalysis [1]

pH
Specific Gravity
Renal Epithelial Cells, /HPF
Squamous Epithelial Cells, /HPF
Granular Casts, /LPF
Hyaline Casts, /LPF
RBC Casts, /LPF
Erythrocytes, /HPF
Leukocytes, /HPF
WBC Casts, /LPF
Waxy Casts, /LPF
Protein *
Glucose *
Ketones *
Bilirubin *
Nitrite *
Urobilinogen *
Leukocyte Esterase *
Calcium Oxalate Crystals *
Triple Phosphate Crystals *
Uric Acid Crystals *
Bacteria *
Creatinine *
Transitional Epithelial Cells *
Occult Blood *
Yeast Cells *

EFFICACY LABS

Clinical Chemistry

Total Bilirubin, mg/dL [2]
Direct Bilirubin (conjugated), mg/dL [2]
ALT, U/L [2]
AST, U/L [2]
ALP, U/L [2]
GGT, U/L [2]
Albumin, g/dL [2]
[redacted]

Cholestasis Biomarkers

Total Serum Bile Acid, µmol/L [2]
7 alpha-hydroxy-4-cholesten-3-one (C4), ng/mL
[redacted]

[redacted]

[1] Listing only
[2] Safety and efficacy lab tests
[3] Calculated lab parameters (see Sec 6.1.8)

Appendix 2: Listing of Lipid Soluble Vitamin Deficiency Events

The following MedDRA Preferred Terms associated with lipid soluble vitamin (LSV) deficiency events are included as an AECI:

- Vitamin A deficiency
- Vitamin A abnormal
- Vitamin A decreased
- Vitamin D deficiency
- Vitamin D abnormal
- Vitamin D decreased
- Vitamin E deficiency
- Vitamin E decreased
- Vitamin K deficiency
- Vitamin K decreased
- International normalised ratio increased
- International normalised ratio abnormal
- Blood 1,25-dihydroxycholecalciferol decreased
- Blood 25-hydroxycholecalciferol decreased