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2.0	29Sep2022	Minor: Update document header to read 'Protocol Number MRX-502 (Amendment 4)' across all pages; some pages in Version 1.0 did not include '(Amendment 4)'	Jana Steinmetz

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List of Abbreviations

Abbreviation	Definition
ALGS	alagille syndrome
APRI	AST to platelet ratio index
ATC	anatomical therapeutic chemical
BID	twice daily
BL	baseline
C4	7α hydroxyl-4-cholesten-3-one
CI	confidence interval
CIS	caregiver impression of severity
CMH	Cochran-Mantel-Haenszel
CSS	clinician scratch scale
DMC	data monitoring committee
ECI	events of clinical interest
EDQ	exploratory diary questionnaire
EM	expectation-maximization
EOT	end of treatment
ET	early termination
FGF-19	fibroblast growth factor-19
FIB-4	fibrosis-4
HCC	hepatocellular carcinoma
INR	international normalized ratio
ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Observer-reported Itch Reported Outcome
ItchRO(Pt)™	Patient-reported Itch Reported Outcome
IRT	interactive response technology
K-M	Kaplan-Meier
LLOQ	lower limit of quantitation

Abbreviation	Definition
LS	least squares
LSV	lipid soluble vitamin
MAR	missing at random
MCMC	Markov-Chain Monte-Carlo
MELD	Model for End-Stage Liver Disease
MI	multiple imputation
MMRM	mixed-effects model for repeated measurements
MNAR	missing not at random
nt-PFIC2	non-truncating PFIC2
Obs	observer
PEBD	partial external biliary diversion
PedsQL	pediatric quality of life
PELD	Pediatric End-Stage Liver Disease
PFIC	progressive familial intrahepatic cholestasis
PIS	patient impression of severity
PRO	patient reported outcomes
Pt	patient
PT	preferred term
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
REML	restricted maximum likelihood
SAE	serious adverse event
sBA	serum bile acid
SD	standard deviation
SE	standard error
SI	International System of Units
SOC	system organ class

Abbreviation	Definition
t-PFIC2	truncating PFIC2
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSB	total serum bilirubin
UDCA	ursodeoxycholic acid
ULN	upper limit normal
ULOQ	upper limit of quantitation
VAP	validation analysis plan
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. protocol number 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 10-May-2022. Reference materials for this statistical plan include the protocol 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 Pharmaceuticals, Inc.'s study MRX-502.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to evaluate the efficacy of maralixibat vs. placebo on the ***severity of pruritus*** in the primary cohort, as defined in Section 5.1.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of maralixibat vs. placebo on total serum bile acid (sBA) levels in the primary cohort
- To evaluate the efficacy of maralixibat vs. placebo on the ***severity of pruritus*** in the PFIC cohort, as defined in Section 5.1

- To evaluate the efficacy of maralixibat vs. placebo on total sBA levels in the PFIC cohort
- To evaluate the efficacy of maralixibat vs. placebo on the ItchRO(Obs) responder rate in the primary cohort.
- To evaluate the efficacy of maralixibat vs. placebo on the sBA responder rate in the primary cohort.
- To evaluate the efficacy of maralixibat vs. placebo on the ItchRO(Obs) responder rate in the PFIC cohort.
- To evaluate the efficacy of maralixibat vs. placebo on the sBA responder rate in the PFIC cohort.
- To evaluate the safety, tolerability, and pharmacokinetics (PK) of maralixibat vs. placebo in all participants who received at least 1 dose of study medication (Safety Population)

2.1.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the efficacy of maralixibat vs placebo in the primary cohort and in the PFIC cohort on the following parameters:
    - Liver biochemistry
    - Non-invasive fibrosis markers: Fibrosis-4 (FIB-4), AST to Platelet Ratio Index (APRI), pediatric end-stage liver disease (PELD) score, model for end-stage liver disease (MELD) score
    - Other measures of pruritus including ItchRO(Obs), for parameters not utilized for primary and secondary objectives, ItchRO(Pt), CSS and other Patient Reported Outcomes (PRO), including Caregiver Impression of Severity (CIS), Patient Impression of Severity of Pruritus (PIS), and Exploratory Diary Questionnaire (EDQ)
    - Responder rates for pruritus severity and total sBA
    - Health-related quality of life
    - Quality of sleep
    - Subject growth
    - Markers of bile acid metabolism: Bile acid subspecies, C4, FGF-19, autotaxin
    - Time to liver-associated events
- To evaluate the impact of maralixibat on healthcare utilization
- To evaluate the correlation between sBA and severity of pruritus in terms of levels and changes from baseline

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety and tolerability endpoints of this study include the following:

- Incidence of adverse events (AEs) including serious, related to study drug, leading to withdrawal, events of clinical interest, along with AEs by severity and by relationship to study drug
- Change from baseline in clinical laboratory values
- Change from baseline in physical examination findings (including body weight, height, and BMI)
- Change from baseline in vital signs
- Change from baseline in electrocardiogram (ECG) measures
- Concomitant treatment usage

Vital signs include heart rate, respiratory rate, body temperature, and blood pressure.

Safety laboratory tests, and associated units of measure, that will be used for reporting are listed in Appendix 1. Note that bilirubin (total and direct), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), GGT, FGF-19, and total sBA are considered as both safety and efficacy laboratory tests.

2.2.2. Efficacy Endpoints

For the sequential (hierarchical) testing and the specific study populations used for each primary and secondary endpoints, please refer to Section 6.1.3 (Multiple Comparisons).

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is defined as the mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26, using 4-week average morning ItchRO(Obs) severity scores in the primary cohort.

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the primary cohort (considered as the key secondary endpoint)
- Mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26, using 4-week average morning ItchRO(Obs) severity scores in the PFIC cohort

- Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the PFIC cohort
- Proportion of ItchRO(Obs) responders from Week 15 to Week 26 (reference Section 6.1.8) in the primary cohort
- Proportion of sBA responders from Week 18 to Week 26 (reference Section 6.1.8) in the primary cohort
- Proportion of ItchRO(Obs) responders from Week 15 to Week 26 (reference Section 6.1.8) in the PFIC cohort
- Proportion of sBA responders from Week 18 to Week 26 (reference Section 6.1.8) in the PFIC cohort

2.2.2.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study will be evaluated in the primary cohort and the PFIC cohort, unless otherwise noted, and include the following:

- Mean change from baseline in total sBA level to Weeks 2, 6, 10, 14, 18, 22, and 26
- Mean change from baseline in liver-associated laboratory test levels (i.e., ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, albumin) to Weeks 2, 6, 10, 14, 18, 22, 26, and average of Weeks 18, 22, and 26
- Mean change from baseline in FIB-4, APRI, MELD and PELD score to Weeks 2, 6, 10, 14, 18, 22, 26, and average of Weeks 18, 22, and 26
- Mean change from baseline in average morning ItchRO(Obs) severity scores to Week 6, 10, 14, 18, 22, and 26, using 6-week average for Week 6 and 4-week average afterwards
- Mean change from baseline in average evening ItchRO(Obs) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average highest daily ItchRO(Obs) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average morning ItchRO(Obs) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average evening ItchRO(Obs) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined

- Mean change from baseline in average highest daily ItchRO(Obs) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average morning ItchRO(Pt) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average evening ItchRO(Pt) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average highest daily ItchRO(Pt) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average morning ItchRO(Pt) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average evening ItchRO(Pt) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average highest daily ItchRO(Pt) frequency scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Number of days with a morning ItchRO(Obs) severity score $\leq$1 at the participant level for the last 84 days (i.e., study day 99 through 182, inclusive) of the study
- Mean change from baseline in CSS at Weeks 2, 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Mean change from baseline in CIS at Weeks 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Mean change from baseline in PIS at Weeks 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Mean change from baseline in average morning EDQ(Obs) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Mean change from baseline in average evening EDQ(Obs) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined

- Mean change from baseline in average highest daily EDQ(Obs) severity scores to Weeks 6, 10, 14, 18, 22, 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Number and proportion of participants achieving morning ItchRO(Obs) severity scores ≤1 for more than 50% of the time from post-baseline to Week 6, Weeks 7 to 10, Weeks 11 to 14, Weeks 15 to 18, Weeks 19 to 22, Weeks 23 to 26, and Week 15 to Week 26
- Mean change from baseline over time in quality of life as measured by the PedsQL (parent) total scale score at Weeks 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Mean change from baseline in average morning EDQ(Obs) sleep disturbance scores to Weeks 6, 10, 14, 18, 22, and 26, using 6-week average for Week 6 and 4-week average afterwards, and Weeks 15 to 26 combined
- Proportion of participants with improvement from baseline (i.e., change from baseline <0) in morning EDQ(Obs) sleep disturbance score at Weeks 6, 10, 14, 18, 22, and 26, using 6-week average scores for Week 6 and 4-week average scores afterwards
- Proportion of morning EDQ(Obs) sleep disturbance scores ≤2 at the participant level post-baseline through Week 26
- Mean change from baseline in height z-score and weight z-score at Weeks 2, 4, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Mean change and % change from baseline in total sBA level to Weeks 2, 6, 10, 14, 18, 22, 26, and Weeks 18, 22, and 26 combined
- Number and proportion of subjects with total sBA % decrease from baseline to Weeks 2, 6, 10, 14, 18, 22, and 26 within the following categories: >75%, 0-75%, and <0%
- Mean change from baseline in C4, FGF-19, and autotaxin to Weeks 6, 10, 18, and 26 in the primary cohort
- Time to first liver-associated event (PEBD surgery, listing for liver transplantation, liver decompensation [hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis] events, HCC, death)

Severity scores for the EDQ are based on the EDQ(Obs) question of "How bad was your child's itch at its worst?" and on the EDQ(Pt) question of "How bad was your itch at its worst". "Non-severity" scores are based on all other EDQ questions.

To assess possible improvements in sleep, the sleep-related question from the EDQ(Obs) questionnaire will be summarized. For EDQ(Obs), sleep disturbance is assessed on the morning diary through the question, "Because of itch, my child had trouble staying asleep". Responses are scored on a 5-point scale, where1=Never, 2=Rarely, 3=Sometimes, 4=Often, and 5=Almost Always. For the EDQ sleep-related question, 6-week average scores will be derived for Weeks 1-6 and 4-week average scores will be derived for the remaining time periods.

2.2.3. Other Endpoints

Other endpoints of this study include the following and will be evaluated in the primary cohort, the PFIC cohort, and all cohorts combined (i.e., all subjects):

- Impact of maralixibat treatment on healthcare utilization (incidence of PFIC-related hospitalization, total inpatient days, selected surgical procedures, emergency room visits, and caregiver days missed from work, etc.) between clinic visits from baseline through Week 27 follow-up visit.
- Plasma levels of maralixibat at pre-dose and approximately 2.5 hours after the morning dose at Week 10 and Week 26 (EOT/ET).

3. Overall Study Design and Plan

3.1. Overall Design

This is a 6-month international, multicenter, randomized, double-blind, placebo-controlled phase 3 study in participants with PFIC who are ≥12 months and <18 years of age at time of baseline. This study will be followed by a long-term extension study (MRX-503), during which all participants who complete study MRX-502 will have the opportunity to be treated with maralixibat.

Subjects in the primary cohort will be randomized in a 1:1 ratio to receive maralixibat or placebo. Subjects in the supplemental cohort will be randomized in a 1:1 ratio to receive maralixibat or placebo within the following subcohorts: a) PFIC1; b) PFIC3; c) all other supplemental cohort subjects.

For the purposes of the randomization stratification and enrollment objectives, the primary and supplemental cohorts are defined as follows:

- Primary cohort, defined as participants with genetic testing results consistent with biallelic disease-causing variation in *ABCB11* (PFIC2), based on standard of care genotyping, excluding those PFIC2 participants with complete absence of bile salt excretion pump (BSEP) function, and do not fall under the definition of the supplemental cohort.
- Supplemental cohort, defined as:
    - Subjects with genetic testing results consistent with biallelic disease causing variation in ATP8B1 (PFIC1), ABCB4 (PFIC3), or TJP2 (PFIC4), based on standard-of-care genotyping
    - Subjects with PFIC phenotype without a known mutation or with another known mutation not described above or with intermittent cholestasis as manifested by fluctuating sBA levels

- Subjects with PFIC after internal or external biliary diversion surgery or for whom internal or external biliary diversion surgery was reversed

Further information about the treatment allocation is provided in Section 3.5.

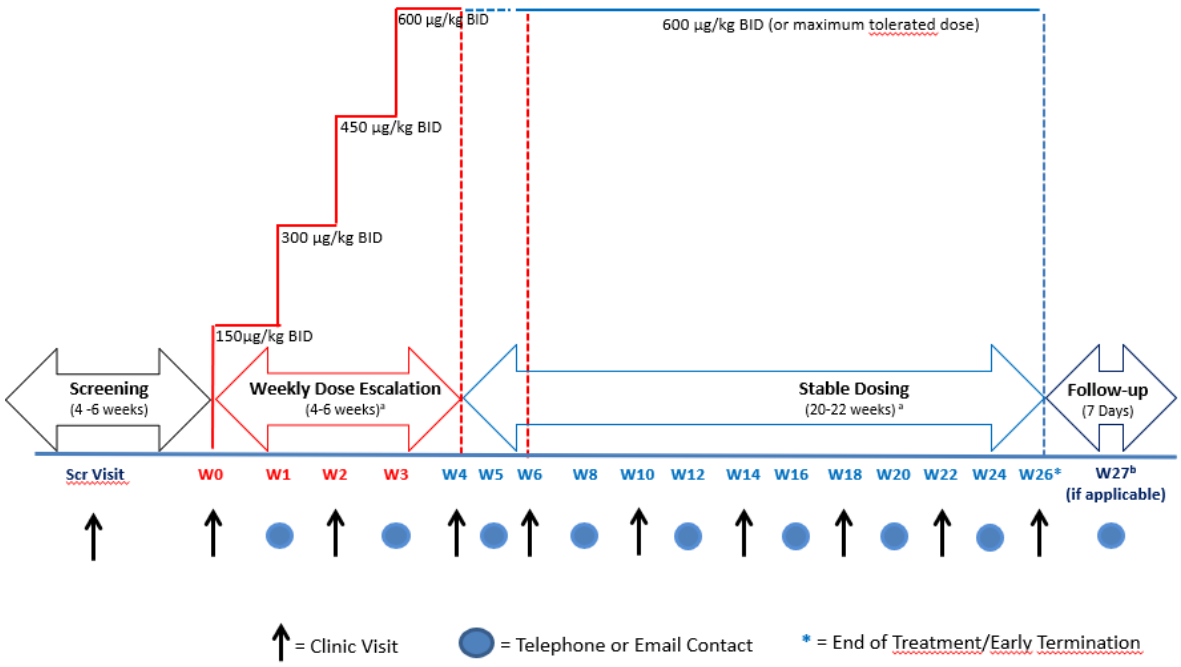
In the primary cohort, approximately 30 participants will be enrolled in order to achieve 26 participants (13 per treatment group) completing the study. In the supplemental cohort, overall enrollment will be capped at a maximum of 60 participants.

The primary analysis will be conducted in the ITT population of participants in the primary cohort. For analysis purposes, post-randomization cohort definitions have been defined (see Section 5.1).

The study will be divided into 4 parts:

1. Screening period (up to 6 weeks)
2. Dose Escalation period (4-6 weeks)
3. Stable Dosing period (20-22 weeks)
4. Safety Follow-up period (7 days from the last dose of study drug for participants not continuing into the extension study [MRX-502])

Figure 1. Study Design Flow Chart



[a] Dose escalation may occur over 4-6 weeks depending on tolerability. Stable dosing will occur over 20-22 weeks, depending on the duration of the dose escalation period.
[b] Safety follow-up visit for subjects not continuing into the extension study (MRX-503).

BID=twice daily; Scr=screening; V=visit; W=week

Subjects randomized to placebo will remain on placebo for the entire duration of the study. The Dose Escalation period will consist of the following weekly steps:

Dose level 1: 150 µg/kg maralixibat BID for 1 week

Dose level 2: 300 µg/kg maralixibat BID for 1 week

Dose level 3: 450 µg/kg maralixibat BID for 1 week

Dose level 4: 600 µg/kg maralixibat BID for the remaining duration of the study

Study drug is administered twice daily over a 26-week treatment period. A participant's maximum duration of participation is expected to be up to 33 weeks.

At the end of the 26-week double-blind treatment period, participants will have the opportunity to enroll into the long-term, extension study (MRX-503). Subjects who do not enroll into the treatment extension study or who discontinue at any time during this study will have a final safety follow-up phone call 7 days after the last dose of study drug. Subjects who discontinue from the study for safety reasons are followed-up as long as clinically indicated or until no further improvement with an adverse event is expected.

The study will be conducted in approximately 40 sites in North America, Europe, Asia, and South America. Other regions may be added, if necessary, for enrollment purposes.

3.2. Sample Size and Power

The sample size was calculated to ensure enrollment of an adequate number of PFIC2 participants who fulfill criteria for the primary cohort (primary endpoint). The sample size is chosen to provide at least 80% of power for the analysis of the primary endpoint.

The primary efficacy endpoint is the mean change from baseline in the average morning ItchRO(Obs) severity score for the last 12 weeks of the study (Weeks 15-26).

The following assumptions were made in estimating the sample size for study MRX-502:

- Between-treatment group (placebo to active) LS mean difference of 0.663
- Pooled SD of 0.563
- Effect size of 1.178 in the mean change from baseline in the 4-week average morning ItchRO(Obs) score

The estimations of LS mean difference, SD and effect size for the sample size justification are based on ItchRO(Obs) data from the maralixibat Phase 2 studies. Maralixibat-treated subjects with PFIC2 from Study LUM001-501 were compared to placebo-treated subjects with ALGS from Studies LUM001-301 and LUM001 302 as no placebo data are available from Study LUM001-501. Since impact and symptoms of itching reported by PFIC patients are also reported by ALGS patients, (i.e., mood changes, scratching, difficulty falling asleep, skin damage, blood from scratching etc.), it is reasonable to assume that the ItchRO outcomes from the ALGS placebo-controlled studies will inform outcomes for this PFIC study due to the similarities in the features of pruritus. Two fundamental assumptions were made: A) the placebo effect in subjects with ALGS is similar to the one expected in subjects with PFIC2. Subjects with ALGS in study LUM001-301/302 had a slightly higher BL ItchRO(Obs) value compared to subjects with PFIC in Study LUM001-501. As subjects with higher BL pruritus generally report a higher placebo response, the use of ALGS subjects from study LUM001-301/302 would therefore lead to a slightly more conservative assumption of the expected effect and sample size. The 2 populations were similar in the other BL characteristics. Besides from the small difference in BL characteristics there are no obvious reasons to believe why the placebo response in subjects with ALGS and PFIC should be difference. Therefore, the comparison of ALGS placebo subjects with treated PFIC subjects is considered a valid approximation for the purpose of assessing the effect size, data variability and the calculation of the sample size. B) the placebo effect does not change after 3 months of treatment; as Studies LUM001-301 and -302 were 13-week studies, data beyond 13 weeks were imputed using the last observation carried forward.

With the assumed values, a total of 26 complete subjects (13 subjects in each treatment group) will be required to provide 80% power for the comparison of the primary endpoint measure between

the maralixibat treatment group and placebo, based on a 2-sided, 2-sample t-test at the 0.05 level of significance.

Including a 10% dropout rate based on the previous PFIC study and rounding up to the next even number, approximately 30 participants (15 participants in each treatment group) will be randomized in the primary cohort of the study.

3.3. Study Population

The study population is comprised of male and female participants with a body weight ≥ 5.0 kg, who are ≥12 months and <18 years of age at time of baseline, with a confirmed diagnosis of PFIC based on clinical/laboratory features and standard of care genotyping. Subjects will not be considered eligible for the study without having cholestasis as manifested by total sBA (primary cohort only) ≥ 3 x ULN (upper limit normal) and an average morning ItchRO(Obs) severity score ≥ 1.5 during 4 consecutive weeks leading to the baseline visit.

3.4. Treatments Administered

Subjects will be randomized to one of two treatment groups:

- maralixibat
- placebo

Eligible participants will be randomly assigned to study drug in a 1:1 allocation ratio, stratified by cohort (see Section 3.1). 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 (150, 300, 450 or 600 µg/kg), and the strength of solution being administered (5, 10, 15, or 20 mg/mL).

Subjects will 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 will take 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 in order 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.

Dosing will occur over a 26-week treatment period.

3.4.1. Dose Escalation Period

For participants assigned to maralixibat, the Dose Escalation period will consist of the following weekly steps:

- Dose level 1: 150 µg/kg maralixibat BID for 1 week
- Dose level 2: 300 µg/kg maralixibat BID for 1 week
- Dose level 3: 450 µg/kg maralixibat BID for 1 week
- Dose level 4: 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 1 week before continuing dose escalation. The minimum dose to continue in the study will be 150 µg/kg maralixibat BID; subjects who cannot tolerate this dose will be discontinued from the study.

3.4.2. Stable Dosing Period

Investigators have up to Week 6 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 20 weeks 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 150 µg/kg BID. Subjects who cannot tolerate this dose will be discontinued from the study.

3.5. Method of Assigning Subjects to Treatment Groups

Subjects who meet study entry criteria will be randomly assigned to maralixibat or placebo in a 1:1 allocation ratio. The randomization schedule will be computer generated by an independent biostatistician using a permuted block algorithm and will randomly allocate each treatment group to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive response technology (IRT) system as participants are entered into the study. The randomization schedule will be stratified by cohort as described in Section 3.1.

The IRT system will be used for screening and enrolling participants, randomization, study drug supply dispensation and management, inventory management and supply ordering, study drug expiration tracking and management, and emergency unblinding. Individual participant treatment is automatically assigned by the IRT to participants who meet study entry criteria. The participant's randomization number represents a unique number corresponding to the treatment allocated to the participant.

At each dosing visit, the Investigator or designee will access the IRT system, and enter participant-specific information (e.g., unique participant number, age [years and months], weight, and information on dose escalation status). For randomized participants, this information will be used by the IRT to identify the appropriate strength of solution and dosing volume, and to assign a corresponding bottle number(s) to be dispensed to the participant.

Siblings enrolled in the study will be assigned in a blinded manner by the IRT system to the same treatment arm.

The randomization schedule will be prepared by Premier Research before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignment. Subjects who discontinue from the study will not be replaced. Study center will not be a blocking factor in the randomization schedule.

3.6. Blinding and Unblinding

All participants, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment.

The treatment assignment must not be unblinded during the study except in emergency situations where the identification of the study drug is required for further treatment of the participant. The Investigator should make an effort to contact the medical monitor before unblinding occurs or as soon as possible after the Investigator has been unblinded without revealing the treatment assignment to the medical monitor. In any event, the medical monitor and Sponsor must be informed about the code break as soon as possible.

If the treatment assignment is unblinded, the date and the signature of the person who was unblinded, and the reason for unblinding are recorded in the source documents. Upon breaking the blind, the participant will be withdrawn from the study, but should be followed up for safety purposes. Unblinding will be processed through the IRT system, and instructions will be available in the user manual.

Data that may potentially unblind treatment assignment (i.e., maralixibat serum concentrations, treatment allocation, post-baseline sBA levels) will be handled with special care during the data cleaning and review process. Prior to unblinding, any data that may potentially unblind study site personnel or study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent audits.

3.7. Schedule of Assessments

A detailed schedule of assessment for the study is provided in Table 1.

Table 1: Schedule of Assessments

Procedures[p]	Screening [a]	Dose Escalation (4-6 weeks)						Stable Dosing (20-22 weeks)											Follow-up
Visit/Subject Contact #	**Screening / V0**	**Baseline / V1**	**Subject contact**	**V2**	**Subject contact**	**V3**	**Subject contact**	**V4**	**Subject contact**	**V5**	**Subject contact**	**V6**	**Subject contact**	**V7**	**Subject contact**	**V8**	**Subject contact**	**EOT/ET V9[b]**	
Study Week	**-6**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**27**
Study Day	**Day -42**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**189**
Window (in days)	**(-5)**		**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±2)**
Informed Consent/Assent	X																		
Eligibility Assessment	X	X																	
Demographics	X																		
Medical History	X																		
Physical & Vital signs[c]	X	X		X		X		X		X		X		X		X		X	
ECG	X	X								X								X	
Liver Ultrasound[d]	X																	X	
Pregnancy Test[e]	S	U				U		U		U		U		U		U		S	
Confirm PFIC Genotype Results[f]	X																		
eDiary Device Provided / Returned[g]	P																	R	
ItchRO(Obs), ItchRO(Pt) & EDQ	Twice-daily completion of ItchRO & EDQ																		
Review eDiary & Assess Compliance		X		X		X		X		X		X		X		X		X	
Randomized		X																	
CIS[h]		X				X		X		X		X		X		X		X	
PIS[i]		X				X		X		X		X		X		X		X	
PIC																		X	
CIC																		X	

Procedures[p]	Screening [a]	Dose Escalation (4-6 weeks)						Stable Dosing (20-22 weeks)											Follow-up
Visit/Subject Contact #	**Screening / V0**	**Baseline / V1**	**Subject contact**	**V2**	**Subject contact**	**V3**	**Subject contact**	**V4**	**Subject contact**	**V5**	**Subject contact**	**V6**	**Subject contact**	**V7**	**Subject contact**	**V8**	**Subject contact**	**EOT/ET V9[b]**	
Study Week	**-6**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**27**
Study Day	**Day -42**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**189**
Window (in days)	**(-5)**		**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±2)**
PedsQL[j]		X				X		X		X		X		X		X		X	
Clinician Scratch Scale	X	X		X		X		X		X		X		X		X		X	
CBC with Differential	X	X		X				X		X		X		X		X		X	
Coagulation	X	X		X				X		X		X		X		X		X	
Chemistry Panel	X	X		X				X		X		X		X		X		X	
Lipid Panel[k]	X	X		X				X		X		X		X		X		X	
Urinalysis		X						X		X				X				X	
FGF-19, Autotaxin, C4[k]		X						X		X				X				X	
sBA collection[k]	X	X		X				X		X		X		X		X		X	
Lipid Soluble Vitamins[k,l]		X						X		X		X		X		X		X	
AFP Sample		X								X								X	
PK Sample[m]										X								X	
Serum storage sample		X		X				X		X		X		X		X		X	
Healthcare Utilization				X				X		X		X		X		X		X	X
Study drug Supplied[n]		X		X		X		X		X		X		X		X			
Study drug Administration[o]		Twice-daily administration																	
Assess AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AFP=a-fetoprotein; C4=7a-hydroxy-4-cholesten-3-one; CBC=complete blood count; CIS=Caregiver Impression of Severity; CIC=Caregiver Impression of Change; ECG=electrocardiogram; EDQ=exploratory diary questionnaire; EOT=end of treatment; ET=early termination; FGF-19=fibroblast growth factor-19; ItchRO=Itch Reported Outcome; P=Provided; PedsQL=Pediatric Quality of Life Inventory; PIC=Patient Impression of Change; PIS=Patient Impression of Severity of Pruritus; PK=pharmacokinetic; R=Returned; S=Serum; U= Urine; V=visit

[a] Subjects who initially fail to meet eligibility criteria may be re-assessed during the 6-week screening period prior to being captured as a screen failure. Subjects may also be re-screened

[b] 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

[c] Blood pressure, heart rate, temperature, respiration rate. Height and weight will be measured by trained staff using standardized methodology, incl. calibrated stadiometer or headboard and calibrated balance, respectively

[d] Screening ultrasound not required if an ultrasound or liver MRI less than 6 months old is available

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

[f] Genotyping results will be reviewed by Sponsor or designee

[g] Caregivers and age-appropriate participants will be instructed to complete their eDiary twice daily (morning and evening)

[h] To be completed by caregivers for all participants

[i] To be completed only by participants aged ≥9 years at screening

[j] To be completed by participants and caregivers using the age-appropriate PedsQL module

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

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

[m] PK samples will be drawn pre-dose, and approximately 2.5 hours after the morning dose

[n] If needed, study drug may be supplied via direct-to-patient shipments in between site visits, see Section 6.4 of the protocol (amendment 4).

[o] Subjects will self-administer (or will be administered) the first dose of study drug in the clinic on Visit 1/Day 0 after breakfast under the supervision of the Investigator or trained site staff.

[p] See Appendix 10 of the protocol (amendment 4) for management of study procedures during pandemic.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of participants with non-missing values (n), mean, 2-sided 95% CI for the mean, standard deviation (SD) and/or standard error (SE) if appropriate, median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the particular category for each possible value. In general, the denominator for the percentage calculation will be based upon the total number of participants in the analysis population (and cohort where applicable) with available data for each treatment group, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (i.e., SD or SE) will be reported to 2 degrees of precision more than the observed data. Confidence intervals (CIs) for the mean are reported to the same degree of precision as the mean.

The minimum and maximum values for derived and select observed values will be reported as follows, with measures of location and spread following the above rules. Derived values for corrected sodium (mEq/L), calculated osmolarity (mOsm/kg), osmolar gap (mOsm/kg), anion gap (mEq/L), MELD and PELD scores will be presented as integers. Derived values for PedsQL summary and total scale scores will be presented to 1 decimal place. Serum bile acid levels (total and sub-species), and derived values of height, weight, and BMI z-scores, EDQ and ItchRO average scores, FIB-4, APRI, retinol:RBP molar ratio (mol/mol), and ratio of α-tocopherol to the sum of cholesterol and triglycerides (mg/g), will be reported to 2 decimal places.

Percentages will be presented to 1 decimal place, unless otherwise specified. Where the number of participants in a particular category is zero, a percentage (i.e., 0.0%) will not be displayed.

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a p-value of ≤ 0.05 will be considered statistically significant. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests.

A p-value of ≤ 0.10 but > 0.05 will be considered evidence of a trend.

To control for the overall type I error rate, hierarchical testing based on a fixed sequence procedure will be used. If statistical significance is declared for the primary efficacy analysis, formal hypothesis testing will be done for the secondary efficacy endpoints in the pre-specified sequence until a non-significant result is reached. All other p-values from secondary endpoints, after a non-significant p-value is reached, will be considered nominal and will be interpreted with appropriate caution when considering the extent to which results from secondary endpoints provide support for evidence of efficacy.

4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

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, 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 will be available prior to the enrollment of the first participant. There is no study stop planned based on the efficacy results during the study and no alpha spending will occur prior to the completion of the study.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population:** The Safety Population will consist of all participants who receive at least 1 dose of study drug.
- **Intent-To-Treat (ITT) Population:** The ITT Population will consist of all randomized participants.
- **Per Protocol (PP) Population**: The PP Population will consist of all participants in the ITT Population who receive at least 1 dose of study drug and do not have any important protocol violations or deviations that have a potential impact on the efficacy analysis. Important protocol violations/deviations will be identified prior to database lock.

Membership in the analysis populations will be determined prior to database lock.

The primary efficacy endpoint and the key secondary efficacy endpoint (i.e., change from baseline in sBA) will be analyzed for the ITT and PP analysis populations. The other secondary and exploratory efficacy endpoints will be analyzed in the ITT population.

The number of participants excluded from each analysis will be presented.

Safety, tolerability, and PK analyses will be conducted in the Safety Population.

Because PFIC is a rare disease, siblings are allowed to enroll in this study. Each sibling will be considered for each analysis population described above. A sensitivity analysis on the primary efficacy endpoint and the key secondary efficacy endpoint will include only 1 sibling in the ITT analysis population. The choice of sibling will be made at random. The method of choosing a sibling is described in Section 6.1.9.

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 which are recorded on the Genotype Adjudication file (see Section 6.1.9).

- **Primary cohort**: All non-truncated PFIC2 (nt-PFIC2) participants.
- **PFIC cohort**: PFIC1, nt-PFIC2, PFIC3, PFIC4, PFIC5 and PFIC6 participants (i.e., all genotypes except for truncating PFIC2 [t-PFIC2] participants, and participants with heterozygosis, low or fluctuating sBAs, a history of surgery, or where there is no established variant linked to PFIC disease)
- **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.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

In general, baseline values are defined as data measured or collected at the baseline visit, Visit 1 (Day 0), before the first dose of study drug is administered. If data is 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 are assayed at Frontage Laboratories, while screening sBA samples are assayed at ACM Global Laboratories. Only pre-dose samples assayed at Frontage Laboratories will be used as a baseline sample.

Baseline ItchRO and EDQ average morning, evening, and highest scores (observer and patient) are constructed as the average of 4 weekly (7-day) average scores in the period consisting of the 28 days immediately before the date of first dose of 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 the average of data collected between Screening and Visit 1 (Day 0), or the last non-missing measurement before receiving the first dose of study drug if only one value is available. Pre-dose measurements obtained from a local laboratory will only be used if no other data are available. For the derived non-invasive fibrosis markers of APRI, FIB-4, PELD, and MELD, the same (derived/average) liver-biochemistry baseline value will be used.

6.1.2. Adjustments for Covariates

Efficacy variables that are continuous measures assessed over time will be analyzed using a mixed-effects model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed, categorical effects of treatment group, analysis visit, and treatment group-by-visit interaction as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction.

For the PFIC cohort (as defined in Section 5.1), PFIC type will also be used as a covariate in the MMRM analysis. For this analysis, due to the small sample sizes, PFIC4, PFIC5, and PFIC6 will be grouped together. Within the PFIC cohort, 4 levels of PFIC types are included in the covariate: nt-PFIC2, PFIC1, PFIC3, and other (PFIC4, PFIC5, and PFIC6 group).

No other covariates will be included in the analyses of the efficacy endpoints.

6.1.3. Multiple Comparisons

The type I error rate of $\alpha = 0.05$ will be maintained for the study by using sequential (hierarchical) testing for primary and secondary efficacy endpoints.

The testing will be done in the following order, noting the primary and PFIC cohorts are defined in Section 5.1:

1. Primary: Mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26 in the primary cohort

2. Key Secondary: Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the primary cohort
3. Secondary: Mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26 in the PFIC cohort
4. Secondary: Mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 in the PFIC cohort
5. Secondary: Proportion of ItchRO(Obs) responders from Week 15 to Week 26 (reference Section 6.1.8) in the primary cohort
6. Secondary: Proportion of sBA responders from Week 18 to Week 26 (reference Section 6.1.8) in the primary cohort
7. Secondary: Proportion of ItchRO(Obs) responders from Week 15 to Week 26 in the PFIC cohort
8. Secondary: Proportion of sBA responders from Week 18 to Week 26 in the PFIC cohort

Because the testing is sequential, the type I error rate of $\alpha = 0.05$ is maintained. Failure at any stage in the sequence implies no type I error control for the additional subsequent tests. All p-values for each comparison without adjustments will be provided in the summary tables for informational purposes.

6.1.4. Handling of Dropouts or Missing Data

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

The primary analysis population for all efficacy analyses will be the ITT Population. For the analysis of primary efficacy endpoint and the key secondary efficacy endpoint, based on the ITT Population over the primary and PFIC cohorts (separately), several methods will be used to handle missing data for average morning ItchRO(Obs) severity and total sBA, including:

- MMRM
- multiple imputation (MI) using standard MAR approach
- MI using tipping point approach

The MMRM method will be used for the primary analysis on all continuous, repeated efficacy measures. Sensitivity analyses using the 2 MI methods will be performed on the primary efficacy endpoint and the key secondary efficacy endpoint to assess the robustness of alternate imputation assumptions.

The above procedures are described in the below sub-sections, along with the handling of missing individual ItchRO and EDQ scores, PedsQL scale scores, and adverse event severity and relationship to study drug.

6.1.4.1. MMRM Analysis Method

Efficacy variables that are continuous measures assessed over time will be analyzed using a MMRM model as the primary analysis method, with change from baseline as the dependent variable and fixed, categorical effects of treatment group, visit, and treatment group-by-visit interaction as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. For PFIC cohort analyses, PFIC type (i.e., PFIC1, nt-PFIC2, PFIC3, and the combination of PFIC4, PFIC5, and PFIC6) will also be included in the MMRM model as a covariate.

The MMRM method has been demonstrated extensively as an appropriate choice for the primary analysis in longitudinal confirmatory clinical trials with continuous endpoints (Mallinckrodt et al, 2008). This analysis method, which is from a broader class of direct-likelihood analyses methods, makes use of fully and partially observed data sequences from individual participants by estimating the covariance between data from different time points (Molenberghs et al, 2007). Further, it is often useful to implement MMRM using an unstructured approach to modeling both the treatment-by-time means and the variances and covariances, leading to what is essentially a multivariate normal model wherein treatment group means at the primary time point are adjusted to reflect both the actual observed data and the projected outcomes from the participants with missing data (Cnaan et al, 1997, Molenberghs et al, 2004, Molenberghs et al, 2007).

As a direct likelihood method, the MMRM method is a preferred approach for handling missing data in such designs and will be used as the primary analysis method for all efficacy and safety endpoints where assessments are made over time. MMRM is a full multivariate model in nature, which avoids potential bias as a predetermined model and operates in a more general missing at random (MAR) framework (Mallinckrodt et al, 2001). Data are considered MAR if, conditional upon the independent variables in the analytic model, the missingness depends on the observed outcomes of the variable being analyzed but does not depend on the unobserved outcomes of the variable being analyzed. This assumption implies that the behavior of the post dropout observations can be predicted from the observed variables, and therefore that treatment effect can be estimated without bias using the observed data (EMA, 2010). For studies of missing data in a controlled clinical trial setting, MAR is usually considered as a plausible underlying missing mechanism (Molenberghs et al, 2007; Siddiqui et al, 2009, Mallinckrodt et al, 2008, Mallinckrodt et al, 2013). The assumption of MAR is often reasonable because, particularly in longitudinal studies wherein the evolution of treatment effects is assessed by design over time, the observed data and the models used to analyze them can explain much of the missingness (Little et al, 1987, Verbeke et al, 2000). This point may be especially relevant in well-controlled studies, in which extensive efforts are made to observe all outcomes and factors that influence

them while participants are following protocol-defined procedures. Thus, longitudinal clinical trials by their very design aim to reduce the amount of missing not at random (MNAR) data (missingness explained by unobserved responses), thereby increasing the plausibility of MAR (Mallinckrodt et al, 2008).

The following SAS pseudocode will be used for the MMRM models:

```
proc mixed data = example;
    class <subjectid> <visit> <treatment>;
    model chg = <baseline score> <treatment> <visit> <treatment>*<visit> <baseline score>*<visit> /
ddfm = kr;        *** PFIC type is included in the model for analyses of the PFIC cohort ***;
    repeated <visit> / subject = <subjectid>(<treatment>) type = un;
    lsmeans <treatment>*<visit> / cl pdiff;
lsmestimate <treatment>*<visit> 'Weeks 15-18 MRX LS Mean=0'    0 0 1 0 0 0 0 0 0 0 0 0  divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 15-18 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 1 0 0 0 divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 15-18 MRX LS Mean = Placebo LS Mean' 0 0 1 0 0 0 0 0 -1 0 0 0
divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 19-22 MRX LS Mean=0'    0 0 0 1 0 0 0 0 0 0 0 0  divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 19-22 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 1 0 0 divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 19-22 MRX LS Mean = Placebo LS Mean' 0 0 0 1 0 0 0 0 0 -1 0 0
divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 23-26 MRX LS Mean=0'    0 0 0 0 1 0 0 0 0 0 0 0  divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 23-26 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 0 1 0 divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 23-26 MRX LS Mean = Placebo LS Mean' 0 0 0 0 1 0 0 0 0 0 -1 0
divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 15-26 MRX LS Mean=0'    0 0 1 1 1 0 0 0 0 0 0 0  divisor=3 / cl;
lsmestimate <treatment>*<visit> 'Weeks 15-26 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 1 1 1 0 divisor=3 / cl;
lsmestimate <treatment>*<visit> 'Weeks 15-26 MRX LS Mean = Placebo LS Mean' 0 0 1 1 1 0 0 0 -1 -1 -1
0  divisor=3 / cl;
run;
```

6.1.4.2. Multiple Imputation Methods

Although the assumption of MAR, as used for the primary efficacy analysis method, is often reasonable in clinical trials, the possibility of MNAR data cannot be ruled out. Therefore, analysis valid under MNAR will also be performed. Both MNAR- and MAR-based analyses using MI methods will be the basis upon which sensitivity of the analysis to missing data are assessed.

Any participant who withdraws or is discontinued from the study or who misses a scheduled visit or assessment up through Week 26 will have their primary and key secondary efficacy missing data analyzed as imputed using MI techniques. This analysis will be presented as a sensitivity analysis.

Multiple imputation is a simulation-based approach where missing values are replaced using an appropriate stochastic model given the observed data and covariates, creating multiple completed data sets. These completed datasets are then analyzed using standard analysis methods (MMRM for this study), and the different parameter estimates across the datasets are then combined to produce unique point estimates, standard errors, and confidence intervals taking into account the uncertainty of the imputation process.

In most randomized clinical trials that collect data over time, the great majority of missing data follow a monotone pattern. That is, once a participant has missing data for some visit, data will be missing for all subsequent visits. Typically, there is also a small amount of non-monotone missing data (i.e., some participants have missing values for intermediate visits, but have non-missing data at subsequent visits).

The following 2 MI analysis models, one based on the standard MAR approach and the other based on the MNAR approach, will be used to examine robustness of the primary analysis results.

Standard MAR Imputation

The MAR imputation model will impute missing values using a regression-based multiple imputation model (Little et al, 1996). For participants with complete data up to a particular timepoint (e.g., time period average score for the primary endpoint and analysis visit for the key secondary endpoint), a multiple regression model will be fit that includes the outcome at that time point as the dependent variable and observed data (e.g., outcomes at previous time points, treatment, and baseline) as independent variables. Separate models will be similarly constructed for each time point. Using these regression models, a missing value for a participant at a particular time point will be imputed as a draw from the predictive distribution given the outcomes at previous time points (some possibly imputed), treatment group, etc. This process will be repeated a given number of times (as specified below), resulting in the same number of complete analysis data sets. The MMRM analyses will be performed separately for each of the completed analysis data sets, and the results will be combined into one multiple imputation inference (Little et al, 1996, Schafer, 1997). This strategy is appropriate for data sets that have a monotone missing data pattern. If the data set does not precisely have this pattern, a monotone data augmentation method, as described below in Step 1, will be used to impute the small amount of missing data that is required to make the missing data pattern monotone before applying the MI algorithm described above.

Multiple imputation based on a standard MAR imputation approach will be performed in SAS using a general three-step approach:

Step 1: If the data has a non-monotone pattern of missingness, then a monotone data augmentation method using Markov-Chain Monte-Carlo (MCMC) will be used to impute data that is missing and required to make the missing data pattern monotone. Twenty datasets with a

monotonic missing pattern will be generated. This method will use a non-informative Jeffreys prior to derive the posterior mode from the expectation-maximization (EM) algorithm as the starting values for the MCMC method. Intermittent missing values will be imputed using the MCMC method assuming a multivariate normal distribution over all variables included in the imputation model (i.e., treatment group, baseline, and each post-baseline visit). The MCMC statement of the MI procedure in SAS (PROC MI) will specify the CHAIN=MULTIPLE option, so that the procedure uses multiple chains and completes the default 200 burn-in iterations before each imputation, and the IMPUTE=MONOTONE option to create the 20 partially imputed datasets with a monotone missing pattern. The seed of the pseudorandom number generator used to randomly generate imputations for the missing values in Step 1 is 3590145.

Assumptions underlying the partial imputation step are such that participants with missing data follow the same model as other participants in their respective treatment arm that have complete data.

If the raw data has a monotone pattern of missingness, then the same procedures described above can be followed to create 20 identical datasets that will be used as an input dataset for the next step.

Pseudocode for imputation of primary efficacy missing data is provided below:

```
proc mi data=example nimpute=20 seed=3590145 minimum = 0 maximum = 4 out=example_1;
        by <treatment>;
        MCMC chain=multiple impute=monotone;
        var <baseline score> <week 1-6>…… <week 23-26>;
run;
```

Step 2: Using a standard MAR-based MI approach, the remaining missing data will be imputed using a method for monotone missingness. The dataset that contains the multiple (20) partially imputed datasets is first sorted by imputation number and treatment group. The MI procedure used to complete the imputation will use a BY imputation number statement and request one imputed dataset within each BY group. The variables in the imputation model include treatment group, baseline, and each post-baseline visit. The final 20 fully imputed datasets will be generated using a regression-based multiple imputation model (PROC MI statement MONOTONE REGRESSION). For participants with complete data up to a particular visit, a multiple regression model will be fit that includes the outcome at that visit as the dependent variable and outcomes at previous visits and treatment group as independent variables. Using these regression models, a missing value for a participant at a particular time point will be imputed as a draw from the predictive distribution given the outcomes at previous time points (some possibly imputed) and treatment group. The seed number of 9482038 will be used for the imputation procedure described in Step 2.

For both Steps 1 and 2, minimum and maximum values for average ItchRO severity scores (i.e., 0 and 4) will be specified in the MI procedure to avoid imputed values outside the possible range of values. When an intended imputed value is less than the minimum or greater than the maximum value specified, the MI procedure in SAS will redraw another value for imputation.

Pseudocode for this step is below:

```
proc sort data= example_1;
        by <imputationnumber> <treatment>;
run;

proc mi data= example_1 nimpute=1 seed=9482038 minimum = 0 maximum = 4 out= example_2;
        by <imputationnumber>;
        monotone regression;
        var <treatment> <baseline score> <week 1-6>…… <week 23-26>;
run;
```

Step 3: MMRM analyses will be performed separately for each of the 20 complete analysis datasets, and the results will be combined into one multiple imputation inference (estimated treatment effect, standard error, p-value and associated 95% confidence interval) using the SAS MIANALYZE procedure. The treatment difference will be tested at the 2-sided 0.05 level and corresponding 95% CIs will be calculated. In the case that there is no missing data for a particular visit, p-values and 95% confidence intervals will come from the MMRM analysis on the observed data.

SAS pseudocode for the MMRM analysis is as follows:

```
ods output   lsmestimates= lsm_diff;
proc mixed data = example_3;
        by <imputationnumber>;
        class <subjectid> <treatment> <visit>;
        model chg = <baseline score> <treatment> <visit> <treatment>*<visit> <baseline score>*<visit>
/ddfm = kr;    *** PFIC type is included in the model for analyses of the PFIC cohort ***;     repeated
<visit> / subject = <subjectid>(<treatment>) type = un;
    lsmeans <treatment>*<visit> / cl pdiff;
 lsmestimate <treatment>*<visit> 'Weeks 15-18 MRX LS Mean=0'   0 0 1 0 0 0 0 0 0 0 0 0  divisor=1 / cl;
 lsmestimate <treatment>*<visit> 'Weeks 15-18 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 1 0 0 0 divisor=1 /
cl;
 lsmestimate <treatment>*<visit> 'Weeks 15-18 MRX LS Mean = Placebo LS Mean' 0 0 1 0 0 0 0 0 -1 0 0 0
divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 19-22 MRX LS Mean=0'   0 0 0 1 0 0 0 0 0 0 0 0  divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 19-22 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 1 0 0 divisor=1 / cl;
```

```
lsmestimate <treatment>*<visit> 'Weeks 19-22 MRX LS Mean = Placebo LS Mean' 0 0 0 1 0 0 0 0 0 -1 0 0
divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 23-26 MRX LS Mean=0'    0 0 0 0 1 0 0 0 0 0 0 0  divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 23-26 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 0 0 1 0 divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Weeks 23-26 MRX LS Mean = Placebo LS Mean' 0 0 0 0 1 0 0 0 0 0 -1 0
divisor=1 / cl;
 lsmestimate <treatment>*<visit> 'Weeks 15-26 MRX LS Mean=0'    0 0 1 1 1 0 0 0 0 0 0 0  divisor=3 / cl;
lsmestimate <treatment>*<visit> 'Weeks 15-26 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 1 1 1 0 divisor=3 / cl;
lsmestimate <treatment>*<visit> 'Weeks 15-26 MRX LS Mean = Placebo LS Mean' 0 0 1 1 1 0 0 0 -1 -1 -1
0  divisor=3 / cl;
run;


proc mianalyze data=diff;
  by <visit> ;
  modeleffects estimate;
  STDERR stderr;
  ods output parameterestimates=dif_2;
run;

proc mianalyze data=lsm;
  by <visit> <treatment>;
  modeleffects estimate;
  stderr stderr;
  ods output parameterestimates=lsmn_2;
run;
```

Pseudocode for imputation of key secondary efficacy missing data is provided below. There is a potential need to add option MAXITER=nnn to the MI procedure if the analysis fails to converge with 200 iterations.

Step 1:

```
proc mi data=example nimpute=XX seed=3590145 minimum = yy maximum = yy out=example_1;
        by <treatment>;
        MCMC chain=multiple impute=monotone;
        var <baseline> <week 2>…… <week 26>;
run;
```

XX will be determined based on the proportion of missing data across visits. The minimum and maximum values for total sBA level will be specified as the minimum and maximum values of the calculated results.

Step 2:

```
proc sort data= example_1;
        by <imputationnumber> <treatment>;
run;

proc mi data= example_1 nimpute=1 seed=9482038 minimum = yy maximum = yy  out= example_2;
        by <imputationnumber>;
        monotone regression;
        var <treatment> <baseline> <week 2>…… <week 26>;
run;
```

Step 3:

```
ods output  lsmestimates= lsm_diff;
proc mixed data = example_3;
        by <imputationnumber>;
        class <subjectid> <treatment><visit> ;
        model chg = <baseline> <treatment> <visit> <treatment>*<visit> <baseline>*<visit> /ddfm = kr;
        *** PFIC type is included in the model for analyses of the PFIC cohort ***;
        repeated <visit> / subject = <subjectid>(<treatment>) type = un;
        lsmeans <treatment>*<visit> / cl pdiff;
lsmestimate <treatment>*<visit> 'Week 18 MRX LS Mean=0'   0 0 1 0 0 0 0 0 0 0 0 0 0 0 divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Week 18 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 1 0 0 0 0 divisor=1 / cl;
 lsmestimate <treatment>*<visit> 'Week 18 MRX LS Mean = Placebo LS Mean' 0 0 1 0 0 0 0 0 0 -1 0 0 0 0
divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Week 22 MRX LS Mean=0'   0 0 0 0 1 0 0 0 0 0 0 0 0 0  divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Week 22 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 0 0 1 0 0 divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Week 22 MRX LS Mean = Placebo LS Mean' 0 0 0 0 1 0 0 0 0 0 0 -1 0 0
divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Week 26 MRX LS Mean=0'    0 0 0 0 0 1 0 0 0 0 0 0 0 0  divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Week 26 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 0 0 0 1 0 divisor=1 / cl;
lsmestimate <treatment>*<visit> 'Week 26 MRX LS Mean = Placebo LS Mean' 0 0 0 0 0 1 0 0 0 0 0 0 0 -1 0
divisor=1 / cl;
 lsmestimate <treatment>*<visit> 'Weeks 18-26 MRX LS Mean=0'    0 0 1 0 1 1 0 0 0 0 0 0 0 0  divisor=3 /
cl;
lsmestimate <treatment>*<visit> 'Weeks 18-26 Placebo LS Mean=0' 0 0 0 0 0 0 0 0 0 0 1 0 1 1 0 divisor=3 /
cl;
lsmestimate <treatment>*<visit> 'Weeks 18-26 MRX LS Mean = Placebo LS Mean' 0 0 1 0 1 1 0 0 0 -1 0 -1
-1 0  divisor=3 / cl;
run;
```

```
proc mianalyze data=diff;
  by <visit> ;
  modeleffects estimate;
  STDERR stderr;
  ods output parameterestimates=dif_2;
run;

proc mianalyze data=lsm;
  by <visit> <treatment>;
  modeleffects estimate;
  stderr stderr;
  ods output parameterestimates=lsmn_2;
run;
```

Tipping Point Analysis

As a sensitivity analysis to the standard MAR imputation approach, a tipping point analysis will be performed in order to determine the inflection point at which the inference under the MNAR assumption changes substantially. This will be used to check the robustness of the imputation.

The sensitivity analysis will be performed by using a specified sequence of shift parameters, which will adjust the imputed values for observations in each treatment group. The range of shift parameters to be included in this analysis are -2 to 2 by 0.2. Thus, the value at which the results of the analysis are shifted from significant (i.e., $\alpha \leq 0.05$) to non-significant (i.e., $\alpha > 0.05$) will be determined.

A heatmap figure will be generated to display p-values corresponding to all combinations of shifts from the imputed data.

The seed number of 2740211 will be used for the imputation procedure described in Step 2.

Steps 1 and 3 of the analysis will be the same as for the multiple imputation analysis as described in the Standard MAR Imputation above. However, Step 2 of the analysis is the step that the shift parameters will be applied. Pseudocode for Step 2 is as follows:

```
proc mi data=example_1  seed=2740211 nimpute =1 OUT= example_2;
        class <treatment>;
        by <imputationnumber>;
        monotone regression;
        var <baseline score> <week 1-6>…… <week 23-26>;
        mnar adjust ( <week 1-6>/ shift=YY adjustobs=(treatment ='active') );
        mnar adjust ( <week 1-6>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 7-10>/ shift =YY adjustobs =( treatment ='active'));
```

```
        mnar adjust ( <week 7-10>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 11-14>/ shift =YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 11-14>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 15-18>/ shift = YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 15-18>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 19-22>/ shift =YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 19-22>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 23-26>/ shift =YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 23-26>/ shift =YY adjustobs =( treatment ='placebo') );
run;
```

YY will encompass the range of shift parameters as pre-specified above.

For the secondary endpoint the planned range of shift parameters to be included in this analysis are -100 to 100 by 1.

Pseudocode for Step 2 for imputation of key secondary efficacy missing data is as follows:

```
proc mi data=example_1  seed=2740211 nimpute =1 OUT= example_2;
        class <treatment>;
        by <imputationnumber>;
        monotone regression;
        var <baseline> <week 2>…… <week 26>;
        mnar adjust ( <week 2>/ shift=YY adjustobs=(treatment ='active') );
        mnar adjust ( <week 2>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 6>/ shift =YY adjustobs =( treatment ='active'));
        mnar adjust ( <week 6>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 10>/ shift =YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 10>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 14>/ shift = YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 14>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 18>/ shift =YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 18>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 22>/ shift =YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 22>/ shift =YY adjustobs =( treatment ='placebo') );
        mnar adjust ( <week 26>/ shift =YY adjustobs =( treatment ='active') );
        mnar adjust ( <week 26>/ shift =YY adjustobs =( treatment ='placebo') );
run;
```

6.1.4.3. Missing ItchRO/EDQ/PedsQL Scores

In deriving the highest daily ItchRO/EDQ severity/frequency score, if either the morning or evening reports are not completed, the available score is used as the highest daily score. If both morning and evening reports are not completed, the highest daily score for that day is treated as missing data.

For weekly (7-day) morning/evening/highest ItchRO(Obs)/ItchRO(Pt)/EDQ(Obs)/EDQ(Pt) severity/frequency scores, if >50% (i.e., >3 of 7) of the daily scores are missing, the average score for that weekly time period will be treated as missing.

For 4- and 6-week time period ItchRO/EDQ scores (i.e., baseline, post-baseline to Week 6, Week 7 to 10, Week 11 to 14, Week 15 to 18, Week 19 to 22, and Week 23 to 26), if >50% of the weekly scores are missing, the respective time period score will be treated as missing. Thus, to derive a 4-week time period score, 2 or more of the respective weekly scores must be non-missing; for a 6-week time period score, 3 or more weekly scores must be non-missing.

For Pediatric Quality of Life Inventory (PedsQL) scale scores, if >50% of the items in the scale are missing, the scale score is not computed.

6.1.4.4. Missing Responder Definition Data

For the sBA responder endpoint, a participant is defined as a non-responder if the baseline value is missing OR sBA values are missing at all of the 3 time points (i.e., Weeks 18, 22, and 26).

For the ItchRO responder endpoint, a participant is defined as a non-responder from Week 15 to 26 if the 4-week average baseline score is missing OR all of the three 4-week average (post-baseline) scores (i.e., Weeks 15-18, 19-22, and 23-26) are missing.

For the number of days the morning ItchRO(Obs) severity score is ≤1 over the last 84 days (i.e., study day 99 through 182, inclusive, relative to the day of 1st dose of study drug), days with missing data would not be considered to have met the "≤1" criteria for that day. In computing the total number of days that the score is ≤1 within the specified time period (for each participant), missing data will be treated as having a score of >1.

For the number and proportion of participants achieving morning ItchRO(Obs) severity scores ≤1 for more than 50% of the time within pre-specified time periods, days with missing data would not be considered to have met the "≤1" criteria for that day. In computing the % of time the score is ≤1 within each time period for each participant, the denominator of the proportion would include all days within the specified time period (i.e., days with missing and non-missing data), while the numerator only includes those days that the score is 0 or 1.

For the proportion of participants with improvement from baseline in EDQ sleep scores, a participant is defined as having no improvement (i.e., non-responder) for an analysis visit if the 4-week average baseline score is missing OR the 4-week (or 6-week for the first time period) average sleep score at the analysis visit is missing.

For the proportion of EDQ sleep scores ≤2, missing scores are treated as a non-responder (i.e., >2).

6.1.4.5. 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".

6.1.5. Analysis Visit Windows

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. Scheduled visits will be selected over unscheduled visits. The below table addresses scheduled post-baseline in-clinic visits; baseline assessments are described in Section 6.1.1.

Table 2: Analysis Visit Windows

Analysis Visit	Analysis Visit Name	Target Day of Planned Visit	Assessment Window (Study Days[1])
2	Week 2	14	1[2] – 20
4	Week 4	28	21 – 34
6	Week 6	42	35 – 55
10	Week 10	70	56 – 83
14	Week 14	98	84 – 111
18	Week 18	126	112 – 139
22	Week 22	154	140 – 167
26	Week 26	182	168 – x

[1] Study day relative to the date of first dose of study drug.
[2] Only data collected post-dose on Day 1 will be considered.
x = last dose date plus 7 days

For those participants who discontinue early from the study, Table 2 will also be used to assign the appropriate analysis visit.

The study day will be calculated for each scheduled or ET post-baseline visit and compared to the assessment window presented in Table 2 to define the visit window used for analyses. The analysis visit windows only apply to those visits that are applicable to the specific assessment. For example, if the scheduled or ET visit falls at Week 4 but a specific assessment (e.g., sBA sample) was not scheduled at that visit (see Table 1, Schedule of Assessments), then that assessment will not be used for analyses.

If more than 1 assessment occurs within a single visit window, then the analysis will use the assessment closest to the target day. If 2 assessments within the same visit window are equidistant from the target day, then the analysis will use the later assessment.

Efficacy assessments performed >7 days after the last dose of study drug will not be included in any efficacy analyses.

6.1.6. Investigative Sites

An investigative site is defined as a single principal investigator (including sub-investigators) who enroll participants for 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 that did not enroll the participant. Unless otherwise specified, the investigative site of the enrolling investigator will be used for the unique participant ID.

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

6.1.7. Treatment Period Definitions

- "Dose Escalation Period" is defined for analysis purposes as the period of time between the first dose of study drug and the end of study Week 6 (i.e., through the Week 6 visit date).

- "Stable Dosing Period" is defined for analysis purposes as the period of time between the beginning of Week 7 (i.e., Week 6 visit date plus 1 day) and the EOT visit (inclusive).

6.1.8. Derived Variables

Select derived variables will be rounded for presentation purposes (see Section 4.1).

- **Age (years) at baseline**

  The reported age in years at baseline will be used.

- **Age (months) at baseline**

  The reported age in years and months at baseline will be used:

  Age (months) at baseline = (12 x Reported age in years at baseline) + Reported number of months at baseline

- **Date of Birth**

  Date of Birth = Baseline Visit Date – [365.25 x (Age in yrs + (months/12))]

  Age in years and months at baseline, as reported on the CRF, is used. If only age in years (at baseline) is reported, then 6 months will be used.

  If the derived date of birth is later than the PFIC diagnosis date, the earliest complete medical history event start date, or the earliest complete reported prior/concomitant treatment start date, will be used to derive the date of birth by selecting the earliest of these 3 dates.

- **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

- **UDCA usage at baseline**: A subject reporting the use of UDCA, based on ATC Class Level 5 (chemical substance), with a start date on or prior to the first dose of study drug and either be ongoing or have a stop date on or after the first dose of study drug would be considered as using UDCA at baseline.

- **Rifampicin usage at baseline**: A subject reporting the use of Rifampicin, based on ATC Class Level 5 (chemical substance), with a start date on or prior to the first dose of study drug and either be ongoing or have a stop date on or after the first dose of study drug would be considered as using Rifampicin at baseline.

- **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 and EDQ scores, "value" is the average score as defined below.

- **% Change from baseline** = 100 x change from baseline / value at baseline

- **Highest daily ItchRO and EDQ scores** = maximum of morning and evening scores

  If either the morning or evening reports are not completed, the available score is used as the highest daily score. If both morning and evening reports are not completed, the highest daily score for that day is treated as missing data.

- **Baseline ItchRO and EDQ scores:**

  Baseline morning, evening, and highest ItchRO and EDQ scores used for analysis purposes are calculated using the daily scores from the 28 days (4 weeks) immediately before the date of first dose. Pre-dose weekly scores are first calculated for each of the 4-week, 7-day periods. 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/EDQ efficacy variable, a baseline score is derived as the average of the 4 pre-dose weekly average scores.

  The handling of missing daily and weekly average scores is addressed in Section 6.1.4.3. 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 and EDQ scores:**

  Post-baseline morning, evening, and highest ItchRO and EDQ scores used for analysis purposes are calculated using the daily scores from the 182 days (26 weeks) immediately after the date of first dose. Post-dose weekly scores are first calculated for each of the 26-week, 7-day periods. The first 7-day period is considered 'Week 1', whereas the last 7-day period is considered as 'Week 26'. For each subject and ItchRO/EDQ efficacy variable, post-baseline scores are derived as the average of the 4- or 6-week post-dose weekly average scores for the following time periods: post-baseline to Week 6 (42 days), Week 7 to 10 (28 days), Week 11 to 14 (28 days), Week 15 to 18 (28 days), Week 19 to 22 (28 days), and Week 23 to 26 (28 days).

  The handling of missing daily and weekly average scores is addressed in Section 6.1.4.3. 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.

  For the purpose of determining response, the average severity score from the three 4-week periods (Weeks 15-18, 19-22, and 23-26) will be computed and used.

  Before the database lock, the definition of an ItchRO(Obs) Responder may be re-defined based on outcomes of the ItchRO instrument validation performed on the analysis of data blinded to treatment. This blinded analysis, performed according to the Validation Analysis Plan (VAP), will be used to estimate a threshold of clinically meaningful change (i.e., responder definition) in the 4-week average morning ItchRO(Obs) pruritus scores. Details of the analysis will be included in a standalone VAP; results will be presented in a standalone validation analysis report.

- **sBA Responder** is defined as a subject having an average sBA level of <102 µmol/L (applies only if baseline sBA level was ≥102 µmol/L), OR a ≤-75% average percent change from baseline.

  For the purpose of determining response, the average sBA value from Weeks 18, 22, and 26 values will be computed and used.

- **FIB-4** = $\frac{Age\ (years)\ x\ AST\left(\frac{U}{L}\right)}{platelet\ count\left(\frac{10^3}{\mu L}\right) x \sqrt{ALT}\left(\frac{U}{L}\right)}$ *, where age is years at sample collection time point*

- **APRI** = 100 x $\frac{AST\left(\frac{U}{L}\right) / AST\ ULN\left(\frac{U}{L}\right)}{platelet\ count\left(\frac{10^3}{\mu L}\right)}$ *, where ULN = upper limit normal*

- **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]

- **PELD/MELD Scores**

  Pediatric end-stage liver disease (PELD) score will be calculated for children under 12 years of age at the baseline visit. For children 12 years or older at the baseline visit, the model for end-stage liver disease (MELD) score will be calculated.

  PELD Score = 4.80 × ln(total bilirubin [mg/dL]) + 18.57 × ln(INR) – 6.87 × ln(albumin [g/dL]) + 4.36 (if patient <1 year: scores for patients listed for liver transplantation before the patient's first birthday continue to include the value assigned for age (<1 year) until the patient reaches the age of 24 months) + 6.67 (if the patient has growth failure, where growth failure is defined as a weight z-score <-2.00)

  Laboratory values in the PELD equation that are <1.0 will be set to 1.0 for the calculation of the PELD score.

  MELD Score = 3.78 × ln (total bilirubin [in mg/dL]) + 11.2 × ln(INR) + 9.57 × ln(creatinine [in mg/dL]) + 6.43.

  Laboratory values in the MELD equation that are <1.0 will be set to 1.0 and serum creatinine values greater than 4.0 mg/dL (equivalent of 353.6 µmol/L) will be set to 4.0 for calculation of the MELD score.

  Scores from PELD and MELD will be summarized separately.

- **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) not calculated for placebo participants.

- **PedsQL Scoring Algorithm**

  For each item of the PedsQL instrument (parent and participant), a 5-point response scale is used (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always). Items are reverse-scored and linearly transformed to a 0-100 scale (0 → 100, 1 → 75, 2 → 50, 3 → 25, 4 → 0), so that higher scores indicate better HRQoL (less negative impact). Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed. See PedsQL (2021) reference in Section 12 for scoring instructions on the PedsQL.

  PedsQL scale scores are computed for the following:

  - Total Scale Score – computed as the sum of the items over the number of items answered on the PedsQL Generic Core Scales (up to 45 items)
  - Physical Health Summary Score – computed as the sum of the items over the number of items answered in the Physical Functioning Scale (and Physical Symptoms Scale for infants) from the PedsQL Generic Core Scales (up to 19 items)

- Psychosocial Health Summary Score – computed as the sum of the items over the number of items answered in the Emotional, Social, and Nursery/Day Care/School Functioning Scales for children ages 2 to 18 years or Emotional, Social, and Cognitive Functioning Scales for infants (<2 years) from the PedsQL Generic Core Scales (up to 26 items)
- Multidimensional Fatigue Scale Score – computed as the sum of the items over the number of items answered in the PedsQL Multidimensional Fatigue Scales (18 items)
- Family Impact Total Scale Score – computed as the sum of the items over the number of items answered in the PedsQL Family Impact module (36 items)
- Parent Functioning Summary Score – computed as the sum of the items over the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning Scales from the PedsQL Family Impact module (20 items)
- Family Impact Summary Score – computed as the sum of the items over the number of items answered in the Daily Activities and Family Relationships Scales from the PedsQL Family Impact module (8 items)

Total scale, physical health summary, psychosocial health summary, and multidimensional fatigue scale scores are computed individually for the parent and participant reports. Family impact and parent functioning total scale and summary scores are based on parent-reported items.

- **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 (for participants not participating in the extension study) or reported through the Week 26/EOT visit (for participants participating in the extension study). For participants with > 7 days of study drug interruption/withdrawal, the definition of a TEAE considers both the date of the last dose prior to drug interruption and the actual last dose (see Section 6.1.9).

  Any event which 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 body mass index (BMI) z-scores are based on a participant's sex and age at each scheduled visit. For participants less 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

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

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, and not what is reported within the IRT system or on the eCRF. A listing of any discrepancies between the PFIC type recorded in IRT or the eCRF and the centrally adjudicated PFIC type will be presented.

Subject Age

The age of a participant at screening will be used to determine the age-specific module or instrument for the appropriate ItchRO and EDQ clinical outcome questionnaire or assessment (i.e., ItchRO, EDQ, PedsQL, PIS). The same module or instrument will be completed for the duration of the study, regardless of subsequent birthdays throughout the study.

The PIC will be completed by subjects who are 9 years of age or older at the Week 26 (EOT) visit.

Handling of Siblings

Because PFIC is a rare disease, siblings are allowed to enroll in the study. Siblings enrolled in the study will be assigned in a blinded manner to the same treatment arm. The data from all enrolled participants (including siblings) will be used for all primary efficacy and safety analysis. The data for only 1 sibling will be used for a sensitivity analysis on the primary efficacy endpoint and the key secondary efficacy endpoint for the primary and PFIC cohorts, independently, in the ITT Population. The choice of sibling to use in the sensitivity analysis will be made at random, unless only 1 sibling is evaluable in the specific cohort and ITT Population and the other sibling is not. In this case, the evaluable sibling will be used in the sensitivity analyses. Sibling selection for the purposes of the sensitivity analysis will be completed prior to data lock.

Adverse Event and Concomitant Medication Coding

Adverse events 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 the study (Week 26 or Week 27), inclusive. For participants not continuing into the extension study, this period of participation is from the first day of screening through the last contact at Week 27. For participants continuing into the extension study, this period is from the first day of screening through the Week 26 visit.

Treatments that started before the first dose of study drug are considered prior treatments whether or not 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 participants participating in the extension study, concomitant treatments that are ongoing as of the Week 26 visit are closed-out with a stop date of "ongoing". Concomitant treatments that are continuing from the core study (MRX-502) are copied into the extension study database with start dates entered as the original start date in the core study.

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 participants participating in the extension study, AEs that are ongoing as of the Week 26 visit are closed-out with a stop date of "ongoing". Adverse events that are continuing from the core study (MRX-502) are copied into the extension study database with start dates entered as the original start date in the core study.

Events of Clinical Interest

The following events have been defined as events of clinical interest (ECI) due to the nature of PFIC disease as well as of maralixibat:

- Diarrhoea events
- Lipid soluble vitamin (LSV) deficiency events
- Elevated transaminases events
- Elevated bilirubin events

PFIC is associated with LSV deficiency and fluctuating transaminase elevations. Maralixibat is associated with gastrointestinal disturbances such as diarrhoea.

The list of PTs used to identify LSV deficiency events are provided in Appendix 2.

Diarrhoea events include PTs of:

- 'Diarrhoea',
- 'Intermittent Diarrhoea',
- 'Increased stool frequency'
- 'Gastroenteritis'

Elevated transaminases events include PTs of:

- 'Elevated liver enzymes'
- 'Transaminases abnormal'
- 'Transaminases increased'
- 'Alanine aminotransferase increased',
- 'Aspartate aminotransferase increased'
- 'Aspartate aminotransferase abnormal'
- 'Alanine aminotransferase abnormal'

Elevated bilirubin events include the PT of:

- 'Blood bilirubin increased',
- 'Blood bilirubin abnormal'
- 'Hyperbilirubinaemia'

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 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 baseline, as defined in Section 6.1.8.

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.

Dose Used in Safety Analysis

For all safety and tolerability analyses, participants will be analyzed by the treatment received. For the maralixibat treatment group, the dose of IP received at the end of the dose-escalation period, or the last dose received if the participant discontinued from the IP during the dose escalation period, will be used for the safety analysis, where specified.

Treatment Received in Adverse Event Listings

For all AE listings, treatment received at the start of the event will be presented. 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.

Treatment Duration and Exposure

For participants who are missing the date of last study drug application, 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 study drug administration 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.

7. Study Subjects and Demographics

Subject disposition, demographics, disease history and baseline disease, important protocol deviations, prior medications, and study drug exposure and compliance will be summarized, unless otherwise noted, by randomized treatment group and overall 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 subjects, including screen failures.

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 participants screened for eligibility, the number of screen failures, the number of participants

randomly assigned to study treatment, and the number of families with siblings enrolled in the study, along with the total number of siblings.

The number and proportion of randomized and completed participants by country and investigative site, individually, will also be tabulated. Percentages will be based on the number of participants randomly assigned to study treatment.

Study drug accountability and compliance listings will be prepared for all participants, showing when the planned dosing schedule was not followed, along with the date and type of dosing deviation. Other 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 Plan for this study.

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 randomized treatment group.

The final decision regarding inclusion and exclusion of participants from the analysis populations will be based on a final listing of protocol deviations. 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.

Additionally, inclusion and exclusion criteria not met and reasons for screen failures will be listed.

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, defined as 1 to <6, 6 to <13, and 13-18 years of age, will also be presented. Given the small number of participants in the study, age categories may be

combined for presentation and analysis (e.g., <9 and ≥9). Unless otherwise noted, age is the participant's age at the 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
- participants with baseline UDCA usage
- participants with baseline Rifampicin usage
- 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:
  - clinician scratch scale (CSS) score
  - patient impression of severity (PIS)
  - caregiver impression of severity (CIS)
  - ItchRO (Obs) 4-week morning average severity score
  - ItchRO (Pt) 4-week morning average severity score
  - ItchRO (Obs) 4-week evening average severity score
  - ItchRO (Pt) 4-week evening average severity score
  - ItchRO (Obs) 4-week highest daily average severity score
  - ItchRO (Pt) 4-week highest daily average severity score
  - ItchRO (Obs) 4-week morning average frequency score
  - ItchRO (Pt) 4-week morning average frequency score
  - ItchRO (Obs) 4-week evening average frequency score
  - ItchRO (Pt) 4-week evening average frequency score
  - ItchRO (Obs) 4-week highest daily average frequency score
  - ItchRO (Pt) 4-week highest daily average frequency score

- 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
  - FGF-19
  - autotaxin
  - 7α hydroxyl-4-cholesten-3-one (C4)
  - 25-hydroxyvitamin D
  - alpha tocopherol
  - prothrombin intl. normalized ratio
  - vitamin A
  - APRI
  - FIB-4
  - PELD score
  - MELD score

Subject demographics and baseline characteristics, and medical and surgical history information and prior medications, will be presented in a participant listing by randomized treatment group.

7.4. Prior Medications/Therapies

Prior 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).

Prior treatments will be presented separately from concomitant treatments.

7.5. Exposure and Compliance

Treatment exposure will be calculated for each participant exposed to maralixibat during the study and summarized descriptively. This analysis will be conducted for the overall 26-week treatment period.

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 randomized treatment group. Dosing details will be listed separately.

8. Efficacy Analysis

Efficacy analyses will be conducted in the ITT population separately on the primary cohort and the PFIC cohort. Analysis of the primary efficacy endpoint and the key secondary efficacy endpoint (i.e., change from baseline in sBA level) will also be performed on the primary cohort in the PP population.

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

The primary efficacy analysis will be performed in the primary cohort for the ITT population.

For all efficacy analyses, participants will be analyzed by the randomized treatment group assignment (maralixibat or placebo), 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. All efficacy data will be presented in participant listings.

For the PFIC cohort analyses, PFIC type will also be used as a covariate in the MMRM analysis. For this analysis, due to the small sample sizes, PFIC4, PFIC5, and PFIC6 will be grouped together. Within the PFIC cohort, 4 PFIC types are include in the covariate: nt-PFIC2, PFIC1, PFIC3, and other (PFIC4, PFIC5, and PFIC6 group).

8.1. Primary Efficacy Analysis

For this study, the primary estimand is the improvement in pruritus measured as change from baseline in the average morning ItchRO(Obs) severity score in the maralixibat treatment group relative to the placebo group. In the course of the 26-week randomized treatment period, participants may be exposed to possible known or unknown inter-current events that could possibly impact the interpretation of the measures associated with the clinical question of interest, such as treatment discontinuation due to a specific adverse effect or perhaps a lack of effect. The “Hypothetical Strategy” has been adopted for handling all known inter-current events

in this study. To this end, a restricted maximum likelihood (REML)-based MMRM model conducted on the primary cohort in the ITT population will be used as the primary analysis method.

The repeated measures include post-baseline time periods during the dose escalation period (i.e., Week 1-6) and stable dosing period (i.e., Weeks 7-10, 11-14, 15-18, 19-22, and 23-26), with change from baseline in the 6- or 4-week average morning ItchRO(Obs) severity score as the dependent variable. The MMRM model will include the fixed, categorical effects of treatment group, time period, and treatment group-by-time period interaction as well as the continuous, fixed covariates of baseline 4-week average morning ItchRO(Obs) severity score and the baseline score-by-time period interaction. The MMRM analysis method is further described in Section 6.1.4.1.

The unstructured variance/covariance matrix will be used to model the variances and covariances for the six time points included in the model. The unstructured variance/covariance does not impose any restrictions on the pattern of the matrix elements. If there is a convergence issue with the unstructured covariance model, the following variance/covariance matrix structures will be used in the following order: 1) heterogeneous Toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry. The first variance/covariance structure which does not have a convergence problem will be the one used for the analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward et al, 1997).

The primary efficacy analysis will compare maralixibat and placebo using the contrast (difference in least squares [LS] means) between treatment groups across the last 12 weeks of the study (i.e., Weeks 18, 22, and 26 combined). The analytical solution of the overall treatment effect obtained from MMRM is an equally weighted average of the 3 individual visit-specific estimates over the time period of interest (i.e., the last 12 weeks of the study). Significance tests will be based on LS means using a 2-sided significance level (2-sided 95% confidence intervals [CIs]).

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

> H_{01}: mean change in average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26 over the primary cohort in the two treatment groups are equal

The null hypothesis of equal treatment effect will be rejected if the statistical analysis results in a 2-sided p-value for treatment over the last 12 weeks of the study of less than or equal to 0.05. Least squares (LS) means will be calculated for each treatment group for each post-baseline time period in the model. The difference between maralixibat and placebo change from baseline in average morning ItchRO(Obs) severity score will be estimated, with the corresponding 2-sided 95% CI constructed for each time period, and the last 12 weeks (i.e., last 3 visits) of the study

combined. The change from baseline LS means with standard error, 95% CI for the LS means, p-value for testing if the LS mean is zero, LS mean difference between treatment groups (maralixibat minus placebo) with standard error, 95% CI for the LS mean difference, and p-value for testing if the treatment LS means are equal will be presented.

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

8.2. Secondary Efficacy Analysis

Analysis similar to that described for the primary efficacy endpoint will be performed for each of the change from baseline secondary efficacy endpoints. 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. Barnard's exact unconditional test will be used to calculate the p-value for the difference between treatment groups.

The null hypotheses for the secondary efficacy endpoints of the equality of maralixibat and placebo are:

H_{02}: mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 over the primary cohort in the two treatment groups are equal

H_{03}: mean change in the average morning ItchRO(Obs) severity score between baseline and Week 15 through Week 26 over the PFIC cohort in the two treatment groups are equal

H_{04}: mean change in total sBA level between baseline and average of Weeks 18, 22, and 26 over the PFIC cohort in the two treatment groups are equal

H_{05}: proportion of ItchRO(Obs) responders from Week 15 to Week 26 on participants in the primary cohort in the 2 treatment groups are equal

H_{06}: proportion of sBA responders from Week 15 to Week 16 on participants in the primary cohort in the 2 treatment groups are equal

H_{07}: proportion of ItchRO(Obs) responders from Week 15 to Week 26 on participants in the PFIC cohort in the 2 treatment groups are equal

H_{08}: proportion of sBA responders from Week 18 to Week 26 on participants in the PFIC cohort in the 2 treatment groups are equal

A hierarchical testing procedure, as described in Section 6.1.3 will be used in the comparisons between maralixibat and placebo on the primary and secondary efficacy endpoints in the ITT population.

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

8.3. Sensitivity and Supportive Analyses for Primary and Secondary Endpoints

Sensitivity and/or supportive analysis will be performed on the primary and secondary efficacy endpoints to quantify the possible impact of missing data and the use of potentially correlated sibling data, and to demonstrate the robustness of the conclusions.

Sensitivity analysis will be performed on the primary efficacy endpoint and key secondary efficacy endpoint in the primary cohort and PFIC cohort, individually, in the ITT analysis population.

Although the assumption of MAR, as used for the primary efficacy analysis method, is often reasonable in clinical trials, the possibility of MNAR data cannot be ruled out. Sensitivity analyses to deal with missing data will use MI methods where missing values are imputed individually under both a plausible MAR and MNAR scenario. Two sensitivity analysis models, one based on the standard MAR imputation approach and the other on a tipping point analysis, will be used to examine robustness of the primary analysis results (see Section 6.1.4.2).

If siblings are evaluable for efficacy, the primary analysis method described above for the primary efficacy endpoint and the key secondary efficacy endpoint will be repeated as a sensitivity analysis in which only one of sibling pairs or multiples will be used. The choice of which sibling to use in the sensitivity analysis will be made at random before the MRX-502 study is unblinded (see Section 6.1.9).

Summary statistics on the primary efficacy endpoint and the key secondary efficacy endpoint will also be presented descriptively by treatment group and visit, overall and for each of the following subgroups on the primary cohort in the ITT analysis population:

- Region (Asia, Europe, Middle East, North America, and South and Central America)
- Age at baseline (1 year to <6 years old, 6 years to < 13 years, and 13-18 years old)
- Sex (male, female)
- Race (White, Asian, Black or African American, American Indian or Alaska Native, Multiple)
- Baseline sBA (< median, ≥ median; where only subjects in the primary cohort are used to calculate the baseline median sBA level)
- Baseline ursodeoxycholic acid (UDCA) usage (yes, no)

- Baseline Rifampicin usage (yes, no)
- BSEP type of primary cohort (non-truncating PFIC2) participants (BSEP 1, BSEP 2)

8.4. Adjustment for Multiplicity

A hierarchical testing procedure will be used in the comparisons between maralixibat and placebo on the primary and secondary efficacy endpoints in the ITT population using the primary analysis method (as described for the primary endpoint). The hierarchical order for testing the null hypotheses is listed in Section 6.1.3.

The effect of such a procedure maintains study-wide Type I error control, ensuring that no confirmatory claims can be based on the endpoint(s) that have a testing rank lower than that endpoint whose null hypothesis was the first that could not be rejected. Those tests will be considered as exploratory without any type I error control for the additional subsequent tests.

8.5. Exploratory Efficacy Analysis

Analyses will be conducted for the exploratory efficacy endpoints separately on the primary cohort and the PFIC cohort.

Analysis similar to that described for the primary efficacy endpoint (i.e., MMRM) will be performed for each exploratory endpoint that is based on change from baseline values on continuous variables. The repeated measures in the MMRM model will include the post-baseline visits as specified for each above-listed endpoint, with change from baseline value as the dependent variable. The MMRM model will include the fixed, categorical effects of treatment group, visit, and treatment group-by-visit interaction as well as the continuous, fixed covariates of baseline and the baseline-by-visit interaction. Least squares means will be calculated for each treatment group for each post-baseline visit in the model. The difference between maralixibat and placebo change from baseline in each outcome variable will be estimated, with the corresponding 2-sided 95% CI constructed for each visit. Change from baseline LS means with standard error, 95% CI for the LS means, p-value for testing if the LS mean is zero, LS mean difference between treatment groups (maralixibat minus placebo) with standard error, 95% CI for the LS mean difference, and p-value for testing if the treatment LS means are equal will be calculated for each visit. For the ItchRO (Obs and Pt) and EDQ (Obs and Pt) endpoints that compare treatment groups across the last 12 weeks of the study, the same methods as described for the primary analysis of the primary efficacy endpoint will be applied. The number of observations, mean, 95% CI on the mean, standard deviation, median, minimum, and maximum on both the observed and change from baseline values will also be summarized by treatment group for each visit including the end of study visit (Week 26/EOT).

For responder-type endpoints (i.e., efficacy variables involving binary outcomes), 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. Barnard's exact unconditional test will be used to calculate the p-value for the difference between treatment groups.

For responder-type endpoints with ordinal measures, the Cochran-Mantel-Haenszel (CMH) test will be applied to test for no association between treatment group and the variable of interest. For the OL and ARW treatment phases, the number and percentage of subjects at each level of the 7- or 5-point scale, for PIC/CIC or CGTB respectively, will be presented overall and for each treatment group during the RW phase. For the RW phase, the number and percentage of subjects at each level will be presented by the randomized treatment group. For ordinal non-binary outcomes, the CMH test will be used to take the ordinal nature of the variable into account.

The number and proportion of subjects with total sBA % decrease from baseline to Weeks 2, 6, 10, 14, 18, 22, and 26 within the following categories: >75% (large decrease), 0-75% (decrease), and <0% (increase) will be analyzed using a CMH test to test for no association between treatment group and the variable of interest at each analysis visit.

A Student's t-test, assuming unequal variances, will be used to compare treatment differences on the number of days the morning ItchRO(Obs) severity score ≤ 1 over the last 84 days (i.e., study day 99 through 182, inclusive). Satterthwaite's method for computing standard error of the mean of the difference will be used. A conservative approach will be taken for subjects with missing morning severity scores during this 84-day period, including those subject that withdraw early from the study. Missing data will be treated as a severity score of >1.

Time to first liver-associated event (PEBD surgery, listing for liver transplantation, liver decompensation [hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis] events, HCC, and death) will be compared among treatments using Kaplan-Meier product-limit survival curve estimates. The median and other quartiles for time to first liver-associated event, along with 2-sided 95% CIs, will be estimated based on the Kaplan-Meier method. Both a log-rank test and a Wilcoxon test will be used to test for treatment differences.

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

Sensitivity analyses are not planned to be performed on the exploratory efficacy endpoints.

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, the PFIC cohort, and all cohorts combined (all subjects).

Safety measures including AEs, clinical laboratory values, physical examination findings (including body weight, height, and BMI), vital signs, ECGs, and concomitant treatment usage will be summarized descriptively. No inferential statistical tests will be performed, unless

otherwise specified. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation, minimum, and maximum will be presented for observed and change from baseline values at each study visit. Qualitative variables will be summarized using counts and percentages.

Safety data collected at the baseline visit (Visit 1/Day 0) or the last preceding visit if not collected at Visit 1 will be used as the baseline value for safety analyses.

All safety and tolerability data 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, SAEs, and deaths 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.

Additionally, the following subgroup analyses will be explored for the summary of TEAEs and the incidence of TEAEs by SOC and PT indicated above:

- Age at baseline (1 year to <6 years old, 6 years to < 13 years, and 13-18 years old)
- Sex (male, female)
- Race (available races in the study)

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 will be presented in by-participant listings, detailing the participant cohort (primary [nt-PFIC2], PFIC or other), treatment received at the start of the event including dose for active study drug, 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.

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.

Any deaths that occur during the study will be presented in a participant listing. The listing will include 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. Events of Clinical Interest

Due to the nature of PFIC disease, as well as maralixibat, the following events have been defined as ECI: diarrhoea events, LSV deficiency events, elevated transaminases, and elevated bilirubin. For each of the ECI, the PTs are described in Section 6.1.9.

The incidence of ECI will be summarized in the same manner as AEs that lead to permanent discontinuation of study drug.

The clinical protocol references adverse events of special interest; however, the study has no such events.

9.2. Clinical Laboratory Evaluations

Safety laboratory test results will be summarized descriptively by study visit and treatment group as observed and change from baseline values. The number and proportion of participants with clinical laboratory values below, within, or above the normal range by time point and in relation to baseline will be tabulated for each select lipid soluble vitamin laboratory analytes by treatment group in a shift table. The shift table will include the following LSVs: 25-hydroxyvitamin D (ng/mL), alpha tocopherol (mg/dL), INR, and vitamin A (µg/dL).

All safety laboratory test parameters will be presented by panel in participant listings.

Efficacy laboratory tests (i.e., total sBA, ALT, AST, ALP, total and direct bilirubin, GGT, C4, FGF-19, autotaxin, FIB-4, APRI, PELD and MELD) will not be included in safety summaries or listings. A separate participant listing for efficacy labs will be presented.

9.3. Vital Signs and Weight/Height Measurements

Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate), weight, height, and BMI will be summarized descriptively by study visit and treatment group as observed and change from baseline values. Weight, height, and BMI measurements will also be summarized as a z-score for a participant's age and sex.

9.4. Electrocardiograms

Descriptive summaries will be presented for ECG measures of PR interval, QRS duration, and QT interval corrected using both Bazett's and Fridericia's formula (QTcB and QTcF). The number and proportion of participants with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG results will also be summarized. These summaries will be presented by study visit and treatment group.

9.5. Liver Ultrasound

Liver ultrasound (or MRI) results will be presented in participant listings.

9.6. 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).

Prior treatments will be presented separately from concomitant treatments. Any treatments continuing or starting after the first dose of study drug will be considered concomitant. If a

treatment starts prior to the first dose of study drug and continues after the first dose of study drug, it will be considered both prior and concomitant.

10. Other Planned Analysis

Healthcare utilization and pharmacokinetic analyses will be performed on the Safety Population, conducted separately on the primary cohort, the PFIC cohort, and all cohorts combined (all subjects).

10.1. Healthcare Utilization

Healthcare resource utilization variables include the number of hospitalizations, emergency room visits, the length of stay for hospitalization (days), surgeries and procedures related to the participant's PFIC condition, and the number of days the caregiver missed from work due to healthcare resource utilization events. Healthcare utilization data is collected at Weeks 2, 6, 10, 14, 18, 22, 26, and the Week 27 follow-up and covers the time period since the last on-site visit.

Subjects that visit the emergency room and the visit results in the subject being admitted to the hospital will be counted in both categories.

Number and percent of subjects and number of occurrences will be presented across the entire post-baseline study period, between clinic visits from baseline through Week 27 Follow-up, by treatment group for PFIC-related hospitalizations and ER visits. For length of hospital stays and number of days a caregiver missed work, summary statistics on a subject-level basis will be presented.

10.2. Pharmacokinetic Analyses

Systemic concentrations of maralixibat in plasma will be determined at pre-dose and at approximately 2.5 hours after the morning dose at Week 10 and Week 26 (EOT/ET). Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) will be determined for maralixibat concentrations at each analysis visit.

11. Changes from Protocol Planned Analysis

The PP Population has been re-defined as all participants in the ITT Population who receive at least 1 dose of study drug and do not have any important protocol violations or deviations that have a potential impact on the efficacy analysis.

The sensitivity analysis using placebo-based MI for handling missing data has been replaced with a tipping point approach.

The number and proportion of subjects with total sBA % decrease from baseline to Weeks 2, 6, 10, 14, 18, 22, and 26 within the following categories: >75%, 0-75%, and <0% have been added as an exploratory endpoint. The analysis will be performed using a CMH test.

The number of days morning ItchRO(Obs) severity score ≤1 for the last 12 weeks (84 days) of the study has been added as an exploratory endpoint. The analysis will be performed using a Student's t-test.

The following exploratory endpoints listed in the protocol have been removed. They may be included after the finalization of the analysis plan for adhoc or posthoc analyses:

- Proportion of participants with elevated liver biochemistry (i.e., >ULN at baseline), whose liver biochemistry normalize (≤ULN) at Weeks 2, 6, 10, 14, 18, 22, and 26
- Mean change from baseline in weekly average morning, evening, and highest daily ItchRO(Obs) severity and frequency scores, individually, to each post-baseline week, and Weeks 15 to 26 combined
- Proportion of days with a morning/evening/highest daily ItchRO(Obs)/ItchRO(Pt) severity/frequency score ≤1, individually, at the participant level from baseline to Week 6 (overall and weekly), Weeks 7-10, 11-14, 15-18, 19-22, 23-26, and 15-26
- Proportion of participants in each change from baseline category of the CSS at Weeks 2, 4, 6, 10, 14, 18, 22, and 26
- Proportion of participants in each change from baseline category of the CIS and PIS, individually, at Weeks 4, 6, 10, 14, 18, 22, and 26
- Mean change from baseline in average (6 week average for Week 6 and 4 week average afterwards) morning, evening, and highest daily EDQ(Pt) severity scores, individually, to Weeks 6, 10, 14, 18, 22, 26, and Weeks 15 to 26 combined
- Proportion of responders at Weeks 6, 10, 14, 18, 22, 26, and any of those weeks, where a responder is defined as having:
    a) 4-week average morning ItchRO(Obs) severity change from baseline of ≤-1.0 or an average score of ≤1.0 AND a normalization or change from baseline in sBA of ≤-75%, or average sBA level <102 µmol/L
    b) 4-week average morning ItchRO(Obs) severity change from baseline of ≤-1.0 or a score of ≤1.0
    c) a normalization or percent change from baseline in sBA of ≤-75%, or average sBA level <102 µmol/L

- Mean change from baseline in average sleep disturbance scores over time (4-week average score at Weeks 6, 10, 14, 18, 22, 26, and average of Weeks 18, 22, and 26), based on sleep-related questions on the PedsQL (parent), Child PedsQL (young child), and Child PedsQL (child and teen) questionnaires, individually
- Proportion of "no" answers for sleep-related questions on the ItchRO(Obs) morning, ItchRO(Obs) evening, and ItchRO(Pt) morning, individually, at the participant level for post-baseline to Week 6, Weeks 7 to 10, Weeks 11 to 14, Weeks 15 to 18, Weeks 19 to 22, Weeks 23 to 26, Week 15 to Week 26, and overall (post-baseline to Week 26)
- Proportion of participants who experience an improvement from baseline in height z-score or weight z-score (i.e., change from baseline >0) at Weeks 2, 4, 6, 10, 14, 18, 22, and 26
- Mean change from baseline in bile acid subspecies to Weeks 10, 18, and 26
- Mean change from baseline in C4, FGF-19, and autotaxin to Weeks 6, 10, 18, and 26 in the PFIC cohort
- Proportion of participants with an elevated liver biochemistry laboratory value at baseline that normalize post-baseline for sBA, ALT, AST and TSB, independently
- Correlation analyses between sBA and pruritus severity

The exploratory objective of evaluating the efficacy of maralixibat vs placebo in the primary cohort on responder rates for various pruritus measures, sBA and biomarkers has been updated to only include responder rates for pruritus severity and total sBA.

In general, analysis on continuous repeated-measures efficacy variables will include a comparison of maralixibat and placebo using the contrast between treatment groups across the last 12 weeks of the study (i.e., Weeks 18, 22, and 26 combined) as described in Section 8.1.

Sensitivity analyses will be performed on the primary efficacy endpoint and the key secondary efficacy endpoint in the primary cohort and PFIC cohort, individually, in the ITT analysis population. The clinical protocol describes sensitivity analysis on the primary and all secondary efficacy endpoints.

Analysis of the primary efficacy endpoint and the key secondary efficacy endpoint (i.e., change from baseline in sBA level) will be performed on the primary cohort in the PP population. The clinical protocol describes analysis in the PP population on all secondary efficacy endpoints.

Treatment-emergent AEs will not be summarized by severity and relationship to study drug.

The clinical protocol references adverse events of special interest; however, the study has no such events.

Total lipids, referenced in the clinical protocol, were not measured. For the following laboratory parameters the sum of cholesterol and triglycerides were used: ratio of alpha tocopherol to the sum of cholesterol and triglycerides, and corrected sodium (see Section 6.1.8).

The clinical protocol states that the number and proportion of subjects with potentially clinically important values for select vital signs, laboratory, and ECG results, individually, will be presented by treatment group. These analyses have been removed from the planned analysis.

Continuous healthcare resource utilization measures will be summarized as the number and percent of subjects and number of occurrences, presented across the entire post-baseline study period (between clinic visits from baseline through Week 27 follow-up), instead of as described in the protocol.

12. References

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13. Tables, Listings, and Figures

All listings, tables, and figures will have a header showing the sponsor company name (Mirum Pharmaceuticals, Inc.) and protocol (MRX-502), and a page footer showing the file name and path, and the date/time of program execution along with the database data cut date.

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize the presentation with common notations.

General Reporting Conventions

- All tables and data listings will be developed in landscape orientation.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used on a table, figure, or data listing.

- Adverse events with missing MedDRA coding will have their system organ class and/or preferred term presented as "Not Coded" in the tables. The "Not Coded" frequencies will be sorted to the end of the tables. Adverse events that are not coded are not expected.
- Programming notes may be inserted into the shells, these notes will not appear in the final output.

Population Summary Conventions

- Population sizes may be presented for each classification factor as totals in the column header as (N=xxx), where appropriate.
- All population summaries for categorical variables will include all categories that were planned and for which the participants may have had a response. Percentages corresponding to null categories (cells) will be suppressed; however, counts and percentages of missing values may be needed. Counts of zero will be presented as '0', without the percentage.
- All population summaries for continuous variables will include: n, mean, SD, median, minimum, and maximum. Other summaries (e.g., number missing, geometric mean, median, quartiles, 95% CIs, and coefficient of variation [CV] or % CV) may be used as appropriate. The precision of the maximum and minimum will match the maximum precision in the data. The mean and median will have 1 additional decimal place. The SD will have 2 additional decimal places.
- All percentages are rounded and reported to a single decimal point (xx.x%).

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number MRX-502. The table numbers are place holders only and will be determined when the tables are produced. The efficacy outputs are ordered to account for the hierarchical testing structure as outlined in Section 6.1.3, where possible. For cases where multiple study visits for the same parameter are tested, those visits are consolidated on a single table for ease of review and referencing results. Similarly, for cases where multiple analysis populations or cohort groups are presented, this data will be consolidated on a single table, when practical.

The table shells will be provided under a separate document.

13.1.1. Subject Data

Table 3: Subject Data Summary Tables

Number	Population	Title
14.1.1.1	All Subjects	Subject Disposition
14.1.1.2	Safety	Number of Randomized and Completed Subjects by Country

14.1.1.3	Safety	Number of Randomized and Completed Subjects by Investigative Site
14.1.2	Safety	Important Protocol Violations/Deviations
14.1.3	Safety	Demographics and Baseline Characteristics
14.1.4	Safety	Disease History and Baseline Disease Characteristics
14.1.5	Safety	Prior Medications/Therapies
14.1.6	Safety	Study Drug Compliance

13.1.2. Efficacy Data

Table 4: Efficacy Data Summary Tables

Number	Population	Title
14.2.1.x Primary Analysis		
14.2.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Severity Score MMRM Model Effects
14.2.2.x Secondary Analysis		
14.2.2.1.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.2.1.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Severity Score MMRM Model Effects
14.2.2.2.1	ITT	Change from Baseline in Total sBA (µmol/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.2.2.2	ITT	Change from Baseline in Total sBA (µmol/L) MMRM Model Effects
14.2.2.3	ITT	Proportion of Responders
14.2.3.x Sensitivity Analysis		
14.2.3.1.1	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score – Sibling Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.1.2	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score – Sibling Sensitivity Analysis MMRM Model Effects

Number	Population	Title
14.2.3.2	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score – Multiple Imputation Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.3	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score to Average of Last 12 Weeks – Tipping Point Sensitivity Analysis
14.2.3.4.1	ITT	Change from Baseline in Total sBA (µmol/L) – Sibling Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.4.2	ITT	Change from Baseline in Total sBA (µmol/L) – Sibling Sensitivity Analysis MMRM Model Effects
14.2.3.5	ITT	Change from Baseline in Total sBA (µmol/L) – Multiple Imputation Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.6	ITT	Change from Baseline in Total sBA (µmol/L) to Average of Weeks 18, 22, and 26 – Tipping Point Sensitivity Analysis
14.2.4.x Exploratory Analysis		
14.2.4.1.1	PP – Primary Cohort	Change from Baseline in Morning ItchRO(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.1.2	PP – Primary Cohort	Change from Baseline in Morning ItchRO(Obs) Severity Score MMRM Model Effects
14.2.4.2.1	PP – Primary Cohort	Change from Baseline in Total sBA (µmol/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.2.2	PP – Primary Cohort	Change from Baseline in Total sBA (µmol/L) MMRM Model Effects
14.2.4.3.1	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score Descriptive Statistics by Analysis Week
14.2.4.3.2	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Region Descriptive Statistics by Analysis Week
14.2.4.3.3	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Age at Baseline Descriptive Statistics by Analysis Week

Number	Population	Title
14.2.4.3.4	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Sex Descriptive Statistics by Analysis Week
14.2.4.3.5	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Race Descriptive Statistics by Analysis Week
14.2.4.3.6	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline Median sBA Descriptive Statistics by Analysis Week
14.2.4.3.7	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline UDCA Usage Descriptive Statistics by Analysis Week
14.2.4.3.8	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline Rifampicin Usage Descriptive Statistics by Analysis Week
14.2.4.3.9	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by BSEP Type Descriptive Statistics by Analysis Week
14.2.4.4.1	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) Descriptive Statistics by Analysis Week
14.2.4.4.2	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Region Descriptive Statistics by Analysis Week
14.2.4.4.3	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Age at Baseline Descriptive Statistics by Analysis Week
14.2.4.4.4	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Sex Descriptive Statistics by Analysis Week
14.2.4.4.5	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Race Descriptive Statistics by Analysis Week
14.2.4.4.6	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Baseline Median sBA Descriptive Statistics by Analysis Week
14.2.4.4.7	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Baseline UDCA Usage Descriptive Statistics by Analysis Week
14.2.4.4.8	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Baseline Rifampicin Usage Descriptive Statistics by Analysis Week

Number	Population	Title
14.2.4.4.9	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by BSEP Type Descriptive Statistics by Analysis Week
14.2.4.5.1	ITT	Change from Baseline in ALT (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.5.2	ITT	Change from Baseline in ALT (U/L) MMRM Model Effects
14.2.4.6.1	ITT	Change from Baseline in AST (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.6.2	ITT	Change from Baseline in AST (U/L) MMRM Model Effects
14.2.4.7.1	ITT	Change from Baseline in Total Bilirubin (mg/dL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.7.2	ITT	Change from Baseline in Total Bilirubin (mg/dL) MMRM Model Effects
14.2.4.8.1	ITT	Change from Baseline in Direct Bilirubin (mg/dL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.8.2	ITT	Change from Baseline in Direct Bilirubin (mg/dL) MMRM Model Effects
14.2.4.9.1	ITT	Change from Baseline in ALP (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.9.2	ITT	Change from Baseline in ALP (U/L) MMRM Model Effects
14.2.4.10.1	ITT	Change from Baseline in GGT (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.10.2	ITT	Change from Baseline in GGT (U/L) MMRM Model Effects
14.2.4.11.1	ITT	Change from Baseline in FIB-4 Tabulation of Fitted Summary Statistics from MMRM
14.2.4.11.2	ITT	Change from Baseline in FIG-4 MMRM Model Effects
14.2.4.12.1	ITT	Change from Baseline in APRI Tabulation of Fitted Summary Statistics from MMRM

Number	Population	Title
14.2.4.12.2	ITT	Change from Baseline in APRI MMRM Model Effects
14.2.4.13.1	ITT	Change from Baseline in PELD Tabulation of Fitted Summary Statistics from MMRM
14.2.4.13.2	ITT	Change from Baseline in PELD MMRM Model Effects
14.2.4.14	ITT	Total sBA Shift from Baseline: Number and Proportion of Subjects
14.2.4.15	ITT	Number of Days Morning ItchRO(Obs) Severity Score ≤1 Over the Last 84 Study Days
14.2.4.16	ITT	Number and Proportion of Subjects with Morning ItchRO(Obs) Severity Score ≤1 for >50% of Time Period
14.2.4.17.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Frequency Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.17.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Frequency Score MMRM Model Effects
14.2.4.17.2.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Frequency Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.17.2.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Frequency Score MMRM Model Effects
14.2.4.18.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.18.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Severity Score MMRM Model Effects
14.2.4.18.2.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.18.2.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Severity Score MMRM Model Effects
14.2.4.19.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Frequency Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.19.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Frequency Score MMRM Model Effects
14.2.4.19.2.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Frequency Score Tabulation of Fitted Summary Statistics from MMRM

Number	Population	Title
14.2.4.19.2.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Frequency Score MMRM Model Effects
14.2.4.20.1	ITT	Change from Baseline in Clinician Scratch Scale (CSS) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.20.2	ITT	Change from Baseline in Clinician Scratch Scale (CSS) MMRM Model Effects
14.2.4.21.1	ITT	Change from Baseline in Caregiver Impression of Severity (CIS) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.21.2	ITT	Change from Baseline in Caregiver Impression of Severity (CIS) MMRM Model Effects
14.2.4.22.1	ITT	Change from Baseline in Patient Impression of Severity (PIS) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.22.2	ITT	Change from Baseline in Patient Impression of Severity (PIS) MMRM Model Effects
14.2.4.23.1.1	ITT – Primary Cohort	Change from Baseline in EDQ(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.23.1.2	ITT – Primary Cohort	Change from Baseline in EDQ(Obs) Severity Score MMRM Model Effects
14.2.4.23.2.1	ITT – PFIC Cohort	Change from Baseline in EDQ(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.23.2.2	ITT – PFIC Cohort	Change from Baseline in EDQ(Obs) Severity Score MMRM Model Effects
14.2.4.24.1	ITT	Change from Baseline in Morning EDQ(Obs) Sleep Disturbance Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.24.2	ITT	Change from Baseline in Morning EDQ(Obs) Sleep Disturbance Score MMRM Model Effects
14.2.4.25	ITT	Number and Proportion of Subjects with Improvement from Baseline in Morning EDQ(Obs) Sleep Disturbance Score
14.2.4.26	ITT	Number and Proportion of Subjects with Morning EDQ(Obs) Sleep Disturbance Scores ≤2 from Post-Baseline through Week 26
14.2.4.27.1	ITT	Change from Baseline in PedsQL Total Scale Score Tabulation of Fitted Summary Statistics from MMRM

Number	Population	Title
14.2.4.27.2	ITT	Change from Baseline in PedsQL Total Scale Score MMRM Model Effects
14.2.4.28.1	ITT	Change from Baseline in Height z-Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.28.2	ITT	Change from Baseline in Height z-Score MMRM Model Effects
14.2.4.29.1	ITT	Change from Baseline in Weight z-Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.29.2	ITT	Change from Baseline in Weight z-Score MMRM Model Effects
14.2.4.30.1	ITT	Percent Change from Baseline in Total sBA Tabulation of Fitted Summary Statistics from MMRM
14.2.4.30.2	ITT	Percent Change from Baseline in Total sBA MMRM Model Effects
14.2.4.31.1	ITT	Change from Baseline in 7 Alpha-hydroxy-4-cholesten-3-one (C4), ng/mL Tabulation of Fitted Summary Statistics from MMRM
14.2.4.31.2	ITT	Change from Baseline in 7 Alpha-hydroxy-4-cholesten-3-one (C4), ng/mL MMRM Model Effects
14.2.4.32.1	ITT	Change from Baseline in Fibroblast Growth Factor 19 (pg/mL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.32.2	ITT	Change from Baseline in Fibroblast Growth Factor 19 (pg/mL) MMRM Model Effects
14.2.4.33.1	ITT	Change from Baseline in Autotaxin (ng/mL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.33.2	ITT	Change from Baseline in Autotaxin (ng/mL) MMRM Model Effects
14.2.4.34.1	ITT	Change from Baseline in Albumin (g/dL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.34.2	ITT	Change from Baseline in Albumin (g/dL) MMRM Model Effects
14.2.4.35	ITT	Time to First Liver-Associated Event (Days)

13.1.3. Safety Data

Table 5: Safety Data Summary Tables

Number	Population	Title
14.3.1 Study Drug Exposure		
14.3.1	Safety	Maralixibat Exposure
14.3.2 Displays of Adverse Events		
14.3.2.1.1	Safety	Overall Summary of Treatment-Emergent Adverse Events
14.3.2.1.2	Safety	Overall Summary of Treatment-Emergent Adverse Events by Age Group
14.3.2.1.3	Safety	Overall Summary of Treatment-Emergent Adverse Events by Sex
14.3.2.1.4	Safety	Overall Summary of Treatment-Emergent Adverse Events by Race
14.3.2.2.1	Safety	Incidence of Treatment-Emergent Adverse Events
14.3.2.2.2	Safety	Incidence of Treatment-Emergent Adverse Events by Age Group
14.3.2.2.3	Safety	Incidence of Treatment-Emergent Adverse Events by Sex
14.3.2.2.4	Safety	Incidence of Treatment-Emergent Adverse Events by Race
14.3.3 Summary of Deaths, Other Serious and Significant Adverse Events		
14.3.3.1	Safety	Incidence of Treatment-Emergent Serious Adverse Events
14.3.3.2	Safety	Incidence of Treatment Related Adverse Events
14.3.3.3	Safety	Incidence of Treatment Related Adverse Events Leading to Permanent Discontinuation of Study Drug
14.3.3.4.1	Safety	Incidence of Events of Clinical Interest – Diarrhoea Events
14.3.3.4.2	Safety	Incidence of Events of Clinical Interest – LSV Deficiency Events
14.3.3.4.3	Safety	Incidence of Events of Clinical Interest – Elevated Transaminases
14.3.3.4.4	Safety	Incidence of Events of Clinical Interest – Elevated Bilirubin
14.3.4 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
14.3.4.1	Safety	Listing of Serious Adverse Events
14.3.4.2	Safety	Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug
14.3.4.3	Safety	Listing of Deaths

Number	Population	Title
14.3.5 Laboratory Data Summary Tables		
14.3.5.1	Safety	Summary of Safety Laboratory Data: Chemistry
14.3.5.2	Safety	Summary of Safety Laboratory Data: Hematology
14.3.5.3	Safety	Summary of Safety Laboratory Data: Lipid Panel
14.3.5.4	Safety	Summary of Safety Laboratory Data: Lipid Soluble Vitamins (LSV)
14.3.5.5	Safety	Summary of Safety Laboratory Data: Alpha-Fetoprotein (ng/mL)
14.3.5.6	Safety	Shift Table for Select Safety Laboratory Tests
14.3.6 Physical Examination, Vital Signs, and ECG Safety Data Summary Tables		
14.3.6.1	Safety	Summary of Subject Height, Weight, and BMI z-Scores
14.3.6.2	Safety	Summary of Vital Signs
14.3.6.3.1	Safety	Summary of Electrocardiogram Parameters
14.3.6.3.2	Safety	Summary of Electrocardiogram Interpretation
14.3.7 Other Safety Data Summary Tables		
14.3.7	Safety	Summary of Concomitant Therapies/Medications

13.1.4. Other Data

Table 6: Other Data Summary Tables

Number	Population	Title
14.4 Other Data Summary Tables		
14.4.1	Safety	Summary of Healthcare Utilization Measures
14.4.2	Safety	Summary of Plasma Sample Maralixibat Concentrations (ng/mL)

13.2. Planned Figure Descriptions

The following are planned summary figures for protocol number MRX-502. The figure numbers are place holders only and will be determined when the figures are produced.

Estimates from the MMRM model (over time) will be graphically displayed for select efficacy variables in the ITT population for the primary and PFIC cohorts, separately. These plots will display the LS Mean ±SE for each treatment group at each analysis visit/time period, as appropriate. Each of the treatment group LS means will be displayed side-by-side, with vertical lines emanating from each LS Mean to represent the standard error. At minimum, these graphical displays will be presented for the change from baseline in morning ItchRO(Obs) severity score and change from baseline in sBA levels, over time. The number of subjects with non-missing change from baseline values, for each treatment group and analysis visit, will be displayed along the horizontal axis at each time point, baseline through Week 26.

Tipping point results, for the sensitivity analysis of the primary efficacy endpoint and the key secondary efficacy endpoint, will be presented in a heatmap. This figure will be generated to display p-values corresponding to all combinations of shifts from the imputed data. For the heatmap figure, each cell will be colored according to the p-value: green for p-values < 0.05; yellow for p-values of 0.05 to < 0.10; orange for p-values of 0.10 to < 0.20; and red for p-values of 0.20 to 1.00.

Additional figures may be added post-hoc to further examine study data.

13.2.1. Efficacy Data

Table 7: Efficacy Data Summary Figures

Number	Population	Title
14.2.1.x Primary Analysis		
14.2.1.1	ITT – Primary Cohort	Plot of MMRM LS Mean (± SE) Change from Baseline in Morning ItchRO(Obs) Severity Score Over Time
14.2.2.x Secondary Analysis		
14.2.2.2.1	ITT – Primary Cohort	Plot of MMRM LS Mean (± SE) Change from Baseline in Total sBA (µmol/L) Over Time
14.2.3.x Sensitivity Analysis		
14.2.3.3	ITT – Primary Cohort	Heatmap Displaying p-values from Tipping Point Analysis on Change from Baseline in Morning ItchRO(Obs) Severity Score to Average of Last 12 Weeks

Number	Population	Title
14.2.3.6	ITT – Primary Cohort	Heatmap Displaying p-values from Tipping Point Analysis on Change from Baseline in Total sBA (µmol/L) to Average of Weeks 18, 22, and 26

13.3. Planned Listing Descriptions

In general, listings produced will include the participant data collected on associated CRF pages. All listings will be sorted by treatment, PFIC type, and subject ID. For safety data (i.e., study drug exposure, AEs, vital signs, laboratory tests, ECG, physical examination, and plasma maralixibat concentration levels), listings will be presented by treatment received. For all other listings (including efficacy laboratory tests), where applicable, data will be presented by randomized treatment group.

For listings of efficacy variables, change from baseline values will be included, as appropriate.

For adverse event listings, study day relative to the date of first dose of study drug will be provided along with stop and start dates. The dose of study drug at the onset of AEs in the maralixibat treatment group will also be provided. For partial event dates, study day will be derived using an imputed date as described in Section 6.1.9.

Study day relative to the first dose of study drug will also be included on laboratory listings, along with laboratory collection dates, and on study drug exposure listings, along with start and stop dates.

For the concomitant treatment listing, medications that are ongoing at the time of informed consent will be indicated.

Weight, height, and BMI will be presented in the vital signs listing, rather than the physical examination listing.

PedsQL listings will present total scale and summary scores, including PedsQL Total Scale Score, Physical Health Summary Score, Psychosocial Health Summary Score, Multidimensional Fatigue Scale Score, Family Impact Total Scale Score, Parent Functioning Summary Score, and Family Impact Summary Score. Subject listings of PedsQL raw scores for each of the model items will not be included.

Assessments denoted as clinic visit “Week 26/ET” in listings will include assessments performed at the Early Termination visit for participants who withdraw early from the study.

In all listings a blank line will be placed between participants. Within a data listing, if an item appears line after line (e.g., repetition of participant number), then only the first occurrence will be displayed.

The listing shells will be provided under a separate document.

13.4. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all Tables, Listings, and Figures (TLFs) in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

Figure 2. Standardized Layout

Mirum Pharmaceuticals Inc. Page xx of xx
Protocol: MRX-502 Version xxxxx

<Table, Listing, Figure> xx.x.x

<Title of Table Listing or Figure>

<Study Population and if applicable subgroup Description>

Body of Table, Listing or Figure

<Abbreviations: If applicable>

<Note: If applicable>

Footnote 1 <if applicable> Recommendation is to keep footnotes to a minimum
Footnote 2 <if applicable>
Footnote n <if applicable>

<pgm path and name>
<Executed on <date> at <time> on data from <data cut date>

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]
APRI [3]
FIB-4 [3]
PELD [3]
MELD [3]

Cholestasis Biomarkers

Serum Bile Acids, µmol/L [2]
7 alpha-hydroxy-4-cholesten-3-one (C4), ng/mL
Autotaxin, ng/mL
FGF-19, pg/mL [2]
Bile Acid Subspecies, µmol/L (15 subspecies) [1]

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; APRI = AST to platelet ratio index; AST = aspartate aminotransferase; FGF-19 = fibroblast growth factor 19; FIB-4 = fibrosis-4; GGT = gamma-glutamyl transferase; PT = prothrombin time; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MELD = model for end-stage liver disease; PELD = pediatric end-stage liver disease; WBC = white blood cell; * Qualitative urinalysis

[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

Sponsor	Mirum Pharmaceuticals Inc.
Protocol Title:	Randomized Double-blind Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Children with Progressive Familial Intrahepatic Cholestasis (PFIC) – MARCH-PFIC
Protocol Number:	MRX-502 (Amendment 4)
Premier Research PCN:	MIRU8967
Document Author:	Jana Steinmetz
Document Version:	Final 1.0
Document Date:	09Oct2022

1. Table Conventions, Titles, and Shells

All tables will have a page header showing the sponsor company name (Mirum Pharmaceuticals Inc.) and protocol (MRX-502), and a page footer showing the file name and path, and the date/time of program execution along with the database data cut date.

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize the presentation with common notations.

General Reporting Conventions

- All tables will be developed in landscape orientation.
- Abbreviations, general note, specific item footnotes, and source of data (as applicable), in this order, will be presented on each page of a table.
- In general, specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text will not be used in tables unless they add significant value.
- Only standard keyboard characters will be used in the tables. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used.
- Adverse events with missing MedDRA coding will have their system organ class and/or preferred term presented as “Not Coded”. The “Not Coded” frequencies will be sorted to the end of the tables. Adverse events that are not coded are not expected.
- Programming notes may be inserted into the shells, these notes will not appear in the final output.

Population Summary Conventions

- Population sizes may be presented for each cohort, treatment group, subgroup, and classification factor, where appropriate, as totals in the column header as (N=xxx).
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed; however, counts and percentages of missing values may be needed. Counts of zero will be presented as ‘0’, without the percentage.
- In general, population summaries for continuous variables will include: n, mean, SD, SE, median, Q1, Q3, minimum, and maximum. Other summaries (e.g., number missing, geometric mean, 95% CIs, and coefficient of variation [CV] or % CV) may be used as appropriate. The precision of the maximum and minimum will match the maximum precision in the data. The mean, median, Q1, and Q3 will have 1 additional decimal place. The SD will have 2 additional decimal places.
- All percentages are rounded and reported to a single decimal point (xx.x%).

1.1. Planned Table Descriptions

The following are planned summary tables for protocol number MRX-502. The table numbers are place holders only and will be determined when the tables are produced. The efficacy outputs are ordered to account for the hierarchical testing structure as outlined in the SAP, where possible. For cases where multiple subject cohorts or, in the case of ItchRO and EDQ morning, evening, and highest daily scores are presented, data columns are consolidated on a single table, when practical, for ease of review and referencing results.

1.1.1. Subject Data

Table 1: Subject Data Summary Tables

Number	Population	Title
14.1.1.1	All Subjects	Subject Disposition
14.1.1.2	Safety	Number of Randomized and Completed Subjects by Country
14.1.1.3	Safety	Number of Randomized and Completed Subjects by Investigative Site
14.1.2	Safety	Important Protocol Violations/Deviations
14.1.3	Safety	Demographics and Baseline Characteristics
14.1.4	Safety	Disease History and Baseline Disease Characteristics
14.1.5	Safety	Prior Medications/Therapies
14.1.6	Safety	Study Drug Compliance

1.1.2. Efficacy Data

Table 2: Efficacy Data Summary Tables

Number	Population	Title
14.2.1.x Primary Analysis		
14.2.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Severity Score MMRM Model Effects
14.2.2.x Secondary Analysis		
14.2.2.1.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM

Number	Population	Title
14.2.2.1.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Severity Score MMRM Model Effects
14.2.2.2.1	ITT	Change from Baseline in Total sBA (µmol/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.2.2.2	ITT	Change from Baseline in Total sBA (µmol/L) MMRM Model Effects
14.2.2.3	ITT	Proportion of Responders
14.2.3.x Sensitivity Analysis		
14.2.3.1.1	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score – Sibling Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.1.2	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score – Sibling Sensitivity Analysis MMRM Model Effects
14.2.3.2	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score – Multiple Imputation Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.3	ITT	Change from Baseline in Morning ItchRO(Obs) Severity Score to Average of Last 12 Weeks – Tipping Point Sensitivity Analysis
14.2.3.4.1	ITT	Change from Baseline in Total sBA (µmol/L) – Sibling Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.4.2	ITT	Change from Baseline in Total sBA (µmol/L) – Sibling Sensitivity Analysis MMRM Model Effects
14.2.3.5	ITT	Change from Baseline in Total sBA (µmol/L) – Multiple Imputation Sensitivity Analysis Tabulation of Fitted Summary Statistics from MMRM
14.2.3.6	ITT	Change from Baseline in Total sBA (µmol/L) to Average of Weeks 18, 22, and 26 – Tipping Point Sensitivity Analysis

Number	Population	Title
14.2.4.x Exploratory Analysis		
14.2.4.1.1	PP – Primary Cohort	Change from Baseline in Morning ItchRO(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.1.2	PP – Primary Cohort	Change from Baseline in Morning ItchRO(Obs) Severity Score MMRM Model Effects
14.2.4.2.1	PP – Primary Cohort	Change from Baseline in Total sBA (µmol/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.2.2	PP – Primary Cohort	Change from Baseline in Total sBA (µmol/L) MMRM Model Effects
14.2.4.3.1	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score Descriptive Statistics by Analysis Week
14.2.4.3.2	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Region Descriptive Statistics by Analysis Week
14.2.4.3.3	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Age at Baseline Descriptive Statistics by Analysis Week
14.2.4.3.4	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Sex Descriptive Statistics by Analysis Week
14.2.4.3.5	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Race Descriptive Statistics by Analysis Week
14.2.4.3.6	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline Median sBA Descriptive Statistics by Analysis Week
14.2.4.3.7	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline UDCA Usage Descriptive Statistics by Analysis Week

Number	Population	Title
14.2.4.3.8	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline Rifampicin Usage Descriptive Statistics by Analysis Week
14.2.4.3.9	ITT – Primary Cohort	Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by BSEP Type Descriptive Statistics by Analysis Week
14.2.4.4.1	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) Descriptive Statistics by Analysis Week
14.2.4.4.2	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Region Descriptive Statistics by Analysis Week
14.2.4.4.3	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Age at Baseline Descriptive Statistics by Analysis Week
14.2.4.4.4	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Sex Descriptive Statistics by Analysis Week
14.2.4.4.5	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Race Descriptive Statistics by Analysis Week
14.2.4.4.6	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Baseline Median sBA Descriptive Statistics by Analysis Week
14.2.4.4.7	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Baseline UDCA Usage Descriptive Statistics by Analysis Week
14.2.4.4.8	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by Baseline Rifampicin Usage Descriptive Statistics by Analysis Week
14.2.4.4.9	ITT – Primary Cohort	Change from Baseline in Total sBA (µmol/L) by BSEP Type Descriptive Statistics by Analysis Week
14.2.4.5.1	ITT	Change from Baseline in ALT (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.5.2	ITT	Change from Baseline in ALT (U/L) MMRM Model Effects

Number	Population	Title
14.2.4.6.1	ITT	Change from Baseline in AST (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.6.2	ITT	Change from Baseline in AST (U/L) MMRM Model Effects
14.2.4.7.1	ITT	Change from Baseline in Total Bilirubin (mg/dL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.7.2	ITT	Change from Baseline in Total Bilirubin (mg/dL) MMRM Model Effects
14.2.4.8.1	ITT	Change from Baseline in Direct Bilirubin (mg/dL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.8.2	ITT	Change from Baseline in Direct Bilirubin (mg/dL) MMRM Model Effects
14.2.4.9.1	ITT	Change from Baseline in ALP (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.9.2	ITT	Change from Baseline in ALP (U/L) MMRM Model Effects
14.2.4.10.1	ITT	Change from Baseline in GGT (U/L) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.10.2	ITT	Change from Baseline in GGT (U/L) MMRM Model Effects
14.2.4.11.1	ITT	Change from Baseline in FIB-4 Tabulation of Fitted Summary Statistics from MMRM
14.2.4.11.2	ITT	Change from Baseline in FIB-4 MMRM Model Effects
14.2.4.12.1	ITT	Change from Baseline in APRI Tabulation of Fitted Summary Statistics from MMRM
14.2.4.12.2	ITT	Change from Baseline in APRI MMRM Model Effects
14.2.4.13.1	ITT	Change from Baseline in PELD Tabulation of Fitted Summary Statistics from MMRM

Number	Population	Title
14.2.4.13.2	ITT	Change from Baseline in PELD MMRM Model Effects
14.2.4.14	ITT	Total sBA Shift from Baseline: Number and Proportion of Subjects
14.2.4.15	ITT	Number of Days Morning ItchRO(Obs) Severity Score ≤1 Over the Last 84 Study Days
14.2.4.16	ITT	Number and Proportion of Subjects with Morning ItchRO(Obs) Severity Score ≤1 for >50% of Time Period
14.2.4.17.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Frequency Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.17.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Obs) Frequency Score MMRM Model Effects
14.2.4.17.2.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Frequency Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.17.2.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Obs) Frequency Score MMRM Model Effects
14.2.4.18.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.18.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Severity Score MMRM Model Effects
14.2.4.18.2.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.18.2.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Severity Score MMRM Model Effects
14.2.4.19.1.1	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Frequency Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.19.1.2	ITT – Primary Cohort	Change from Baseline in ItchRO(Pt) Frequency Score MMRM Model Effects
14.2.4.19.2.1	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Frequency Score Tabulation of Fitted Summary Statistics from MMRM

Number	Population	Title
14.2.4.19.2.2	ITT – PFIC Cohort	Change from Baseline in ItchRO(Pt) Frequency Score MMRM Model Effects
14.2.4.20.1	ITT	Change from Baseline in Clinician Scratch Scale (CSS) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.20.2	ITT	Change from Baseline in Clinician Scratch Scale (CSS) MMRM Model Effects
14.2.4.21.1	ITT	Change from Baseline in Caregiver Impression of Severity (CIS) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.21.2	ITT	Change from Baseline in Caregiver Impression of Severity (CIS) MMRM Model Effects
14.2.4.22.1	ITT	Change from Baseline in Patient Impression of Severity (PIS) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.22.2	ITT	Change from Baseline in Patient Impression of Severity (PIS) MMRM Model Effects
14.2.4.23.1.1	ITT – Primary Cohort	Change from Baseline in EDQ(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.23.1.2	ITT – Primary Cohort	Change from Baseline in EDQ(Obs) Severity Score MMRM Model Effects
14.2.4.23.2.1	ITT – PFIC Cohort	Change from Baseline in EDQ(Obs) Severity Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.23.2.2	ITT – PFIC Cohort	Change from Baseline in EDQ(Obs) Severity Score MMRM Model Effects
14.2.4.24.1	ITT	Change from Baseline in Morning EDQ(Obs) Sleep Disturbance Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.24.2	ITT	Change from Baseline in Morning EDQ(Obs) Sleep Disturbance Score MMRM Model Effects
14.2.4.25	ITT	Number and Proportion of Subjects with Improvement from Baseline in Morning EDQ(Obs) Sleep Disturbance Score

Number	Population	Title
14.2.4.26	ITT	Number and Proportion of Subjects with Morning EDQ(Obs) Sleep Disturbance Scores ≤2 from Post-Baseline through Week 26
14.2.4.27.1	ITT	Change from Baseline in PedsQL Total Scale Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.27.2	ITT	Change from Baseline in PedsQL Total Scale Score MMRM Model Effects
14.2.4.28.1	ITT	Change from Baseline in Height z-Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.28.2	ITT	Change from Baseline in Height z-Score MMRM Model Effects
14.2.4.29.1	ITT	Change from Baseline in Weight z-Score Tabulation of Fitted Summary Statistics from MMRM
14.2.4.29.2	ITT	Change from Baseline in Weight z-Score MMRM Model Effects
14.2.4.30.1	ITT	Percent Change from Baseline in Total sBA Tabulation of Fitted Summary Statistics from MMRM
14.2.4.30.2	ITT	Percent Change from Baseline in Total sBA MMRM Model Effects
14.2.4.31.1	ITT	Change from Baseline in 7 Alpha-hydroxy-4-cholesten-3-one (C4), ng/mL Tabulation of Fitted Summary Statistics from MMRM
14.2.4.31.2	ITT	Change from Baseline in 7 Alpha-hydroxy-4-cholesten-3-one (C4), ng/mL MMRM Model Effects
14.2.4.32.1	ITT	Change from Baseline in Fibroblast Growth Factor 19 (pg/mL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.32.2	ITT	Change from Baseline in Fibroblast Growth Factor 19 (pg/mL) MMRM Model Effects
14.2.4.33.1	ITT	Change from Baseline in Autotaxin (ng/mL) Tabulation of Fitted Summary Statistics from MMRM

Number	Population	Title
14.2.4.33.2	ITT	Change from Baseline in Autotaxin (ng/mL) MMRM Model Effects
14.2.4.34.1	ITT	Change from Baseline in Albumin (g/dL) Tabulation of Fitted Summary Statistics from MMRM
14.2.4.34.2	ITT	Change from Baseline in Albumin (g/dL) MMRM Model Effects
14.2.4.35	ITT	Time to First Liver-Associated Event (Days)

1.1.3. Safety Data

Table 3: Safety Data Summary Tables

Number	Population	Title
14.3.1 Study Drug Exposure		
14.3.1	Safety	Maralixibat Exposure
14.3.2 Displays of Adverse Events		
14.3.2.1.1	Safety	Overall Summary of Treatment-Emergent Adverse Events
14.3.2.1.2	Safety	Overall Summary of Treatment-Emergent Adverse Events by Age Group
14.3.2.1.3	Safety	Overall Summary of Treatment-Emergent Adverse Events by Sex
14.3.2.1.4	Safety	Overall Summary of Treatment-Emergent Adverse Events by Race
14.3.2.2.1	Safety	Incidence of Treatment-Emergent Adverse Events
14.3.2.2.2	Safety	Incidence of Treatment-Emergent Adverse Events by Age Group
14.3.2.2.3	Safety	Incidence of Treatment-Emergent Adverse Events by Sex
14.3.2.2.4	Safety	Incidence of Treatment-Emergent Adverse Events by Race
14.3.3 Summary of Deaths, Other Serious and Significant Adverse Events		
14.3.3.1	Safety	Incidence of Treatment-Emergent Serious Adverse Events
14.3.3.2	Safety	Incidence of Treatment Related Adverse Events
14.3.3.3	Safety	Incidence of Treatment Related Adverse Events Leading to Permanent Discontinuation of Study Drug
14.3.3.4.1	Safety	Incidence of Events of Clinical Interest – Diarrhoea Events
14.3.3.4.2	Safety	Incidence of Events of Clinical Interest – LSV Deficiency Events

Number	Population	Title
14.3.3.4.3	Safety	Incidence of Events of Clinical Interest – Elevated Transaminases
14.3.3.4.4	Safety	Incidence of Events of Clinical Interest – Elevated Bilirubin
14.3.4 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
14.3.4.1	Safety	Listing of Serious Adverse Events
14.3.4.2	Safety	Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug
14.3.4.3	Safety	Listing of Deaths
14.3.5 Laboratory Data Summary Tables		
14.3.5.1	Safety	Summary of Safety Laboratory Data: Chemistry
14.3.5.2	Safety	Summary of Safety Laboratory Data: Hematology
14.3.5.3	Safety	Summary of Safety Laboratory Data: Lipid Panel
14.3.5.4	Safety	Summary of Safety Laboratory Data: Lipid Soluble Vitamins (LSV)
14.3.5.5	Safety	Summary of Safety Laboratory Data: Alpha-Fetoprotein (ng/mL)
14.3.5.6	Safety	Shift Table for Select Safety Laboratory Tests
14.3.6 Physical Examination, Vital Signs, and ECG Safety Data Summary Tables		
14.3.6.1	Safety	Summary of Subject Height, Weight, and BMI z-Scores
14.3.6.2	Safety	Summary of Vital Signs
14.3.6.3.1	Safety	Summary of Electrocardiogram Parameters
14.3.6.3.2	Safety	Summary of Electrocardiogram Interpretation
14.3.7 Other Safety Data Summary Tables		
14.3.7	Safety	Summary of Concomitant Therapies/Medications

1.1.4. Other Data

Table 4: Other Data Summary Tables

Number	Population	Title
14.4 Other Data Summary Tables		
14.4.1	Safety	Summary of Healthcare Utilization Measures
14.4.2	Safety	Summary of Plasma Sample Maralixibat Concentrations (ng/mL)

1.2. Planned Table Shells

Table 14.1.1.1
Subject Disposition
All Subjects

Status or Variable/Statistic	Primary Cohort			PFIC Cohort			All Subjects		
	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)
Screened for Eligibility									xx
Screen Failure									xx
Randomized [1]	xx	xx	xx	xx	xx	xx	xx	xx	xx
Families with Siblings enrolled	xx	xx	xx	xx	xx	xx	xx	xx	xx
Total number of Siblings	xx	xx	xx	xx	xx	xx	xx	xx	xx
Safety Population [2]	xx	xx	xx	xx	xx	xx	xx	xx	xx
ITT Population [1, 3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Per-Protocol Population [4]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Completed Study Treatment	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Discontinued Early [1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Abbreviation: ITT = intent-to-treat; PEBD = partial external biliary diversion
Note: Percentages are based on the number of subjects in the Safety Population. Siblings (within the same family) are assigned in a blinded manner to the same treatment group.
[1] One subject (Subject 023004) was randomized in error within the IRT system on 14Sep2020, the date of the baseline visit. This subject was not dispensed study drug, and was discontinued from the study due to 'administrative error' on the baseline visit day. On 15Oct2022, this same subject was re-randomized as Subject 023005. This subject is only counted once, as Subject 023005, in the Randomized and ITT Population groups, and not counted in the Discontinued Early group.
[2] The Safety Population includes all subjects who receive at least 1 dose of study drug.
[3] The ITT Population includes all randomized subjects.
[4] The Per-Protocol population includes all subjects in the ITT Population who receive at least 1 dose of study drug and do not have any important protocol violations or deviations that have a potential impact on the efficacy analysis.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.1.1.1 (Cont'd)
Subject Disposition
All Subjects

Status or Variable/Statistic	Primary Cohort			PFIC Cohort			All Subjects		
	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)
Reason for Discontinuation									
Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-compliance with study drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lack of efficacy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Physician decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pregnancy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Liver transplant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PEBD surgery	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Protocol violation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Withdrawal of consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Study terminated by sponsor	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Disease Progression	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 14.1.1.2
Number of Randomized and Completed Subjects by Country
Safety Population

	Primary Cohort			PFIC Cohort			All Subjects		
Country	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)
xxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxx xxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are 100*n/N.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.1.1.3
Number of Randomized and Completed Subjects by Investigative Site
Safety Population

Programming Notes: Repeat Table 14.1.1.2 with Investigative Site and change 1st column header to 'Investigative Site ID'.)

Table 14.1.2
Important Protocol Violations/Deviations
Safety Population

	Primary Cohort			PFIC Cohort			All Subjects		
Category/Type [1]	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)
Informed consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Inclusion	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Exclusion	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overdose/misuse	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Prohibited co-medication	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Assessment – efficacy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Assessment – safety	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Laboratory/endpoint data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Visit Window	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc…									

Note: Percentages are 100*n/N.
[1] Important protocol violations/deviations are grouped based on study specific protocol deviation categories as described in the Protocol Deviation Guidance Plan for the Maralixibat-502 clinical protocol. Subjects were counted only once for each category/type.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.1.3
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
Age (years) [1]									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Age Category [1]									
1 to <6 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
6 to <13 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
13 to 18 years	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Sex									
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: Percentages are 100*n/N.
[1] Age at baseline visit.
[2] Height, weight, and BMI z-scores are based on a subject's sex and age at the baseline visit. The World Health Organization (WHO) grouth charts were used to derive z-scores for subjects less than 24 months old and the Center for Disease Control (CDC) grouth charts were used to derive z-scores for subjects equal to or greater than 24 months old.
Source: Reference Listings xx.x.x, xx.x.x

Programming Note: If a particular category (e.g., race, ethnicity) is not reported, add a category for "Not reported". Subjects reporting more than 1 race will be counted in a "More than one race" category for purpose of tabulating summary statistics for race.

Table 14.1.3 (Cont'd)
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
Race									
American Indian or Alaska Native	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Asian	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Black or African American	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Native Hawaiian or Other Pacific Islander	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
White	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
More than one race	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Reported	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ethnicity									
Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Reported	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Region									
Asia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Europe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Middle East	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
North America	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
South and Central America	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 14.1.3 (Cont'd)
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
Height (cm)									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Height z-score [2]									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Weight (kg)									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Weight z-score [2]									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Table 14.1.3 (Cont'd)
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
BMI (kg/m2)									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
BMI z-score [2]									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Table 14.1.4
Disease History and Baseline Disease Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
Analysis PFIC Type [1]									
nt-PFIC2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
nt-PFIC2-IsBA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
nt-PFIC2-surg	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
t-PFIC2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC1-surg	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC4-surg	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
nt-PFIC2-het	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC1-het	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No-variant-found	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile; UDCA = ursodeoxycholic acid
Note: Percentages are 100*n/N, unless otherwise noted. Subjects with PFIC1 through PFIC6 all have the biallelic disease.
[1] nt-PFIC2 = non-truncated PFIC2 (primary cohort); nt-PFIC2-IsBA = non-truncated PFIC2 with low or fluctuating serum bile acids; nt-PFIC2-surg = non-truncated PFIC2 with a history of surgery; t-PFIC2 = truncated PFIC2; PFIC1-surg = PFIC1 with a history of surgery; PFIC4-surg = PFIC4 with a history of surgery; nt-PFIC2-het = non-truncated PFIC2 with heterozygosis; PFIC1-het = PFIC1 with heterozygosis; No-variant-found = No established variant linked to PFIC disease
[2] nt-PFIC2 = partial loss of BSEP function; t-PFIC2 = complete loss of BSEP function
Only applicable for PFIC2 subjects, with exception of one nt-PFIC2 subject (015002) with heterozygosis ABCB11 mutation; N/A for all other subjects.
[3] One subject (015002) had heterozygous ABCB11 mutation, and another (021006) had heterozygous ATP8B1 mutation.
[4] Partial dates were imputed based on the SAP.
[5] For the number and percent of subjects below and above the median baseline sBA level, the median is calculated separately for the Primary Cohort, PFIC Cohort, and All Subjects.
[6] PELD score is calculated for children <12 years of age at the baseline visit; MELD score is calculated for children 12 years or older at the baseline visit.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.1.4 (Cont'd)
Disease History and Baseline Disease Characteristics
Safety Population

Variable	Primary Cohort			PFIC Cohort			All Subjects		
Statistic or Category	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=93)
Analysis PFIC Type (genotype)									
PFIC2 (ABCB11) [2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
nt-PFIC2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
BSEP1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
BSEP2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
t-PFIC2 (BSEP3)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC1 (ATP8B1)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC3 (ABCB4)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC4 (TJP2)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PFIC6 (MYO5B)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Heterozygous variant [3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No-variant-found	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Liver masses detected at baseline									
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 14.1.4 (Cont'd)
Disease History and Baseline Disease Characteristics
Safety Population

Variable	Primary Cohort			PFIC Cohort			All Subjects		
Statistic or Category	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)
Time Since Original Diagnosis of PFIC (months) [4]									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xxx	xx, xxx	xx, xxx	xx, xxx	xx, xxx	xx, xxx	xx, xxx	xx, xxx	xx, xxx
Baseline UDCA Usage									
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Baseline Rifampicin Usage									
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Clinical Scratch Scale (CSS) Score									
n	xx	xx	xx	Xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 14.1.4 (Cont'd)
Disease History and Baseline Disease Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
Patient Impression of Severity (PIS)									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Caregiver Impression of Severity (CIS)									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 14.1.4 (Cont'd)
Disease History and Baseline Disease Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
ItchRO (Obs) 4-wk Morning Avg Severity Score									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
ItchRO (Pt) 4-wk Morning Avg Severity Score									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
ItchRO (Obs) 4-wk Evening Avg Severity Score									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
ItchRO (Pt) 4-wk Evening Avg Severity Score									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Table 14.1.4 (Cont'd)
Disease History and Baseline Disease Characteristics
Safety Population

Variable Statistic or Category	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
ItchRO (Obs) 4-wk Highest Daily Avg Severity Score									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
ItchRO (Pt) 4-week Highest Daily Avg Severity Score									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Total Serum Bile Acid (umol/L) [5]									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
< Median	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
≥ Median	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 14.1.4 (Cont'd)
Disease History and Baseline Disease Characteristics
Safety Population

Variable	Primary Cohort			PFIC Cohort			All Subjects		
Statistic or Category	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Overall (N=xx)

Repeat summary statistics for the following:

ItchRO (Obs & Pt) 4-wk avg frequency scores (6 variables); same order as for severity score
Alkaline Phosphate (U/L)
Aspartate Aminotransferase (U/L)
Alanine Aminotransferase (U/L)
Total Bilirubin (mg/dL)
Direct Bilirubin (mg/dL)
Fibroblast Growth Factor 19 (FGF-19) (ng/mL)
Autotaxin (ng/mL)
7 alpha-hydroxyl-4-cholesten-3-one (C4) (ng/mL)
25-Hydroxyvitamin D (ng/mL)
Alpha Tocopherol (mg/dL)
Prothrombin Intl. Normalized Ratio
Vitamin A (µg/dL)
GGT
Albumin (g/dL)
APRI
FIB-4
PELD [6]
MELD [6]

Table 14.1.5
Prior Medications/Therapies
Safety Population

ATC Preferred Term [1]	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
Number of Subjects Taking any Prior Medications	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ACT 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ACT 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc…									

Note: Percentages are 100*n/N.
[1] Medications were coded using World Health Organization Drug Dictionary (WHO-DD Enhanced version September 2019) ATC level 2 and Chemical Substance (generic name). Subjects were counted only once for each Anatomical Therapeutic Chemical (ATC) or Preferred Term. Medications that started prior to the first dose of study drug will be considered a prior treatment, whether or not they were stopped prior to the first dose of study drug. If a treatment started prior to the first dose of study drug and continues after the first dose of study drug, it was considered both prior and concomitant.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.1.6
Study Drug Compliance
Safety Population

Variable Statistic	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	Primary Cohort Overall (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	PFIC Cohort Overall (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)	All Subjects Overall (N=xx)
Compliance (%)									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD (SE)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
<80%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
80-<90%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
90-100%	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: Compliance (%) = 100* (Treatment duration in days - Number of days both morning and evening doses were missed) / Treatment duration in days), where Treatment duration (days) = Date of last dose of study drug – Date of first dose of study drug + 1 day. For subjects that are missing the date of last dose of study drug, the last known contact date is used to calculate treatment duration.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.1.1
Change from Baseline in ItchRO(Obs) Severity Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – Primary Cohort

Post-Baseline	Morning Score		Evening Score		Highest Daily Score	
Analysis Visit Time Period	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic [1]	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
Weeks 1-6						
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (CFB LS Mean = 0)	x.xxxx	x.xxxx	x.xxxx	x.xxxx	x.xxxx	x.xxxx
LS Mean Change from Placebo (SE)	x.xx (x.xxx)		x.xx (x.xxx)		x.xx (x.xxx)	
(95% CI for LS Mean Change from Placebo)	(x.xx, x.xx)		(x.xx, x.xx)		(x.xx, x.xx)	
p-value (Maralixibat LS Mean = Placebo LS Mean)	x.xxxx		x.xxxx		x.xxxx	

(Continue for Time Periods: Weeks 7-10, Weeks 11-14, Weeks 15-18, Weeks 19-22, Weeks 23-26, and Weeks 15-26 [2])

Abbreviations: LS = Least-squares; SE = standard error of the mean; CFB = change from baseline; CI = confidence interval
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction.
[2] Average of time periods Weeks 15-18, 19-22, and 23-26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.
Source: Reference Listings xx.x.x, xx.x.x

Programming Note: There is enough space to fit 2 time periods per page (based on output from t_mmrm.sas used on the 304 IA_NDA analysis).

Table 14.2.1.2
Change from Baseline in ItchRO(Obs) Severity Score
MMRM Model Effects
ITT Population – Primary Cohort

	Overall p-value [1]		
MMRM Model Effect	Morning Score	Evening Score	Highest Daily Score
Treatment Group	x.xxxx	x.xxxx	x.xxxx
Time Period	x.xxxx	x.xxxx	x.xxxx
Treatment Group x Time Period Interaction	x.xxxx	x.xxxx	x.xxxx
Baseline (Covariate)	x.xxxx	x.xxxx	x.xxxx
Baseline (Covariate) x Time Period Interaction	x.xxxx	x.xxxx	x.xxxx

[1] p-value for testing the statistical significance of each effect in the repeated measures model. Change from baseline were analyzed using a restricted maximum likelihood (REML)-based repeated-measures approach. An unstructured covariance structure was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors.
Source: Reference Listings xxxxxxx, xxxxxx

Table 14.2.2.1.1
Change from Baseline in ItchRO(Obs) Severity Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.1; change footnote [1] to:
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, baseline score-by-time period interaction, and PFIC type.

Table 14.2.2.1.2
Change from Baseline in ItchRO(Obs) Severity Score
MMRM Model Effects
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.2, but add a data row as the last row: "PFIC Type (Covariate)" and add in the p-values from the model

Table 14.2.2.2.1
Change from Baseline in Total sBA (µmol/L)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

	Primary Cohort		PFIC Cohort	
Analysis Visit Statistic [1]	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 2				
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (CFB LS Mean = 0)	x.xxxx	x.xxxx	x.xxxx	x.xxxx
LS Mean Change from Placebo (SE)	x.xx (x.xxx)		x.xx (x.xxx)	
(95% CI for LS Mean Change from Placebo)	(x.xx, x.xx)		(x.xx, x.xx)	
p-value (Maralixibat LS Mean = Placebo LS Mean)	x.xxxx		x.xxxx	
(Continue for analysis visits: Week 6, Week 10, Week 14, Week 18, Week 22, Week 26, and Weeks 18-26 [2])				

Abbreviations: LS = Least-squares; SE = standard error of the mean; CFB = change from baseline; CI = confidence interval
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit and treatment-by-visit interaction as well as the continuous fixed covariates of baseline score and baseline score-by-visit interaction. For the PFIC Cohort, PFIC Type is included in the model as an additional covariate.
[2] Average of Weeks 18, 22, and 26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.
Source: Reference Listings xx.x.x, xx.x.x

Programming Note: There is enough space to fit 2 time periods per page (based on output from t_mmrm.sas used on the 304 IA_NDA analysis).

Table 14.2.2.2.2
Change from Baseline in Total sBA (µmol/L)
MMRM Model Effects
ITT Population

MMRM Model Effect	Overall p-value [1]	
	Primary Cohort	PFIC Cohort
Treatment Group	x.xxxx	<0.0001
Time Point (Analysis Visit)	x.xxxx	x.xxxx
Treatment Group x Time Point Interaction	x.xxxx	x.xxxx
Baseline (Covariate)	x.xxxx	x.xxxx
Baseline (Covariate) x Time Point Interaction	x.xxxx	x.xxxx
PFIC Type (Covariate) [2]	NA	x.xxxx

[1] p-value for testing the statistical significance of each effect in the repeated measures model. Change from baseline were analyzed using a restricted maximum likelihood (REML)-based repeated-measures approach. An unstructured covariance structure was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors.
[2] For the PFIC Cohort, PFIC Type is included in the MMRM model as an additional covariate.
Source: Reference Listings xxxxxxx, xxxxxx

Table 14.2.2.3
Proportion of Responders
ITT Population

Responder Type Category	Primary Cohort		PFIC Cohort	
	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
ItchRO Responders [1]				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [3]	x.xxxx		x.xxxx	
sBA Responders [2]				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [3]	x.xxxx		x.xxxx	

Note: Percentages are 100*n/N.
[1] ItchRO responders are 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. For the purpose of determining response, the average severity score from the three 4-week periods (Weeks 15-18, 19-22, and 23-26) are used. A subject is defined as an ItchRO non-responder if the 4-week average baseline score is missing OR all three 4-week average (post-baseline) scores are missing.
[2] sBA responders are defined as a subject having an average sBA level of <102 µmol/L (applies only if baseline sBA level was ≥102 µmol/L), OR a ≤-75% average percent change from baseline. For the purpose of determining response, the average sBA value from Weeks 18, 22, and 26 values are used. A subject is defined as an sBA non-responder if the baseline sBA value is missing OR sBA values are missing at all 3 time points (i.e., Weeks 18, 22, and 26).
[3] p-values comparing maralixibat to placebo treatment groups are calculated using a Barnard's exact test.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.3.1.1
Change from Baseline in Morning ItchRO(Obs) Severity Score – Sibling Sensitivity Analysis
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1; add following Note, and change footnotes [1] and [2] to:
Note: The data from all enrolled subjects (including the 2 pairs of siblings) are used for primary efficacy analysis. The data for only 1 sibling is used for the sensitivity analysis. The choice of sibling is made at random before the database lock, as described in the SAP.
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, and baseline score-by-time period interaction. For the PFIC Cohort, PFIC Type is included in the model as an additional covariate.
[2] Average of time periods Weeks 15-18, 19-22, and 23-26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

Table 14.2.3.1.2
Change from Baseline in Morning ItchRO(Obs) Severity Score – Sibling Sensitivity Analysis
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2; change 'Time Point (Analysis Visit)' in 2nd data row to 'Time Period', and 'Time Period' in data rows 3 and 5 to 'Time Period'

Table 14.2.3.2
Change from Baseline in Morning ItchRO(Obs) Severity Score – Multiple Imputation Sensitivity Analysis
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1; add following Note, and change footnotes [1] and [2] (same as 14.2.3.1.1) to:
Note: Multiple imputation is based on a standard Missing at Random (MAR) imputation approach. The MAR imputation model imputes missing values using a regression-based multiple imputation model.
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, and baseline score-by-time period interaction. For the PFIC Cohort, PFIC Type is included in the model as an additional covariate.
[2] Average of time periods Weeks 15-18, 19-22, and 23-26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

Table 14.2.3.3
Change from Baseline in Morning ItchRO(Obs) Severity Score to Average of Last 12 Weeks – Tipping Point Sensitivity Analysis
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

		Primary Cohort		PFIC Cohort	
Shift Parameters for Maralixibat, Placebo	Statistic [1]	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
x.xx, x.xx	LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
	(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
	p-value (CFB LS Mean = 0)	x.xxxx	x.xxxx	x.xxxx	x.xxxx
	LS Mean Change from Placebo (SE)	x.xx (x.xxx)		x.xx (x.xxx)	
	(95% CI for LS Mean Change from Placebo)	(x.xx, x.xx)		(x.xx, x.xx)	
	p-value (Maralixibat LS Mean = Placebo LS Mean)	x.xxxx		x.xxxx	

(Continue for other shift parameters)

Abbreviations: LS = Least-squares; SE = standard error of the mean; CFB = change from baseline; CI = confidence interval
Note: Average of time periods Weeks 15-18, 19-22, and 23-26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction. For the PFIC Cohort, PFIC Type is included in the model as an additional covariate.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.3.4.1
Change from Baseline in Total sBA (µmol/L) – Sibling Sensitivity Analysis
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1; add Note:
Note: The data from all enrolled subjects (including the 2 pairs of siblings) are used for primary efficacy analysis. The data for only 1 sibling is used for the sensitivity analysis. The choice of sibling is made at random before the database lock, as described in the SAP.

Table 14.2.3.4.2
Change from Baseline in Total sBA (µmol/L) – Sibling Sensitivity Analysis
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.3.5
Change from Baseline in Total sBA (µmol/L) – Multiple Imputation Sensitivity Analysis
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1; add Note:
Note: Multiple imputation is based on a standard Missing at Random (MAR) imputation approach. The MAR imputation model imputes missing values using a regression-based multiple imputation model.

Table 14.2.3.5.2
Change from Baseline in Total sBA (µmol/L) – Multiple Imputation Sensitivity Analysis
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.3.6
Change from Baseline in Total sBA (µmol/L) to Average of Weeks 18, 22, and 26 – Tipping Point Sensitivity Analysis
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.3.3; change Note and footnote to:

Note: Average of Weeks 18, 22, and 26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit and treatment-by-visit interaction as well as the continuous fixed covariates of baseline score and baseline score-by-visit interaction. For the PFIC Cohort, PFIC Type is included in the model as an additional covariate.

Table 14.2.4.1.1
Change from Baseline in Morning ItchRO(Obs) Severity Score
Tabulation of Fitted Summary Statistics from MMRM
Per Protocol Population – Primary Cohort

Post-Baseline Analysis Visit Time Period Statistic [1]	Maralixibat (N=xx)	Placebo (N=xx)
Weeks 1-6		
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (CFB LS Mean = 0)	x.xxxx	x.xxxx
LS Mean Change from Placebo (SE)	x.xx (x.xxx)	
(95% CI for LS Mean Change from Placebo)	(x.xx, x.xx)	
p-value (Maralixibat LS Mean = Placebo LS Mean)	x.xxxx	
(Continue for Time Periods: Weeks 7-10, Weeks 11-14, Weeks 15-18, Weeks 19-22, Weeks 23-26, and Weeks 15-26 [2])		

Abbreviations: LS = Least-squares; SE = standard error of the mean; CFB = change from baseline; CI = confidence interval
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score and baseline score-by-time period interaction.
[2] Average of time periods Weeks 15-18, 19-22, and 23-26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.1.2
Change from Baseline in Morning ItchRO(Obs) Severity Score
MMRM Model Effects
Per Protocol Population – Primary Cohort

MMRM Model Effect	Overall p-value [1]
Treatment Group	x.xxxx
Time Period	x.xxxx
Treatment Group x Time Period Interaction	x.xxxx
Baseline (Covariate)	x.xxxx
Baseline (Covariate) x Time Period Interaction	x.xxxx

[1] p-value for testing the statistical significance of each effect in the repeated measures model. Change from baseline were analyzed using a restricted maximum likelihood (REML)-based repeated-measures approach. An unstructured covariance structure was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors.
Source: Reference Listings xxxxxxx, xxxxxx

Table 14.2.4.2.1
Change from Baseline in Total sBA (µmol/L)
Tabulation of Fitted Summary Statistics from MMRM
Per Protocol Population – Primary Cohort

Analysis Visit Statistic [1]	Maralixibat (N=xx)	Placebo (N=xx)
Week 2		
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (CFB LS Mean = 0)	x.xxxx	x.xxxx
LS Mean Change from Placebo (SE)	x.xx (x.xxx)	
(95% CI for LS Mean Change from Placebo)	(x.xx, x.xx)	
p-value (Maralixibat LS Mean = Placebo LS Mean)	x.xxxx	

(Continue for analysis visits: Week 6, Week 10, Week 14, Week 18, Week 22, Week 26, and Weeks 18-26 [2])

Abbreviations: LS = Least-squares; SE = standard error of the mean; CFB = change from baseline; CI = confidence interval
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, analysis visit and treatment-by-visit interaction as well as the continuous fixed covariates of baseline score and baseline score-by-visit interaction.
[2] Average of Weeks 18, 22, and 26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.2.2
Change from Baseline in Total sBA (µmol/L)
MMRM Model Effects
Per Protocol Population – Primary Cohort

MMRM Model Effect	Overall p-value [1]
Treatment Group	x.xxxx
Time Point (Analysis Visit)	x.xxxx
Treatment Group x Time Point Interaction	x.xxxx
Baseline (Covariate)	x.xxxx
Baseline (Covariate) x Time Point Interaction	x.xxxx

[1] p-value for testing the statistical significance of each effect in the repeated measures model. Change from baseline were analyzed using a restricted maximum likelihood (REML)-based repeated-measures approach. An unstructured covariance structure was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors.
Source: Reference Listings xxxxxxx, xxxxxx

Table 14.2.4.3.1
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)
Week 1		
n	xx	xx
Mean	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx
Week 2		
n	xx	xx
Mean	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx

(Continue for analysis visits: Week 3, 4, . . . , 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean;
Q1 = 25th percentile; Q3 = 75th percentile
Note: Baseline morning ItchRO(Obs) severity score is the average of 4-weekly (7-day) average scores in the period consisting of the 28 days immediately before the date of first dose of study drug.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.3.2
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Region
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

	Europe		Middle East		North America		South and Central America	
Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 1								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Week 2								
n	xx	Xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

(Continue for analysis visits: Week 3, 4, . . . , 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: There are no Primary Cohort subjects in Asia. Baseline morning ItchRO(Obs) severity score is the average of 4-weekly (7-day) average scores in the period consisting of the 28 days immediately before the date of first dose of study drug.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.3.3
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Age at Baseline
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

	1 to <6 Years		6 to <13 Years		13 to 18 Years	
Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 1						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Week 2						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

(Continue for analysis visits: Week 3, 4, . . . , 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: Age groups based in full years. Baseline morning ItchRO(Obs) severity score is the average of 4-weekly (7-day) average scores in the period consisting of the 28 days immediately before the date of first dose of study drug.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.3.4
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Sex
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

	Male		Female	
Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 1				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 2				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

(Continue for analysis visits: Week 3, 4, . . . , 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: Baseline morning ItchRO(Obs) severity score is the average of 4-weekly (7-day) average scores in the period consisting of the 28 days immediately before the date of first dose of study drug.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.3.5
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Race
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.3.2, replacing the 4 Regions with the 4 Races: White, Black or African American, American Indian or Alaska Native, and More than One Race; change 1st sentence in Note to "There is 1 Primary Cohort subject (038002) that did not report their race. No Primary Cohort subjects reported as Asian."

Table 14.2.4.3.6
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline Median sBA
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.3.4, replacing the 2 Sexes with the 2 baseline sBA categories: < Baseline Median sBA, ≥ Baseline Median sBA; add the following as the 1st few sentences to the Note: "Three subjects (002003, 028003, and 031002), all in the Primary Cohort, are missing baseline sBA samples. Only subjects in the Primary Cohort are used to calculate the baseline median sBA level. "

Table 14.2.4.3.7
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline UDCA Usage
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.3.4, replacing the 2 Sexes with the 2 baseline UDCA usage categories: Baseline UDCA Usage, No Baseline UDCA Usage; add abbreviation for UDCA: "UDCA = ursodeoxycholic acid" with other abbreviations; add the following as the 1st sentence to the Note:
"A subject reporting the use of UDCA, based on ATC Class Level 5 (chemical substance), with a start date on or prior to the first dose of study drug and either be ongoing or have a stop date on or after the first dose of study drug would be considered as using UDCA at baseline**."**

Table 14.2.4.3.8
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by Baseline Rifampicin Usage
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.3.4, replacing the 2 Sexes with the 2 baseline Rifampicin usage categories: Baseline Rifampicin Usage, No Baseline Rifampicin Usage; add the following as the 1st sentence to the Note:
"A subject reporting the use of Rifampicin, based on ATC Class Level 5 (chemical substance), with a start date on or prior to the first dose of study drug and either be ongoing or have a stop date on or after the first dose of study drug would be considered as using Rifampicin at baseline**."**

Table 14.2.4.3.9
Change from Baseline in Weekly Average Morning ItchRO(Obs) Severity Score by BSEP Type
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.3.4, replacing the 2 Sexes with the 2 BSEP types: BSEP 1. BSEP 2

Table 14.2.4.4.1
Change from Baseline in Total sBA (µmol/L)
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)
Week 2		
n	xx	xx
Mean	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx
Week 6		
N	xx	xx
Mean	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx

(Continue for analysis visits: Week 10, Week 14, Week 18, Week 22, and Week 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean;
Q1 = 25th percentile; Q3 = 75th percentile
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.4.2
Change from Baseline in Total sBA (µmol/L) by Region
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

	Europe		Middle East		North America		South and Central America	
Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 2								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Week 6								
n	xx	Xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

(Continue for analysis visits: Week 10, Week 14, Week 18, Week 22, and Week 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: There are no Primary Cohort subjects in Asia.
Source: Reference Listings xx.x.x, xx.x.x

Programming Notes: Add 'NE = not estimable' to abbreviations where applicable

Table 14.2.4.4.3
Change from Baseline in Total sBA (µmol/L) by Age at Baseline
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

	1 to <6 Years		6 to <13 Years		13 to 18 Years	
Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 2						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Week 6						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

(Continue for analysis visits: Week 10, Week 14, Week 18, Week 22, and Week 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: Age groups based in full years.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.4.4
Change from Baseline in Total sBA (µmol/L) by Sex
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

	Male		Female	
Analysis Visit Statistic	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 2				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 6				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

(Continue for analysis visits: Week 10, Week 14, Week 18, Week 22, and Week 26)

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.4.5
Change from Baseline in Total sBA (µmol/L) by Race
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.4.2, replacing the 4 Regions with the 4 Races: White, Black or African American, American Indian or Alaska Native, and More than One Race; change 1st sentence in Note to "There is 1 Primary Cohort subject (038002) that did not report their race. No Primary Cohort subjects reported as Asian."

Table 14.2.4.4.6
Change from Baseline in Total sBA (µmol/L) by Baseline Median sBA
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.4.4, replacing the 2 Sexes with the 2 baseline sBA categories: < Baseline Median sBA, ≥ Baseline Median sBA; add the following as the 1st few sentences to the Note: "Three subjects (002003, 028003, and 031002), all in the Primary Cohort, are missing baseline sBA samples. Only subjects in the Primary Cohort are used to calculate the baseline median sBA level."

Table 14.2.4.4.7
Change from Baseline in Total sBA (µmol/L) by Baseline UDCA Usage
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.4.4, replacing the 2 Sexes with the 2 baseline UDCA usage categories: Baseline UDCA Usage, No Baseline UDCA Usage; add abbreviation for UDCA: "UDCA = ursodeoxycholic acid" with other abbreviations; add the following as the 1st sentence to the Note:
"A subject reporting the use of UDCA, based on ATC Class Level 5 (chemical substance), with a start date on or prior to the first dose of study drug and either be ongoing or have a stop date on or after the first dose of study drug would be considered as using UDCA at baseline**."**

Table 14.2.4.4.8
Change from Baseline in Total sBA (µmol/L) by Baseline Rifampicin Usage
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.4.4, replacing the 2 Sexes with the 2 baseline Rifampicin usage categories: Baseline Rifampicin Usage, No Baseline Rifampicin Usage; add the following as the 1st sentence to the Note:
"A subject reporting the use of Rifampicin, based on ATC Class Level 5 (chemical substance), with a start date on or prior to the first dose of study drug and either be ongoing or have a stop date on or after the first dose of study drug would be considered as using Rifampicin at baseline**."**

Table 14.2.4.4.9
Change from Baseline in Total sBA (µmol/L) by BSEP Type
Descriptive Statistics by Analysis Week
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.4.4.4, replacing the 2 Sexes with the 2 BSEP types: BSEP 1. BSEP 2

Table 14.2.4.5.1
Change from Baseline in ALT (U/L)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1

Table 14.2.4.5.2
Change from Baseline in ALT (U/L)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.6.1
Change from Baseline in AST (U/L)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1

Table 14.2.4.6.2
Change from Baseline in AST (U/L)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.7.1
Change from Baseline in Total Bilirubin (mg/dL
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1

Table 14.2.4.7.2
Change from Baseline in Total Bilirubin (mg/dL)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.8.1
Change from Baseline in Direct Bilirubin (mg/dL)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1

Table 14.2.4.8.2
Change from Baseline in Direct Bilirubin (mg/dL)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.9.1
Change from Baseline in ALP (U/L)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1

Table 14.2.4.9.2
Change from Baseline in ALP (U/L)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.10.1
Change from Baseline in GGT (U/L)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1

Table 14.2.4.10.2
Change from Baseline in GGT (U/L)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.11.1
Change from Baseline in FIB-4
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1; add to Abbreviations: 'FIB-4 = fibrosis-4'; add Note: Note: FIB-4 is based on a subject's age in years at the time of sample collection.

Table 14.2.4.11.2
Change from Baseline in FIB-4
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.12.1
Change from Baseline in APRI
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1; add to Abbreviations: 'APRI = AST to platelet ratio index'

Table 14.2.4.12.2
Change from Baseline in APRI
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.13.1
Change from Baseline in PELD
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1; add to Abbreviations: 'PELD = pediatric end-stage liver disease'; add Note: Note: PELD score is calculated for children under 12 years of age at the baseline visit.

Table 14.2.4.13.2
Change from Baseline in PELD
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.14
Total sBA Shift from Baseline: Number and Proportion of Subjects
ITT Population

	Primary Cohort		PFIC Cohort		All Subjects	
Analysis Visit % Decrease from Baseline	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Week 2	nn	nn	nn	nn	nn	nn
>75% (large decrease)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
0 to 75% (decrease)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<0% (any increase)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs Placebo [1]	x.xxxx		x.xxxx		x.xxxx	
Week 6	nn	nn	nn	nn	nn	nn
>75% (large decrease)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
0 to 75% (decrease)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<0% (any increase)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs Placebo [1]	x.xxxx		x.xxxx		x.xxxx	
Week 10	nn	nn	nn	nn	nn	nn
>75% (large decrease)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
0 to 75% (decrease)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<0% (any increase)	xx (xx.x%)	x xx (xx.x%)	x xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs Placebo [1]	x.xxxx		x.xxxx		x.xxxx	

(Continue for analysis visits: Week 14, Week 18, Week 22, and Week 26)

Note: Percentages are 100*n/Number of subjects with non-missing change from baseline in total sBA values at each visit.
[1] p-value is calculated using a Cochran-Mantel-Haenszel (CMH) test.
Source: Reference Listing xx.x.x

Programming Note: nn is # of subjects with non-missing CFB in total sBA data. For these ordinal non-binary outcomes, the CMH test is used to take the ordinal nature of the variable into account.

Table 14.2.4.15
Number of Days Morning ItchRO(Obs) Severity Score ≤1
Over the Last 84 Study Days
ITT Population

	Primary Cohort		PFIC Cohort	
Statistic	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Mean	xx.x	xx.x	xx.x	xx.x
(95% CI for Mean)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Mean Change from Placebo	xx.x		xx.x	
(95% CI for Mean Change from Placebo)	(xx.x, xx.x)		(xx.x, xx.x)	
p-value (Maralixibat Mean = Placebo Mean [1]	x.xxxx		x.xxxx	

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile; CI = confidence interval
Note: ItchRO scores have a range from 0 to 4, with the higher score indicating increasing itch severity. Missing data during the 84-day period is treated using the most conservative approach (i.e., severity score >1).
[1] Student's 2 sample mean t-test, assuming unequal variances, is used to test for treatment differences. Satterthwaite's method for computing standard error of the mean of the difference is used.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.16
Number and Proportion of Subjects with Morning ItchRO(Obs) Severity Score ≤1 for >50% of Time Period
ITT Population

Post-Baseline Analysis Visit Time Period Category	Primary Cohort		PFIC Cohort	
	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Weeks 1-6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 7-10	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 11-14	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 15-18	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 19-22	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	

(Continue for Time Periods: Weeks 23-26, and Weeks 15-26)

Note: Percentages are 100*n/N. Days with missing data are not considered to have met the ≤1 criteria for that day. In computing the % of time the score is ≤1 within each time period for each subject, the denominator of the proportion includes all days within the specified time period (i.e., days with missing and non-missing data), while the numerator only includes those days that the score is 0 or 1.
[1] p-values comparing maralixibat to placebo treatment groups are calculated using a Barnard's exact test.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.17.1.1
Change from Baseline in ItchRO(Obs) Frequency Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.1

Table 14.2.4.17.1.2
Change from Baseline in ItchRO(Obs) Frequency Score
MMRM Model Effects
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.2

Table 14.2.4.17.2.1
Change from Baseline in ItchRO(Obs) Frequency Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.1; change footnote [1] to:
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, baseline score-by-time period interaction, and PFIC type.

Table 14.2.4.17.2.2
Change from Baseline in ItchRO(Obs) Frequency Score
MMRM Model Effects
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.2, but add a data row as the last row: "PFIC Type (Covariate)" and add in the p-values from the model

Table 14.2.4.18.1.1
Change from Baseline in ItchRO(Pt) Severity Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.1

Table 14.2.4.18.1.2
Change from Baseline in ItchRO(Pt) Severity Score
MMRM Model Effects
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.2

Table 14.2.4.18.2.1
Change from Baseline in ItchRO(Pt) Severity Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.1; change footnote [1] to:
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, baseline score-by-time period interaction, and PFIC type.

Table 14.2.4.18.2.2
Change from Baseline in ItchRO(Pt) Severity Score
MMRM Model Effects
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.2, but add a data row as the last row: "PFIC Type (Covariate)" and add in the p-values from the model

Table 14.2.4.19.1.1
Change from Baseline in ItchRO(Pt) Frequency Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.1

Table 14.2.4.19.1.2
Change from Baseline in ItchRO(Pt) Frequency Score
MMRM Model Effects
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.2

Table 14.2.4.19.2.1
Change from Baseline in ItchRO(Pt) Frequency Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.1; change footnote [1] to:
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, baseline score-by-time period interaction, and PFIC type.

Table 14.2.4.19.2.2
Change from Baseline in ItchRO(Pt) Frequency Score
MMRM Model Effects
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.2, but add a data row as the last row: "PFIC Type (Covariate)" and add in the p-values from the model

Table 14.2.4.20.1
Change from Baseline in Clinician Scratch Scale (CSS)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, adding Week 4; add Note:
Note: The CSS provides an assessment of itch severity. The clinician's assessment of the subject's pruritus will focus on scratching and visible damage to the skin as a result of scratching as observed by the physician. The CSS uses a 5-point scale, in which 0 designates no evidence of scratching and 4 designates cutaneous mutilation with bleeding, hemorrhage and scarring.

Table 14.2.4.20.2
Change from Baseline in Clinician Scratch Scale (CSS)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.21.1
Change from Baseline in Caregiver Impression of Severity (CIS)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, replacing Week 2 with Week 4; add Note:
Note: The CIS is designed to assess the caregiver's perception of itch severity of their child, using a 5-point scale, in which 0 designates no itch and 4 designates very severe itch. The questionnaire is administered with a recall period of 1 week.

Table 14.2.4.21.2
Change from Baseline in Caregiver Impression of Severity (CIS)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.22.1
Change from Baseline in Patient Impression of Severity (PIS)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, replacing Week 2 with Week 4; add Note:
Note: Subjects aged ≥9 years self-complete the PIS questionnaire. The PIS is designed to assess the subject's perception of their itch severity using a 5-point scale, in which 0 designates not feeling itchy at all and 4 designates feeling very, very itchy. The questionnaire is administered with a recall period of 1 week.

Table 14.2.4.22.2
Change from Baseline in Patient Impression of Severity (PIS)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

For next 6 EDQ(Obs) tables, add 'Abbreviations: EDQ(Obs) = Exploratory Diary Questionnaire (Observer)'

Table 14.2.4.23.1.1
Change from Baseline in EDQ(Obs) Severity Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.1; add following Note:
Note: Caregivers for all subjects aged <9 years complete the EDQ(Obs) instrument.

Table 14.2.4.23.1.2
Change from Baseline in EDQ(Obs) Severity Score
MMRM Model Effects
ITT Population – Primary Cohort

Programming Notes: Repeat Table 14.2.1.2

Table 14.2.4.23.2.1
Change from Baseline in EDQ(Obs) Severity Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.1; add Note and change footnote [1] to:
Note: Caregivers for all subjects aged <9 years complete the EDQ(Obs) instrument.
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, baseline score-by-time period interaction, and PFIC type.

Table 14.2.4.23.2.2
Change from Baseline in EDQ(Obs) Severity Score
MMRM Model Effects
ITT Population – PFIC Cohort

Programming Notes: Repeat Table 14.2.1.2, but add a data row as the last row: "PFIC Type (Covariate)" and add in the p-values from the model

Table 14.2.4.24.1
Change from Baseline in Morning EDQ(Obs) Sleep Disturbance Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, except use time periods as in Table 14.2.1.1, including updating 1st column header; add Note and update footnotes [1] and [2] to:
Note: Caregivers for all subjects aged <9 years complete the EDQ(Obs) instrument. Sleep disturbance is scored in the morning using a 5-point scale, in which 1 designates because of itch my child never had trouble staying asleep and 5 designates because of itch my child almost always has trouble staying asleep.
[1] Estimates are from a mixed model for repeated measures (MMRM) with change from baseline as the dependent variable and fixed categorical effects of treatment group, time period and treatment-by-time period interaction as well as the continuous fixed covariates of average baseline score, and baseline score-by-time period interaction. For the PFIC Cohort, PFIC Type is included in the model as an additional covariate.
[2] Average of time periods Weeks 15-18, 19-22, and 23-26 obtained from the MMRM as an equally weighted average of the 3 individual visit-specific estimates.

Table 14.2.4.24.2
Change from Baseline in Morning EDQ(Obs) Sleep Disturbance Score
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2; change 'Time Point (Analysis Visit)' in 2nd data row to 'Time Period', and 'Time Period' in data rows 3 and 5 to 'Time Period'

Table 14.2.4.25
Number and Proportion of Subjects with Improvement from Baseline in Morning EDQ(Obs) Sleep Disturbance Score
ITT Population

Post-Baseline Analysis Visit Time Period Category	Primary Cohort		PFIC Cohort	
	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Weeks 1-6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 7-10	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 11-14	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 15-18	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	
Weeks 19-22	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	

(Continue for Time Period: Weeks 23-26)

Abbreviations: EDQ(Obs) = Exploratory Diary Questionnaire (Observer)
Note: Percentages are 100*n/N. Caregivers for all subjects aged <9 years complete the EDQ(Obs) instrument. Sleep disturbance is scored in the morning using a 5-point scale, in which 1 designates because of itch my child never had trouble staying asleep and 5 designates because of itch my child almost always has trouble staying asleep. Improvement is defined as a change from baseline <0, using 4- or 6-week (for the first time period) average scores. A subject is defined as having no improvement (i.e., non-responder) for an analysis visit time period if the 4-week average baseline score is missing OR the average sleep score at the analysis visit is missing.
[1] p-values comparing maralixibat to placebo treatment groups are calculated using a Barnard's exact test.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.26
Number and Proportion of Subjects with Morning EDQ(Obs) Sleep Disturbance Scores ≤2 from Post-Baseline through Week 26
ITT Population

Post-Baseline Analysis Visit Time Period Category	Primary Cohort		PFIC Cohort	
	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Weeks 1-26	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
p-value vs. Placebo [1]	x.xxxx		x.xxxx	

Abbreviations: EDQ(Obs) = Exploratory Diary Questionnaire (Observer)
Note: Percentages are 100*n/N. Caregivers for all subjects aged <9 years complete the EDQ(Obs) instrument. Sleep disturbance is scored in the morning using a 5-point scale, in which 1 designates because of itch my child never had trouble staying asleep and 5 designates because of itch my child almost always has trouble staying asleep. Missing scores are treated as a non-responder (i.e., score >2).
[1] p-values comparing maralixibat to placebo treatment groups are calculated using a Barnard's exact test.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.2.4.27.1
Change from Baseline in PedsQL Total Scale Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, removing Week 2 and adding Week 4; add Abbreviations and Note:

Abbreviations: PedsQL = Pediatric Quality of Life Inventory

Note: PedsQL individual item scores (0-4 scale) are reverse-scored and linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQoL (less negative impact). If >50% of the items in the scale are missing, the scale score is not computed.

Table 14.2.4.27.2
Change from Baseline in PedsQL Total Scale Score
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2; add Abbreviations:

Abbreviations: PedsQL = Pediatric Quality of Life Inventory

Table 14.2.4.28.1
Change from Baseline in Height z-Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, adding Week 4; add Note:
Note: z-scores are based on a subject's sex and age at each analysis visit. For subjects less than 24 months of age, the World Health Organization (WHO) growth charts are used to derive z-scores. For subjects at least 24 months of age, the Center for Disease Control (CDC) growth charts are used to derive z-scores.

Table 14.2.4.28.2
Change from Baseline in Height z-Score
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.29.1
Change from Baseline in Weight z-Score
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, adding Week 4; add Note:
Note: z-scores are based on a subject's sex and age at each analysis visit. For subjects less than 24 months of age, the World Health Organization (WHO) growth charts are used to derive z-scores. For subjects at least 24 months of age, the Center for Disease Control (CDC) growth charts are used to derive z-scores.

Table 14.2.4.29.2
Change from Baseline in Weight z-Score
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.30.1
Percent Change from Baseline in Total sBA
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, changing 'CFB' to '% CFB' in 1st column

Table 14.2.4.30.2
Percent Change from Baseline in Total sBA
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.31.1
Change from Baseline in 7 Alpha-hydroxy-4-cholesten-3-one (C4), ng/mL
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, removing Weeks 2, 14, and 22; change footnote [2] to:
[2] Average of Weeks 18 and 26 obtained from the MMRM as an equally weighted average of the 2 individual visit-specific estimates.

Table 14.2.4.31.2
Change from Baseline in 7 Alpha-hydroxy-4-cholesten-3-one (C4), ng/mL
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.32.1
Change from Baseline in Fibroblast Growth Factor 19 (pg/mL)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, removing Weeks 2, 14, and 22; add 'Note: For analysis, one-half of the lower limit of quantitation (LLOQ=10.0 pg/mL) is used for values reported as <LLOQ.'; and change footnote [2] to:
[2] Average of Weeks 18 and 26 obtained from the MMRM as an equally weighted average of the 2 individual visit-specific estimates.

Table 14.2.4.32.2
Change from Baseline in Fibroblast Growth Factor 19 (pg/mL)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.33.1
Change from Baseline in Autotaxin (ng/mL)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1, removing Weeks 2, 14, and 22; change footnote [2] to:
[2] Average of Weeks 18 and 26 obtained from the MMRM as an equally weighted average of the 2 individual visit-specific estimates.

Table 14.2.4.33.2
Change from Baseline in Autotaxin (ng/mL)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.34.1
Change from Baseline in Albumin (g/dL)
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Programming Notes: Repeat Table 14.2.2.2.1

Table 14.2.4.34.2
Change from Baseline in Albumin (g/dL)
MMRM Model Effects
ITT Population

Programming Notes: Repeat Table 14.2.2.2.2

Table 14.2.4.35
Time to First Liver-Associated Event (Days)
ITT Population

	Primary Cohort		PFIC Cohort	
Kaplan-Meier Estimates [1]	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Number of Events (%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Number Censored (%) [2]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
25th Percentile	xx.x	xx.x	xx.x	xx.x
(95% CI for 25th Percentile)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Median	xx.x	xx.x	xx.x	xx.x
(95% CI for Median)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
75th Percentile	xx.x	xx.x	xx.x	xx.x
(95% CI for 75th Percentile)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
p-value [3]	x.xxxx		x.xxxx	
p-value [4]	x.xxxx		x.xxxx	

Abbreviations: CI = confidence interval
Note: Liver-associated events include partial external biliary diversion (PEBD) surgery, listing for liver transplantation, liver decompensation (i.e., hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis) events, hepatocellular carcinoma (HCC), and death.
[1] Estimates calculated using Kaplan-Meier product-limit survival curve methodology. Missing estimates are due to insufficient events.
[2] 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.
[3] p-value from a log-rank test, comparing maralixibat versus placebo.
[4] p-value from a Wilcoxon test, comparing maralixibat versus placebo.
Source: Reference Listing xx.x.x

Table 14.3.1
Maralixibat Exposure
Safety Population

Variable Statistic	Primary Cohort (N=xx)	PFIC Cohort (N=xx)	All Subjects (N=xx)
Average Daily Dose (µg/kg/day)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Total Dose (µg/kg)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Treatment Duration (days)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx

[Continue for: Treatment Exposure (days)]

Abbreviations: SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: Only subjects exposed to Maralixibat are included. Treatment duration (days) = Date of last dose of study drug – Date of first dose of study drug + 1 day. For subjects that are missing the date of last dose of study drug, the last known contact date is used to calculate treatment duration. Treatment exposure (days) = Treatment duration in days – Number of days both morning and evening doses were missed.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.3.2.1.1
Overall Summary of Treatment-Emergent Adverse Events
Safety Population

	Primary Cohort		PFIC Cohort		All Subjects	
Subjects with at Least One Treatment-Emergent:	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Categorized as Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Categorized as Severe and Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Permanent Study Drug Discontinuation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are 100*n/N. AEs are coded using MedDRA Version 22.1. Subjects who reported more than one adverse event (AE) within each category were only counted once. A treatment-emergent AE (TEAE) is defined as an AE that starts or deteriorates on or after the first dose of study drug and no later than 7 days following the last dose of study drug (for subjects not participating in the extension study) or reported through the Week 26/EOT visit (for subjects participating in the extension study). For subjects with > 7 days of study drug interruption/withdrawal, the definition of a TEAE considers both the date of the last dose prior to drug interruption and the actual last dose.
Source: Reference Listing xx.x.x

Table 14.3.2.1.2
Overall Summary of Treatment-Emergent Adverse Events by Age Group
Safety Population

Age Group: 1 to <6 years

	Primary Cohort		PFIC Cohort		All Subjects	
Subjects with at Least One Treatment-Emergent:	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Categorized as Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Categorized as Severe and Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Permanent Study Drug Discontinuation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are 100*n/N. AEs are coded using MedDRA Version 22.1. Subjects who reported more than one adverse event (AE) within each category were only counted once. A treatment-emergent AE (TEAE) is defined as an AE that starts or deteriorates on or after the first dose of study drug and no later than 7 days following the last dose of study drug (for subjects not participating in the extension study) or reported through the Week 26/EOT visit (for subjects participating in the extension study). For subjects with > 7 days of study drug interruption/withdrawal, the definition of a TEAE considers both the date of the last dose prior to drug interruption and the actual last dose.
Source: Reference Listing xx.x.x

Programming Note: Repeat table for the other 2 age groups: '6 to <13 years' and '13 to 18 years'; N should be the total # of subjects in each age group, cohort, and treatment group

Table 14.3.2.1.3
Overall Summary of Treatment-Emergent Adverse Events by Sex
Safety Population

Programming Note: Same shell as Table 14.3.2.1.2, replacing 'Age Group: xxxxx' at top of table with 'Sex: xxxx', repeating table for each sex (Male, Female))

Table 14.3.2.1.4
Overall Summary of Treatment-Emergent Adverse Events by Race
Safety Population

Programming Note: Same shell as Table 14.3.2.1.2, replacing 'Age Group: xxxxx' at top of table with 'Race: xxxx', repeating table for each race (American Indian or Alaska Native, Asian, Black or African American, White, More than one race, and Not Reported)

Table 14.3.2.2.1
Incidence of Treatment-Emergent Adverse Events
Safety Population

System Organ Class Preferred Term	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)
Number of Subjects with at Least One TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…						

Note: Percentages are 100*n/N. AEs are coded using MedDRA Version 22.1. At each level of summarization (System Organ Class and Preferred Term), subjects who reported more than one adverse event (AE) were only counted once.
Source: Reference Listing xx.x.x

Programming Note: SOC and PT are sorted alphabetically by SOC and descending frequency of PT within each SOC

Table 14.3.2.2.2
Incidence of Treatment-Emergent Adverse Events by Age Group
Safety Population

Age Group: 1 to <6 years

System Organ Class Preferred Term	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)
Number (%) of Subjects with at Least One TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…						

Note: Percentages are 100*n/N. AEs are coded using MedDRA Version 22.1. At each level of summarization (System Organ Class and Preferred Term), subjects who reported more than one adverse event (AE) were only counted once.
Source: Reference Listing xx.x.x

Programming Note: Repeat table for the other 2 age groups: '6 to <13 years' and '13 to 18 years'. N should be the total # of subjects in each age group, cohort, and treatment group.
SOC and PT are sorted alphabetically by SOC and descending frequency of PT within each SOC.

Table 14.3.2.2.3
Incidence of Treatment-Emergent Adverse Events by Sex
Safety Population

Programming Note: Same shell as Table 14.3.2.2.2, replacing 'Age Group: xxxxx' at top of table with 'Sex: xxxx', repeating table for each sex (Male, Female)

Table 14.3.2.2.4
Incidence of Treatment-Emergent Adverse Events by Race
Safety Population

Programming Note: Same shell as Table 14.3.2.2.2, replacing 'Age Group: xxxxx' at top of table with 'Race: xxxx', repeating table for each race (American Indian or Alaska Native, Asian, Black or African American, White, More than one race, and Not Reported)

Table 14.3.3.1
Incidence of Treatment-Emergent Serious Adverse Events
Safety Population

Programming Note: Same shell as Table 14.3.2.2.1

Table 14.3.3.2
Incidence of Treatment Related Adverse Events
Safety Population

Programming Note: Same shell as Table 14.3.2.2.1

Table 14.3.3.3
Incidence of Treatment Related Adverse Events Leading to Permanent Discontinuation of Study Drug
Safety Population

Programming Note: Same shell as Table 14.3.2.2.1

Table 14.3.3.4.1
Incidence of Events of Clinical Interest - Diarrhoea Events
Safety Population

Programming Note: Same shell as 14.3.2.2.1, adding at end of Note: "Refer to SAP Sec. 6.1.9 for the preferred terms included in the definition of each event of clinical interest."

Table 14.3.3.4.2
Incidence of Events of Clinical Interest – LSV Deficiency Events
Safety Population

Programming Note: Same shell as 14.3.2.2.1, adding at end of Note: "Refer to SAP Sec. 6.1.9 for the preferred terms included in the definition of each event of clinical interest."

Table 14.3.3.4.3
Incidence of Events of Clinical Interest – Elevated Transaminases
Safety Population

Programming Note: Same shell as 14.3.2.2.1, adding at end of Note: "Refer to SAP Sec. 6.1.9 for the preferred terms included in the definition of each event of clinical interest."

Table 14.3.3.4.4
Incidence of Events of Clinical Interest – Elevated Bilirubin
Safety Population

Programming Note: Same shell as 14.3.2.2.1, adding at end of Note: "Refer to SAP Sec. 6.1.9 for the preferred terms included in the definition of each event of clinical interest."

Table 14.3.4.1
Listing of Serious Adverse Events
Safety Population

Subject ID	Cohort [1]	Treatment Received [2]	System Organ Class/ Preferred Term/ Verbatim Term	TEAE?	Start Date (Study Day) [3]	End Date (Study Day) [3]	Event Duration (days)	Severity/ Relationship to Study Drug	Outcome/ Study Drug Action Taken	Serious?/Life Threatening?	Treatment Required
XXXXXX	Primary	600	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	Yes	DDMMMYYYY (xx)	DDMMMYYYY (xx)	xx	Moderate/ Not Related	xxxxxxxx/ xxxx xxx xxxxxxx	Yes/ No	None
XXXXXX	PFIC	Placebo	xxxxxxxxxxxxxxx xxxxx/ xxxxxxxxxx/ xxxxxxxxxxxxxx	No	DDMMMYYYY (xx)	DDMMMYYYY (xx)	xx	Severe/ Related	xxxxxxxx/ xxxx xxx xxxxxxx	Yes/ No	xxxxx; xxxxx

Note: AEs are coded using MedDRA Version 22.1. In determining treatment-emergent AEs (TEAEs) and study day, partial dates were imputed based on the SAP.
[1] Subject cohorts include Primary, PFIC, or Other. Subjects in the Primary Cohort, that are all a subset of the PFIC Cohort, are presented as 'Primary'.
[2] Treatment received at the start of the event, including dose (reported in units of µg/kg/day) for subjects on maralixibat. 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. NT = Not Treated (for AEs that started prior to 1st dose of study drug)
[3] Study Day is calculated relative to the date of the first dose of study drug.
Source: Reference Listing xx.x.x

Programming Note: *Sort AEs (within subject) by start date and then by end date; events that are ongoing would be listed after those with end dates (for those events with the same start date). For Treatment Required column, concatenate treatment required (e.g., Medication; Hospitalization). If "Other" is answered, concatenate the specify (e.g., Medication; Other: change settings in hearing aid). If subject was never dosed, Study Day will be reported as "NT".*

Table 14.3.4.2
Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug
Safety Population

Programming Note: Same shell as Table 14.3.4.1

Table 14.3.4.3
Listing of Deaths
Safety Population

Programming Note: Same shell as Table 14.3.4.1

Table 14.3.5.1
Summary of Safety Laboratory Data: Chemistry
Safety Population

< Lab Test (units) >

	Primary Cohort				PFIC Cohort			
Analysis Visit	Maralixibat (N=xx)		Placebo (N=xx)		Maralixibat (N=xx)		Placebo (N=xx)	
Statistic	Obs	CFB	Obs	CFB	Obs	CFB	Obs	CFB
Baseline	x		x		x		x	
n	xx		xx		xx		xx	
Mean	xx.x		xx.x		xx.x		xx.x	
(95% CI for Mean)	(xx.x, xx.x)		(xx.x, xx.x)		(xx.x, xx.x)		(xx.x, xx.x)	
SD (SE)	xx.xx (xx.xx)		xx.xx (xx.xx)		xx.xx (xx.xx)		xx.xx (xx.xx)	
Median	xx.x		xx.x		xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x		xx.x, xx.x		xx.x, xx	
Min, Max	xx, xx		xx, xx		xx, xx		xx, xx	
Week 2	x	x	x	x	x	x	x	X
N	xx	xx	xx	xx	xx	xx	xx	Xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
(95% CI for Mean)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

(Continue for each planned analysis visit: Week 6, Week 10, Week 14, Week 18, Week 22, and Week 26)

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: For analysis, one-half of the lower limit of quantitation (LLOQ) is used for values reported as <LLOQ.
[1] Anion Gap (mEq/L) = sodium (mEq/L) – chloride (mEq/L) – bicarbonate (mEq/L)
[2] Corrected Sodium (mEq/L) = sodium (mEq/L) + [0.002 x triglycerides (mg/dL)]
[3] Calculated Osmolality (mOsm/kg) = [2 x (sodium (mEq/L) + potassium (mEq/L))] + [glucose (mg/dL) / 18] + [BUN (mg/dL) / 2.8]
[4] Osmolar Gap (mOsm/kg) = measured osmolality (mOsm/kg) – calculated osmolality (mOsm/kg)
SOURCE: Listing x.x.x.x

Programming Note: Repeat for each test in lab panel, left justified at top of table (as listed in SAP Appendix 1, under SAFETY LABS), noting footnotes required for derived labs; Min and Max values for the following derived labs should be rounded, for presentation purposes, as follows: Anion Gap [1] (1 decimal), Corrected Sodium [2] (integer), Calculated Osmolality [3] (integer), and Osmolar Gap [4] (integer)

Table 14.3.5.2
Summary of Safety Laboratory Data: Hematology
Safety Population

Programming Note: Same shell as Table 14.3.5.1, replacing footnotes with:

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: For analysis, one-half of the lower limit of quantitation (LLOQ) is used for values reported as <LLOQ.
SOURCE: Listing x.x.x.x

Programming Note (cont'd): Repeat for each test in lab panel, left justified at top of table (as listed in SAP Appendix 1, under SAFETY LABS)

Table 14.3.5.3
Summary of Safety Laboratory Data: Lipid Panel
Safety Population

Programming Note: Same shell as Table 14.3.5.1, replacing footnotes with:

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: For analysis, one-half of the lower limit of quantitation (LLOQ) is used for values reported as <LLOQ.
SOURCE: Listing x.x.x.x

Programming Note (cont'd): Repeat for each test in lab panel, left justified at top of table (as listed in SAP Appendix 1, under SAFETY LABS, except for HDL-C which will only be presented in a subject listing)

Table 14.3.5.4
Summary of Safety Laboratory Data: Lipid Soluble Vitamins (LSV)
Safety Population

Programming Note: Same shell as Table 14.3.5.1, removing Week 2 except for INR, PT, and aPTT, and replacing footnotes with:

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: For analysis, one-half of the lower limit of quantitation (LLOQ) is used for values reported as <LLOQ. For concentrations reported as above the upper limit of quantitation (ULOQ), the ULOQ is used as the analysis value.
[1] 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)]
[2] Retinol:RBP Molar Ratio (mol/mol) = 0.0734 x retinol (µg/dL) / RBP (mg/dL)
SOURCE: Listing x.x.x.x

Programming Note (cont'd): Repeat for each test in lab panel, left justified at top of table (as listed in SAP Appendix 1, under SAFETY LABS), noting footnotes required for derived labs; Min and Max values for the 2 derived labs should be rounded, for presentation purposes, to 2 decimal places

Table 14.3.5.5
Summary of Safety Laboratory Data: Alpha-Fetoprotein (ng/mL)
Safety Population

Programming Note: Same shell as Table 14.3.5.1 except <u>remove</u> 'Lab Test: xxxx' before table; only present Baseline, Week 10, and Week 26, and replace footnotes with:

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: For analysis, one-half of the lower limit of quantitation (LLOQ) is used for values reported as <LLOQ.
SOURCE: Listing x.x.x.x

Table 14.3.5.6
Shift Table for Select Safety Laboratory Tests
Safety Population

Primary Cohort

Lab Test (Unit)/ Analysis Visit Post-Baseline	Baseline									
	Maralixibat (N=xx)					Placebo (N=xx)				
	Below	Within	Above	Missing	Total	Below	Within	Above	Missing	Total
25-Hydroxyvitamin D (ng/mL)										
Week 6										
Below	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Within	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Above	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(Continue for Weeks 10, 14, 18, 22, and 26)										
Alpha Tocopherol (mg/dL)										
Week 6										
Below	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Within	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Above	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
(Continue for following lab tests: Prothrombin Intl. Normalized Ratio, and Vitamin A (µg/dL)										

Note: For analysis, one-half of the lower limit of quantitation (LLOQ) is used for values reported as <LLOQ. For concentrations reported as above the upper limit of quantitation (ULOQ), the ULOQ is used as the analysis value.
Source: Reference Listing xx.x.x

Note to programmer: Repeat for 'PFIC Cohort'; start new page for each cohort and each lab test

Table 14.3.6.1
Summary of Subject Height, Weight, and BMI z-Scores
Safety Population

Programming Note: Same shell as Table 14.3.5.1 except change 'Lab Test: xxxx' to '<parameter> where parameter includes: Height z-score, Weight z-score, and BMI z-score; add Week 4, and replace footnotes with:

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
Note: z-scores are derived using a subject's age and sex. For subjects less than 24 months of age, WHO growth charts are used to derive z-scores. For subjects at least 24 months of age, CDC growth charts are used to derive z-scores.
SOURCE: Listing x.x.x.x

Table 14.3.6.2
Summary of Vital Signs
Safety Population

Programming Note: Same shell as Table 14.3.5.1 except change 'Lab Test: xxxx' to '<parameter> where parameter includes: Systolic BP (mmHg), Diastolic BP (mmHg), Heart Rate (bpm), Respiratory Rate (breaths/min), and Body Temperature (°C); add Week 4, and replace footnotes with:

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile
SOURCE: Listing x.x.x.x

Table 14.3.6.3.1
Summary of Electrocardiogram Parameters
Safety Population

Programming Note: Same shell as Table 14.3.5.1 except change 'Lab Test: xxxx' to '<parameter> where parameter includes: PR Interval (msec), QRS Duration (msec), QTcB Interval (msec), and QTcF Interval (msec); only include Baseline, Week 10, and Week 26, and replace footnotes with:

Abbreviations: Obs = observed values; CFB = change from baseline; CI = confidence interval; SD = standard deviation; SE = standard error of the mean; Q1 = 25th percentile; Q3 = 75th percentile; QTcB = QT interval corrected using Bazett's formula; QTcF = QT Interval corrected using Fridericia's formula
SOURCE: Listing x.x.x.x

Table 14.3.6.3.2
Summary of Electrocardiogram Interpretation
Safety Population

Analysis Visit Category	Primary Cohort		PFIC Cohort	
	Maralixibat (N=xx)	Placebo (N=xx)	Maralixibat (N=xx)	Placebo (N=xx)
Baseline	nn	nn	nn	nn
Abnormal – CS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal – NCS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 10	nn	nn	nn	nn
Abnormal – CS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal – NCS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 26	nn	nn	nn	nn
Abnormal – CS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal – NCS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Abbreviations: CS = Clinically Significant; NCS = Not Clinically Significant
Note: Percentages are 100*n/Number of subjects with ECG interpretation data at each visit.
Source: Reference Listing xx.x.x

Programming Note: nn is # of subjects with non-missing ECG data

Table 14.3.7
Concomitant Medications/Therapies
Safety Population

Programming Notes: Repeat Table 14.1.5 except for changing 'Prior' in 1st data row to 'Concomitant', and footnotes as below

Note: Percentages are 100*n/N.
[1] Medications were coded using World Health Organization Drug Dictionary (WHO-DD Enhanced version September 2019) ATC level 2 and Chemical Substance (generic name). Subjects were counted only once for each Anatomical Therapeutic Chemical (ATC) or Preferred Term. Any treatments continuing or starting after the first dose of study drug will be considered concomitant. If a treatment started prior to the first dose of study drug and continues after the first dose of study drug, it was considered both prior and concomitant.
Source: Reference Listings xx.x.x, xx.x.x

Table 14.4.1
Summary of Healthcare Utilization Measures
Safety Population

Healthcare Utilization Measure Statistic	Primary Cohort Maralixibat (N=xx)	Primary Cohort Placebo (N=xx)	PFIC Cohort Maralixibat (N=xx)	PFIC Cohort Placebo (N=xx)	All Subjects Maralixibat (N=xx)	All Subjects Placebo (N=xx)
Number of ER Visits [1]						
Number and % of Subjects	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Number of Occurrences	xx	xx	xx	xx	xx	xx
Number of PFIC-Related Hospitalizations [1]						
Number and % of Subjects	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Number of Occurrences	xx	xx	xx	xx	xx	xx
Length of Stay for Hospitalizations (days) [2]						
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
Median	x.x	x.x	x.x	x.x	x.x	x.x
Min, Max	x, x	x, x	x, x	x, x	x, x	x, x
Number of Days Caregiver Missed Work Due to Healthcare Resource Utilization Events [2]						
Mean (SD)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)	x.x (x.xx)
Median	x.x	x.x	x.x	x.x	x.x	x.x
Min, Max	x, x	x, x	x, x	x, x	x, x	x, x

Abbreviations: PFIC = progressive familial intrahepatic cholestasis; ER = emergency room; SD = standard deviation
Note: Percentages are 100*n/N. Data are presented across the entire post-baseline study period, between clinic visits from baseline through Week 27 Follow-up.
[1] Subjects that visit the Emergency Room and the visit results in the subject being admitted to the hospital will be counted in both the Number of Hospitalizations and the Number of ER Visits.
[2] For those subjects reporting PFIC-related hospitalizations, summary statistics on the number of days are presented.
Source: Reference Listing xx.x.x

Table 14.4.2
Summary of Plasma Sample Maralixibat Concentrations (ng/mL)
Safety Population

Analysis Visit	Primary Cohort		PFIC Cohort		All Subjects	
Sample Time Point	Maralixibat	Placebo	Maralixibat	Placebo	Maralixibat	Placebo
Statistic	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
Week 10						
Pre-Dose						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
(95% CI for Mean)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
CV (%)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Geometric Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Post-Dose						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
(95% CI for Mean)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
SD (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
CV (%)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Geometric Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

(Repeat for Analysis Visits: Week 14 and Week 26)

Abbreviations: CI = confidence interval; SD = standard deviation; SE = standard error of the mean; CV = coefficient of variation
Note: The lower limit of quantitation (LLOQ) is 0.250 ng/mL. For any concentration reported below this limit, a zero value is used in the calculation of summary statistics. Post-dose samples were drawn approximately 2.5 hours after the morning dose.
Source: Reference Listing xx.x.x

Sponsor	Mirum Pharmaceuticals Inc.
Protocol Title:	Randomized Double-blind Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Children with Progressive Familial Intrahepatic Cholestasis (PFIC) – MARCH-PFIC
Protocol Number:	MRX-502 (Amendment 4)
Premier Research PCN:	MIRU8967
Document Author:	Taryn Robertson
Document Version:	Final 1.0
Document Date:	13Oct2022

Listing Shells

PROGRAMMING NOTE FOR ALL LISTINGS (EXCEPT LISTING 16.2.2.1): Sort by Treatment (Maralixibat or Placebo), then PFIC Type (ordered according to the list below), then Subject ID (and Study Day, when applicable), placing Treatment in sub-title.

Present and sort by PFIC Type in the following order:

- ***nt-PFIC2***
- ***PFIC1***
- ***PFIC3***
- ***PFIC4***
- ***PFIC6***
- ***nt-PFIC2-het***
- ***nt-PFIC2-IsBA***
- ***nt-PFIC2-surg***
- ***t-PFIC2***
- ***PFIC1-het***
- ***PFIC1-surg***
- ***PFIC4-surg***
- ***No-variant-found***

Analysis Visit is presented in addition to Clinic Visit for all data that is available in a single ADaM dataset (ie, not for subject profile listings which merge data from across multiple ADaM datasets).

Listing 16.1.1	Subject Profile: Select Labs and Itch/Scratch Scores
Listing 16.1.2	Subject Profile: Pediatric Quality of Life Inventory – Total Scale and Summary Scores
Listing 16.1.3	Subject Profile: Efficacy and Safety Labs (Serum Bile Acid, Lipids, Lipid Soluble Vitamins, and Coagulation)
Listing 16.1.4	Subject Profile: Sodium and Lipid Soluble Vitamin Level Abnormalities
Listing 16.2.1	Analysis Populations and Siblings
Listing 16.2.2.1	Subject Disposition: Screen Failure Subjects Enrolled in Study
Listing 16.2.2.2	Subject Disposition and Completion: Intent-to-Treat Population
Listing 16.2.3.1	Randomized Subjects by Randomized Cohort and Phenotype
Listing 16.2.3.2	Subjects Where Randomized Cohort Conflicts with PFIC Type
Listing 16.3.1	Inclusion and Exclusion Criteria
Listing 16.3.2	Important Protocol Deviations
Listing 16.4.1	Demographics and Baseline Information
Listing 16.4.2	Long-Term Follow-Up Informed Consent and Disease Progression
Listing 16.4.3	Informed Consent
Listing 16.4.4	Medical History
Listing 16.4.5	Prior and Concomitant Medications/Therapies
Listing 16.5.1	Liver Imaging
Listing 16.5.2	Liver-Associated Events
Listing 16.5.3	Liver Transplant List
Listing 16.6.1	Study Drug Supplied and Compliance
Listing 16.6.2	Study Drug Exposure
Listing 16.6.3	Study Drug Accountability
Listing 16.7.1	Total Serum Bile Acid

Listing 16.7.2	Serum Bile Acid Subspecies
Listing 16.7.3	Clinician Scratch Score
Listing 16.7.4	Itch Reported Outcomes (Subject and Caregiver) Average Morning and Evening Scores
Listing 16.7.5	Exploratory Diary Questionnaire (Subject and Caregiver) Average Morning and Evening Scores
Listing 16.7.6.1	PIC and CIC
Listing 16.7.6.2	PIS and CIS
Listing 16.7.7	Efficacy Laboratory Tests
Listing 16.7.8	Height, Weight, and BMI z-Score
Listing 16.7.9	Sleep Disturbance
Listing 16.8.1	Adverse Events
Listing 16.8.2.1	Adverse Events of Clinical Interest: Diarrhoea Events
Listing 16.8.2.2	Adverse Events of Clinical Interest: Lipid Soluble Vitamin Deficiency Events
Listing 16.8.2.3	Adverse Events of Clinical Interest: Elevated Transaminases Events
Listing 16.8.2.4	Adverse Events of Clinical Interest: Elevated Bilirubin Events
Listing 16.8.3	Treatment Related Adverse Events
Listing 16.8.4.1	Serious Adverse Events
Listing 16.8.4.2	Serious Related Adverse Events
Listing 16.8.5	Adverse Events Leading to Study Drug Discontinuation
Listing 16.8.6	Severe Adverse Events
Listing 16.8.7	Adverse Events Resulting in Death
Listing 16.9.1	Vital Signs
Listing 16.9.2	Physical Examination
Listing 16.9.3	12-Lead Safety ECG
Listing 16.10.1	Clinical Laboratory Tests: Clinical Chemistry
Listing 16.10.2	Clinical Laboratory Tests: Hematology
Listing 16.10.3	Clinical Laboratory Tests: Urinalysis
Listing 16.10.4	Clinical Laboratory Tests: Lipid Soluble Vitamins
Listing 16.10.5	Clinical Laboratory Tests: Lipid Panel
Listing 16.10.6	Clinical Laboratory Tests: Hepatocellular Carcinoma Marker - Alpha-Fetoprotein (AFP)
Listing 16.10.7	Clinical Laboratory Tests: Timing of Sample Collection and Last Meal
Listing 16.10.8	Microbiology Tests
Listing 16.10.9	Pregnancy Tests
Listing 16.10.10	Plasma Sample Maralixibat Concentrations
Listing 16.11	Telephone Contact Log
Listing 16.12	Visit Dates and Type
Listing 16.13	Healthcare Utilization
Listing 16.14	COVID-19 Impact

Listing 16.1.1
Subject Profile: Select Labs and Itch/Scratch Scores
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex/ Country	Analysis Visit	Study Day [2]	MRX PFIC Rcvd [3]	sBA [4] (umol/L)	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL) Direct	Bilirubin (mg/dL) Total	C4 (ng/mL)	ATX (ng/mL)	PELD/ MELD [5]	APRI	FIB-4	CIC/ PIC [6]	CSS	PedsQL Parent Total Score	ItchRO Morning Avg. Severity Score [7] Obs [8]	ItchRO Morning Avg. Severity Score [7] Pt [9]
xxxxxx	xxxxxx	x/x/xxx	Baseline	-x	NT	xx.x	xx	xx	x.x	x.x	xx.x	xxxx	xx	x.x	xxx		x	xx.x	x.xx w	x.xx
			Week 2	xx	300	xx.x b	xx	xx	x.x	x.x	xx.x	xxxx	xx	x.x	xxx	x/x	x	xx.x	[8]	[8]
			Week 4	xx	600															

Continue for all analysis visits

Abbreviations: sBA = serum Bile Acid; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; C4 = 7 alpha-hydroxy-4- cholesten-3-one (C4); ATX = Autotaxin; PELD = pediatric end-stage liver disease; MELD = model for end-stage liver disease; APRI = AST to platelet ratio index; FIB-4 = fibrosis-4; CIC = Caregiver Impression of Change; PIC = Patient Impression of Change; CSS = Clinician Scratch Scale; PedsQL = Pediatric Quality of Life; ItchRO = Itch Reported Outcome; ARG = Argentina; AUT = Austria; BEL = Belgium; BRA = Brazil; CAN = Canada; COL = Columbia; DEU = Germany; FRA = France; GBR = United Kingdom; ITA = Italy; LBN = Lebanon; MEX = Mexico; POL = Poland; SGP = Singapore; TUR = Turkey; USA = United States; Obs = Observer; Pt = Patient

[1] Age (years) at Baseline.

[2] Study Day is calculated relative to the date of the first dose of study drug.

[3] Treatment received (MRX µg/kg BID) on the date of the assessment/sample collection or last MRX BID dose received if dose was missed or administered as QD. NT = not treated (pre-dose or Placebo dose)

[4] 'b' indicates ≥ 75% reduction from baseline (ie, CFB ≤ -75%) OR sBA < 102 umol/L.

[5] PELD is calculated for children < 12 years of age at the baseline visit; MELD is calculated for children ≥ 12 years of age at baseline.

[6] PIC is completed by subjects who are at least 9 years of age.

[7] ItchRO weekly scores calculated relative to first dose of study drug. For each post-baseline analysis visit, average score is calculated for the following periods: Week 1-6 (42 days), Weeks 7-10, 11-14, 15-18, 19-22, and 23-26. Average ItchRO score at baseline is calculated averaging the 4-weekly average scores before the first dose of study drug.

[8] 'w' indicates average ItchRO score change from baseline ≤ -1.0.

[9] ItchRO self-report is completed by subjects who are at least 9 years of age.

Programming Note: Use data from ADaM.ADLB, ADQS. Use raw values; for example, <0.10, not analysis value.

Listing 16.1.2
Subject Profile: Pediatric Quality of Life Inventory – Total Scale and Summary Scores
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex/ Country	Analysis Visit	Study Day [2]	Total Scale Score		Physical Health Summary Score		Psychosocial Health Summary Score		Multidimensional Fatigue Scale Score		Family Impact Total Scale Score	Parent Functioning Summary Score	Family Impact Summary Score
					Parent	Child	Parent	Child	Parent	Child	Parent	Child			
xxxxxx	xxxxxx	x/x/xxx	Baseline	-x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xxx.x
			Week 4	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
			Week 6	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
			Week 10	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
			Week 14	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
			Week 18	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

(Continue for all analysis visits)

Abbreviations: ARG = Argentina; AUT = Austria; BEL = Belgium; BRA = Brazil; CAN = Canada; COL = Columbia; DEU = Germany; FRA = France; GBR = United Kingdom; ITA = Italy; LBN = Lebanon; MEX = Mexico; POL = Poland; SGP = Singapore; TUR = Turkey; USA = United States

Note: Pediatric Quality of Life (PedsQL) self-report is measured in subjects who are 5 to 18 years of age. Individual item scores (0-4 scale) are reverse-scored and linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQoL (less negative impact). Total scale and summary scores are computed as the average score. If more than 50% of the items in the scale are missing, the scale score is not computed. For scoring each total scale and summary score, refer to SAP.

[1] Age (years) at Screening. The age-based questionnaires are based on age at screening.

[2] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: *Use data from ADaM.ADQS.*

Listing 16.1.3
Subject Profile: Efficacy and Safety Labs (Serum Bile Acid, Lipids, Lipid Vitamins, and Coagulation)
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex/ Country	Analysis Visit	Study Day [2]	sBA [3] (umol/L)	Lipids				Lipid Soluble Vitamins				Coagulation		
						CHOL (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	VITD (ng/mL)	VITA (µg/dL)	VITE (mg/dL)	RBP (mg/dL)	aPTT (sec)	PT (sec)	INR
xxxxx	xxxxxx	x/x/xxx	Baseline	-x	xx.x	xxx	xxx	xx	xxx	xx.x	xx.x	x.xx	xx.xx	xx.x	xx.x	x.x
			Week 2	xx	xx.x b	xxx	xxx	xx	xxx	xx.x	xx.x	x.xx	xx.xx	xx.x	xx.x	x.x
			Week 6	xx	xx.x	xxx	xxx	xx	xxx	xx.x	xx.x	x.xx	xx.xx	xx.x	xx.x	x.x
			Week 10	xx	xx.x	xxx	xxx	xx	xxx	xx.x	xx.x	x.xx	xx.xx	xx.x	xx.x	x.x
			Week 14	xx	xx.x	xxx	xxx	xx	xxx	xx.x	xx.x	x.xx	xx.xx	xx.x	xx.x	x.x
			(Continue for all analysis visits)													

Abbreviations: sBA = Serum Bile Acid; CHOL = Cholesterol; LDL = LDL Cholesterol; HDL = HDL Cholesterol; TG = Triglycerides; VITD = 25-Hydroxyvitamin D; VITA = Vitamin A; VITE = Alpha Tocopherol; RBP = Retinol Binding Protein; aPTT = Activated Partial Thromboplastin Time; PT = Prothrombin Time; INR = International Normalized Ratio; ARG = Argentina; AUT = Austria; BEL = Belgium; BRA = Brazil; CAN = Canada; COL = Columbia; DEU = Germany; FRA = France; GBR = United Kingdom; ITA = Italy; LBN = Lebanon; MEX = Mexico; POL = Poland; SGP = Singapore; TUR = Turkey; USA = United States
[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] 'b' indicates ≥ 75% reduction (ie, CFB ≤ -75%) OR sBA < 102 umol/L.

Programming Note: Use data from ADaM.ADLB. Responder indicator needs to be added for sBA (see footnote 4). Add abbreviations to 'Note:' as needed for missing labs

Listing 16.1.4
Subject Profile: Sodium and Lipid Soluble Vitamin Levels
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex/ Country	Analysis Visit	Study Day [2]	VITD (ng/ml)	VITA (ug/dL)	VITE (mg/dL)	Alpha Tocopherol/ CHOL + TG Ratio (mg/g) [3]	RBP (mg/dL)	Retinol: RBP Molar Ratio (mol/mol) [4]	International Normalized Ratio	Sodium (mEq/L)	Corrected Sodium (mEq/L) [5]
xxxxx	xxxxxx	x/M/xxx	Baseline	-x	xx.x	xx.x	x.xx	x.xx	x.xx	x.xx	x.x	xxx	xxx
			Week 2	xx	xx.x	xx.x	x.xx	x.xx	x.xx	x.xx	x.x	xxx	xxx
			Week 4	xxx	xx.x	xx.x	x.xx	x.xx	x.xx	x.xx	x.x	xxx	xxx

(Continue for all analysis visits)

Abbreviations: ARG = Argentina; AUT = Austria; BEL = Belgium; BRA = Brazil; CAN = Canada; COL = Columbia; DEU = Germany; FRA = France; GBR = United Kingdom; ITA = Italy; LBN = Lebanon; MEX = Mexico; POL = Poland; SGP = Singapore; TUR = Turkey; USA = United States; VITD = 25-Hydroxyvitamin D; VITA = Vitamin A; VITE = Alpha Tocopherol; CHOL = Cholesterol; TG = Triglycerides; RBP = Retinol Binding Protein
[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] Ratio (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 (ie, 0.1 mg/dL), half of the minimum quantitation limit is used as the analysis value.
[4] Molar Ratio (mol/mol) = 0.0734 x retinol (ug/dL) / RBP (mg/dL)
[5] Corrected Sodium (mEq/L) = sodium (mEq/L) + [0.002 x triglycerides (mg/dL)]

Programming Note: *Use data from ADaM.ADLB.*

Listing 16.2.1
Analysis Populations and Siblings
All Subjects

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Sibling in Study? [1]	Analysis Population		
			Safety	ITT	Per-Protocol
xxxxxx	XXXXXX		Yes	Yes	Yes
	XXXXXX	Yes	Yes	Yes	Yes
	XXXXXX	Yes	Yes	Yes	No
xxxxxx	XXXXXX		Yes	Yes	No

Abbreviation: ITT = Intent-to-Treat
Note: Safety population consists of all subjects who received at least 1 dose of study drug. ITT population consists of all randomized subjects. Per-protocol population consists of all subjects in the ITT population who receive at least 1 dose of study drug and do not have any important protocol violations or deviations that have a potential impact on the efficacy analysis.
[1] Siblings are assigned in a blinded manner to the same treatment arm. Each sibling is considered for the Safety, ITT, and Per-Protocol populations. One sibling within a family is considered for a sensitivity analysis on the primary and key secondary efficacy endpoints for the primary and PFIC cohorts in the ITT Population. The choice of sibling to use in the sensitivity analysis is made at random, unless only 1 sibling is evaluable in the specific cohort and ITT Population and the other sibling is not. In this case, the evaluable sibling will be used in sensitivity analyses.

Programming Note: *Use data from ADaM.ADSL*

Listing 16.2.2.1
Subject Disposition
Screen Failure Subjects Enrolled in Study

Subject	Protocol Criteria Version	Date Screened	Screen Failure Reason
XXXXXX	Amendment 2 – 22NOV2019	DDMMMYYYY	EXCL08: XXXXXXXXXXXXXXXXXXXXXXXX INCL05: XXXXXXXXXXXXXXXXXXXXXXXX
XXXXXX	xxxxxxxxxxxx	DDMMMYYYY	INCL02: XXXXXXXXXXXXXXXXXXXXXXXX
XXXXXX	xxxxxxxxxxxx	DDMMMYYYY	OTHER: XXXXXXXXXXXXXXXXXXXXXXXX
XXXXXX	xxxxxxxxxxxx	DDMMMYYYY	XXXXXX: XXXXXXXXXXXXXXXXXXXXXXXX

Programming Note: *Only include subjects that were screen failures but were enrolled in the study, regardless of if the Sponsor granted a waiver. Use data from CRF.IE, CRF.SFR and CRF.STATFRM. For Screen Failure Reason, use CRF.IE.IENUM || ': ' || CRF.IE.IEREAS. If CRF.SFR.SFREAS = OTHER then Reason = CRF.SFR.SFREAS||': '||CRF.SFR.SFREASOT.*

Listing 16.2.2.2
Subject Disposition and Completion
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Date Screened	Date Enrolled	Status	Date of Discon-tinuation/ Completion	Specify Reason for Discontinuation from Study	Enroll in MRX 503?	Max Dose [1]	Tol. Min. Dose?/ LTFU?	Date of First Dose	Date of Last Dose (Study Day)	Date of Last Contact (Study Day) [2]
xxxxx	xxxxxx	DDMMMYYYY	DDMMMYYYY	Comp	DDMMMYYYY		Yes	600	Yes/ Yes	DDMMMYYYY	DDMMMYYYY (xx)	DDMMMYYYY (xx)
	xxxxxx	DDMMMYYYY	DDMMMYYYY	Disc	DDMMMYYYY	XXXXXXXXXXXXXX	No	300	Yes/ No	DDMMMYYYY	DDMMMYYYY (xx)	DDMMMYYYY (xx)
xxxx	xxxxxx	DDMMMYYYY	DDMMMYYYY	Disc	DDMMMYYYY		No	450	Yes/ No	DDMMMYYYY	DDMMMYYYY (xx)	DDMMMYYYY (xx)

Abbreviations: Comp = Completed; Disc = Discontinued; Max = Maximum; Tol. Min. Dose? = Did Subject Tolerate Minimum Drug Dose?; LTFU = Willing to provide Informed Consent and Assent as applicable for Long-Term Follow-Up Period?
Note: Study Day is calculated relative to the date of the first dose of study drug.
[1] Maximum dose presented in units of µg/kg/day.
[2] Completed only if subject is lost to follow-up.

Programming Note: *If subject discontinues the study prematurely for Reason=AE, Physician Decision, Protocol Violation, Withdrawal of Consent, or Other, then Reason for d/c is DS.DSTERM concatenated with DS.DSREASSP (e.g., Other: Family Emergency). If DS.DSTERM = Death then Reason for d/c is DS.DSTERM concatenated with DS.DSDEATH. If subject discontinues the study due to Lost to follow-up then Reason=Lost to follow-up concatenated with the DS.DSLFCOMT field (e.g., Lost to follow-up: xxxxxxxxxxxxxx). Date of First Dose pulled from CRF.SDFD. Use data from CRF.DS, SDFD and STATFRM.*

Listing 16.2.3.1
Randomized Subjects by Randomized Cohort and Phenotype
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

				From Dummy Rand File				PFIC Type From Enrollment Log		Analysis			Mutation 1				Mutation 2				
Randomized Phenotype	Mutation in Gene	Subject	Treatment Start Date	Rand. Date	Rand. Num.	Trtmt	Strata	At Screening	At Randomization	BSEP Pheno.	PFIC Type	BSEP Pheno.	cDNA	Protein	BSEP	Zyg.	cDNA	Protein	BSEP	Zyg.	Other Mutation
PFIC2 - Primary Cohort	ABCB11	xxxxxx	DDMMYYYY	DDMMYYYY	xxxx	MRX	PFIC2	PFIC2 - Primary Cohort	PFIC2 - Primary Cohort	BSEP 2	nt-PFIC2	nt	xxxxxxxx	xxxxxxxx xxxxx	BSEP2	HET	xxxxxxxx xx	xxxxxxxx xx	BSEP2	HET	
		xxxxxx	DDMMYYYY	DDMMYYYY	xxxx	MRX	PFIC2	PFIC2 - Supplemental Cohort	PFIC2 - Primary Cohort	BSEP 2	nt-PFIC2	nt	xxxxxxxx xxxxx	xxxxxxxx xxxxxxxx xxxxxxxx xx	BSEP3	HET	xxxxxxxx xxxxxxxx xx	xxxxxxxx xxxxx	BSEP2	HET	
	xxxxx	xxxxxx	DDMMYYYY	DDMMYYYY	xxxx	MRX	PFIC2	PFIC2 - Primary Cohort	PFIC2 - Primary Cohort		No-variant-found	NA			NA	HOM				HOM	

Abbreviations: Rand = Randomization; Trtmt = Treatment; BSEP = bile salt excretion pump; Pheno = Phenotype; cDNA = complementary DNA; Zyg = Zygocity; t = truncated; nt = not truncated; HET = Heterozygous; HOM = Homozygous; NA = not applicable

Note: Sample is used to provide a full characterization and documentation of the mutation type in support of the diagnosis of PFIC. Mutation in Gene data is collected at Screening visit.

Programming Note: *Use data from CRF.RAND, ADSL, CRF.CPGR.*

Listing 16.2.3.2
Subjects Where Randomized Cohort Conflicts with PFIC Type
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

				From Dummy Rand File				PFIC Type From Enrollment Log		Analysis			Mutation 1				Mutation 2				
Randomized Phenotype	Mutation in Gene	Subject	Treatment Start Date	Rand. Date	Rand. Num.	Trtmt	Strata	At Screening	At Randomization	BSEP Pheno.	PFIC Type	BSEP Pheno.	cDNA	Protein	BSEP	Zyg.	cDNA	Protein	BSEP	Zyg.	Other Mutation
PFIC2 - Primary Cohort	ABCB11	xxxxxx	DDMMYYYY	DDMMYYYY	xxxx	MRX	PFIC2	PFIC2 - Primary Cohort	PFIC2 - Primary Cohort	BSEP 2	nt-PFIC2	nt	xxxxxxxx	xxxxxxxx xxxxx	BSEP2	HET	xxxxxxxx xx	xxxxxxxx xx	BSEP2	HET	
		xxxxxx	DDMMYYYY	DDMMYYYY	xxxx	MRX	PFIC2	PFIC2 - Supplemental Cohort	PFIC2 - Primary Cohort	BSEP 2	nt-PFIC2	nt	xxxxxxxx xxxxx	xxxxxxxx xxxxxxxx xxxxxxxx xx	BSEP3	HET	xxxxxxxx xxxxxxxx xx	xxxxxxxx xxxxx	BSEP2	HET	
	xxxxx	xxxxxx	DDMMYYYY	DDMMYYYY	xxxx	MRX	PFIC2	PFIC2 - Primary Cohort	PFIC2 - Primary Cohort		No-variant-found	NA			NA	HOM				HOM	

Abbreviations: Rand = Randomization; Trtmt = Treatment; BSEP = bile salt excretion pump; Pheno = Phenotype; cDNA = complementary DNA; Zyg = Zygocity; t = truncated; nt = not truncated; HET = Heterozygous; HOM = Homozygous; NA = not applicable
Note: Sample is used to provide a full characterization and documentation of the mutation type in support of the diagnosis of PFIC. Mutation in Gene data is collected at Screening visit.

Programming Note: *Use data from CRF.RAND, ADSL, CRF.CPGR.*

Listing 16.3.1
Inclusion and Exclusion Criteria
All Subjects

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Protocol Criteria Version	Meet All Eligibility Criteria?	Criteria Not Met	Reason Eligibility Criteria Not Met
xxxx	XXXXXX	Original – 14MAR2019	No	Excl04	xxxxxxxxxxxxxxx
	XXXXXX	Amendment 1 – 29APR2019	No	Excl04	xxxxxxxxxxxxxx
xxxxx	XXXXXX	Amendment 2 – 22NOV1029	Yes		
	XXXXXX	Amendment 3 – 16JUN2020	Yes		

Programming Note: *Use CRF.IE.IEPVER for Protocol Criteria Version. See IEVER_ format in the eCRF document for proper decoding. Use data from CRF.IE.*

Listing 16.3.2
Important Protocol Deviations
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Event Date (Study Day) [1]	Event Report Date (Study Day) [1]	Excl from PP Pop?	Event Type	Description	Action Taken	Comments	Sponsor Prior Approval?	Date Approved
xxxxx	XXXXXX	DDMMMYYYY (xx)	DDMMMYYYY (xx)	Y	Study/Protocol Procedure	xxxxxxxxxxxxxxx xxxxxxx	xxxx xxxxxxxx	xxxxxx	Yes	DDMMMYYYY
		DDMMMYYYY (xx)	DDMMMYYYY (xx)		Dosing Error (specify)	xxxxxxxxxxxxxxxxxx xxxx	xxxxxxxxxx	xxxxxxxx xxxxx	No	
		DDMMMYYYY (xx)	DDMMMYYYY (xx)		Dosing Error (specify)	xxxxxxxxxxxxxxxx xxxxx xxx	xxxxxxxxx	xxxx	No	
		DDMMMYYYY (xx)	DDMMMYYYY (xx)		Dosing Error (specify)	xxxxxxxxxxxx xxxxxxxxx	xxxxxxxxxx	xxxxxx xxx xxxx	No	
	XXXXXX	DDMMMYYYY (xx)	DDMMMYYYY (xx)	X	Dosing Error (specify)	xxxxxxxxxxxxxxx xxxxxx	xxxxxxxxx	xxx xxxxx	No	
xxxxx	XXXXXX	DDMMMYYYY (xx)	DDMMMYYYY (xx)		Inclusion/Exclusion Criteria	x xxxxxxx xxxxxxxxx	xxx xxxxxxx	xxxxx xxxxxxxxx	No	
		DDMMMYYYY (xx)	DDMMMYYYY (xx)		Dosing Error (specify)	xxxxxxxxxxxxx	xxxxxxxx	xxxxxxx xxxxx	No	

Abbreviations: Excl from PP Pop? = Subject Excluded from Per-Protocol Population?
[1] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: *Use data from SDTM.DV and SDTM.SUPPDV. This listing only includes those deviations which are identified as "Important" or "Important – Non Evaluable". Present 'Y' or 'N' in the Excl from PP Pop? column.*

Listing 16.4.1
Demographics and Baseline Information
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age at Consent (Years, Months) [1]	Age at Baseline (Years, Months) [1]	Country	Sex	Baseline Weight (kg)	Baseline Height (cm)	Baseline BMI (kg/m2)	Ethnicity	Race	ItchRO in Paper?	eDiary Restrictions
xxxxx	XXXXXX	10, 4	10, 5	GBR	Male	xx.x	xxx	xx.x	Hispanic or Latino	White	No	No
	XXXXXX	1, 11	2, 0	USA	Female	xx.x	xxx	xx.x	Not Hispanic or Latino	Asian	No	No
xxxxx	XXXXXX	5, 5	5, 7	FRA	Female	xx.x	xxx	xx.x	Not Hispanic or Latino	Black or African American	No	No

Abbreviations: ARG = Argentina; AUT = Austria; BEL = Belgium; BRA = Brazil; CAN = Canada; COL = Columbia; DEU = Germany; FRA = France; GBR = United Kingdom; ITA = Italy; LBN = Lebanon; MEX = Mexico; POL = Poland; SGP = Singapore; TUR = Turkey; USA = United States; BMI = body mass index; ItchRO = Itch Reported Outcomes
[1] The subject's age at Screening is used to determine the appropriate age category for the ItchRO, Exploratory Diary Questionnaire, Patient Impression of Severity and PedsQL instruments.

Programming Note: *For multiple races, concatenate using ', ' as the delimiter. Use data from CRF.DM and AGE.*

Listing 16.4.2
Long-Term Follow-Up Informed Consent and Disease Progression
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Date of LTFU Parental Informed Consent	Date of LTFU Informed Assent [1]	Date of LTFU Adult Informed Consent [2]	Timepoint	Disease Progression Assessment Performed?	Reason Not Assessed	Date of Assessment	Occurrence Of Disease Progression?	Outcome	Increase in Concomitant Medications?
xxxxx	XXXXXX	DDMMMYYYY	NA	NA	Annual	Yes		DDMMMYYYY	Yes: xxxxxxxxxxxxxxx xxxxxxxxxxxxxx	PEBD Surgery	Yes
	XXXXXX	DDMMMYYYY	NA	NA	Unscheduled	Yes		DDMMMYYYY	No		No
xxxxx	XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	xxxxxxxxx	No	xxxxxxxxxxxxxxxxxx xxxxxxxxxx				No

Abbreviations: LTFU = long-term follow-up; NA = not applicable
[1] Assent is not applicable if the subject is younger than 18 years of age or age of consent at the time of consent.
[2] Adult Informed Consent is applicable if subject turned 18 years old or the age of consent during study participation.

Programming Note: *For Occurrence of Disease Progression, if CRF.DP.DPORRES = YES then concatenate DPORRES||': '||DPSPEC. For Outcome, if CRF.DP.DPOUTO = OTHER then concatenate 'OTHER: '||DPOUTOSP. Use data from CRF.DP.*

Listing 16.4.3
Informed Consent
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Date of Parental Informed Consent	Date of Informed Assent [1]	Subject Turn 18 or Age of Consent?/ Sign AIC?	Date of AIC [2]	Re-consented For Major Protocol Amendment?	Re-consent Type	Re-consent Date	Re-consent Protocol Version
xxxxx	XXXXXX	DDMMMYYYY	NA	No	NA	Yes	Parental/Caregiver Informed Consent	DDMMMYYYY	Amendment 1C – 05AUG2019
	XXXXXX	DDMMMYYYY	DDMMMYYYY	No	NA	xx			
xxxxx	XXXXXX	DDMMMYYYY	NA	Yes/Yes	DDMMMYYYY	xx			

Abbreviation: AIC = Adult Informed Consent
[1] Assent is not applicable if the subject is younger than 18 years of age or age of consent at the time of consent.
[2] Adult Informed Consent is applicable if subject turned 18 years old or the age of consent during study participation.

Programming Note: *Use data from CRF.DM, ICR and AIC.*

Listing 16.4.4
Medical History
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Any History?	System Organ Class	Preferred Term	Verbatim Term	Start Date	End Date
xxxxx	XXXXXX	Yes	XXXXXXXXXXXXXXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXXX	DDMMMYYYY	ONGOING
	XXXXXX	No					
	XXXXXX	Yes	XXXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXX	XXXXXXXXXXX	YYYY	MMMYYYY
			XXXXXXXXXXXXXXXXX	XXXXXXXXXXXXX	XXXXXXXXXX	MMMYYYY	ONGOING
xxxxx	XXXXXX	Yes	XXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXX	XXXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY

Note: Events coded using MedDRA version 22.1.

Programming Note: *Sort medical histories (within subject) by SOC, PT and Verbatim Term. If event is marked as Ongoing, then put "ONGOING" for End Date. Do not include 'UN' or 'UNK' in dates. If entire start or end date is missing then report as 'Unknown'. Use data from CRF.MH.*

Listing 16.4.5
Prior and Concomitant Medications/Therapies
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Date of Informed Consent	Any Meds?	Ongoing At Time Of IC [1]	Anatomic Therapeutic Class/ Preferred Term/ Verbatim Term	Start Date/ End Date	Indication	Dose (Unit)/ Route/ Frequency
xxxxx	XXXXXX	DDMMMYYYY	Yes	Yes	XXXXXXXXXX/ XXXXXX/ XXXXXXXXXXXXXXXXXX	DDMMMYYYY/ ONGOING	XXXXXXXXXXXX	XXXX (XXXX)/ XXXXXXX/ XXXXXXX
	XXXXXX	DDMMMYYYY	No					
xxxxx	XXXXXX	DDMMMYYYY	Yes	Yes	XXXXXXXXXX/ XXXXXX/ XXXXXXXXXXXXXXXXXX	DDMMMYYYY/ ONGOING	XXXXXXXXXXXX	XXXX (XX)/ XXXXXXX/ XXXXXXX
				No	XXXXXXXXXX/ XXXXXX/ XXXXXXXXXXXXXXXXXX	DDMMMYYYY/ DDMMMYYYY	XXXXXXXXXXXX	XXXX (XXXX)/ XXXXXXX/ XXXXXXX

Abbreviation: IC = Informed Consent
Note: Medication coded using WHO-DD (Enhanced version September 2019), Anatomic Therapeutic Class (ATC) Level 2. Preferred term is ATC Level 5.
[1] Indicates whether the medication was ongoing at the time of Informed Consent. Medications that are stopped prior to the time of informed consent are not recorded. Only therapies administered for liver disease should be captured prior to baseline.

Programming Note: *Sort medications (within subject) by start date and then by end date. For any field where answer is "Other", concatenate the specify (e.g., OTHER: mmol) . Use data from CRF.CM.*

Listing 16.5.1
Liver Imaging
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Method of Liver Imaging	Date of Imaging	Masses Observed?	If Masses Observed, Specify	Masses in the Liver?	If Masses in the Liver, Specify
xxxxx	XXXXXX	Ultrasound	DDMMMYYYY	Yes	XXXXXX		
		Ultrasound	DDMMMYYYY	No			
	XXXXXX	Ultrasound	DDMMMYYYY			Yes	XXXXXXXXX
		Ultrasound	DDMMMYYYY			Yes	XXXXXXXX
	XXXXXX	MRI	DDMMMYYYY	No			
xxxxx	XXXXXX	Ultrasound	DDMMMYYYY			No	

Programming Note: *Use data from CRF.IM where formnam = IM and IM2.*

Listing 16.5.2
Liver-Associated Events
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Liver-Associated Event Reported?	Event	Event Start Date (Study Day) [1]
xxxxx	XXXXXX	No		
	XXXXXX	Yes	OTHER: xxxxxxxxxxxxxxx	DDMMMYYYY (xx)
xxxxx	XXXXXX	Yes	PEBD SURGERY	DDMMMYYYY (xx)

[1] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: *Use data from CRF.LAE.*

Listing 16.5.3
Liver Transplant List
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Placed on Liver Transplant List?	Date Placed On Liver Transplant List	Still on Liver Transplant List?	Reason for Removal	Date Removed From Liver Transplant List
xxxxx	XXXXXX	No				
	XXXXXX	Yes	DDMMMYYYY	Yes		
xxxxx	XXXXXX	Yes	DDMMMYYYY	No	xxxxxxxxxxxxxxxxxxxxxxxx	DDMMMYYYY

Programming Note: *Use data from CRF.LT.*

Listing 16.6.1
Study Drug Supplied and Compliance
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Study Drug Quantity Sufficient?	Study Drug Supplied via Shipment?	Study Drug Taken as Prescribed?	Reason Not Fully Supplied	Bottle ID Numbers	Date of Dosing Error		Type of Dosing Error	Comments	Compliance % [2]
							Start (Study Day) [1]	End (Study Day) [1]			
xxxxx	XXXXXX	Yes	No	No		xxxxx, xxxxx	DDMMMYYYY (xx)	DDMMMYYYY (xx)	XXXXXX	XXXXXX	xx.x%
		Yes	No	No		xxxxxx	DDMMMYYYY (xx)	DDMMMYYYY (xx)	XXXXXXXXX	XXXXXXXXX	
		Yes	No	Yes		xxxxxx					
		Yes	No	Yes		xxxxxx					
		Yes	No	Yes		xxxxxx					
		Yes	No	Yes		xxxxxx					
		No	Yes	Yes	xxxxxxxxx						
		Yes	No	Yes		xxxxxx					

Abbreviation: ID = identification
Note: Listing includes all dosing deviations, including those due to an adverse event.
[1] Study Day is calculated relative to the date of the first dose of study drug.
[2] Compliance (%) = 100* (Treatment duration in days – Number of days both morning and evening doses were missed) / Treatment duration in days), where Treatment duration (days) = Date of last dose of study drug – Date of first dose of study drug + 1 day. For subject that are missing the date of last dose of study drug, the last known contact date is used to calculate treatment duration.

Programming Note: *Use data from CRF.DA, formnam = DA3 and SDC. % Compliance is in ADEX.*

Listing 16.6.2
Study Drug Exposure
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Body Weight at Screening (kg)	Admini-stered Study Drug?	Dosage (µg/kg)	Start Date (Study Day) [1]	Stop Date (Study Day) [1]	Treatment Duration (days)	Total Dose (µg/kg) [2]
xxxxx	XXXXXX	xx.x	Yes	150	DDMMMYYYY (xx)	DDMMMYYYY (xx)	x	xxx
			Yes	300	DDMMMYYYY (xx)	DDMMMYYYY (xx)	x	xxx
			Yes	450	DDMMMYYYY (xx)	DDMMMYYYY (xx)	x	xxxx
			Yes	600	DDMMMYYYY (xx)	DDMMMYYYY (xx)	x	xxxxx
xxxxx	XXXXXX	xx.x	xxx	xxx	DDMMMYYYY (xx)	DDMMMYYYY (xx)	x	xxx
			xxx	xxx	DDMMMYYYY (xx)	DDMMMYYYY (xx)	x	xxx
			xxx	xxx	DDMMMYYYY (xx)	DDMMMYYYY (xx)	x	xxxxx
			xxx	xxx	DDMMMYYYY (xx)	DDMMMYYYY (xx)	xx	xxxxxx
			xxx	xxx	DDMMMYYYY (xx)	DDMMMYYYY (xx)	xx	xxxxxx

[1] Study Day is calculated relative to the date of the first dose of study drug.
[2] Total Dose (µg /kg) = Dose (µg/kg) x Number of doses taken between start and stop dates. For subjects who are missing the date of last dose of study drug, the last known contact date is used in the calculation of treatment duration and study drug exposure.

Programming Note: *Use data fromSDTM.EX.*

Listing 16.6.3
Study Drug Accountability
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Study Drug Dispensed?/ If No, Reason	Kit Number	Clinic Visit	Dispense Date (Study Day) [2]	Volume Dispensed (mL)	Return Date (Study Day) [1]	Volume Returned (mL)	Comments
xxxxx	XXXXXX	Yes	xxxxx	VISIT 1	DDMMMYYYY (x)	xx	DDMMMYYYY (x)	xx.x	
		Yes	xxxxx	VISIT 2	DDMMMYYYY (xx)	xx	DDMMMYYYY (xx)	xx.x	
		Yes	xxxxx	VISIT 3	DDMMMYYYY (xx)	xx	DDMMMYYYY (xx)	xx.x	
		No/xxxxx							

[1] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: *Use data from CRF.DA, formnam = DA2.*

Listing 16.7.1
Total Serum Bile Acid
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex	Clinic Visit	Analysis Visit	Collection Date (Study Day) [2]	Total sBA (umol/L)	Flag [3]	Change from Baseline [4]	
								Observed	Percent
xxxxx	XXXXXX	xx/M	Screening	Screening	DDMMMYYYY (-x)	xxx.x			
			Week 0	Baseline	DDMMMYYYY (xx)	xxx.x		xx.x	xx.x
			Week x	Week 2	DDMMMYYYY (xx)	xxx.x	B	xx.x	xx.x
			Week x	Week 6	DDMMMYYYY (xx)	xxx.x	x	xx.x	xx.x
			Week x	Week 10	DDMMMYYYY (xx)	xxx.x	x	xx.x	xx.x
			Week x	Week 14	DDMMMYYYY (xxx)	xxx.x	x	xx.x	xx.x
			Week x	Week 18	DDMMMYYYY (xxx)	xxx.x	x	xx.x	xx.x
			Week x	Week 22	DDMMMYYYY (xxx)	xxx.x	x	xx.x	xx.x
			Week x	Week 26					

Note: Baseline and all post-baseline sBA samples are assayed at Frontage Laboratories, while screening sBA samples are assayed at ACM Global Laboratories. Only pre-dose samples assayed at Frontage Laboratories are used as a baseline sample.
[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] 'b' indicates ≥ 75% reduction from baseline OR sBA < 102 umol/L
[4] Baseline is Day 0 value (prior to first dose of study drug).

Programming Note: *Add footnote for sBA column if needed to explain abbreviation (eg, 'ND = Not Done'); report sBA, observed CFB, and %CFB values to 1 decimal place. Use data from ADaM.ADLB.*

Listing 16.7.2
Serum Bile Acid Subspecies
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex/ Country	Clinic Visit	Study Day [2]	CDCA	CHA	DCA	GCA	GCDCA	GDCA	GLCA	GUDCA	LCA	TCA	TCDCA	TDCA	TLCA	TUDCA	UDCA
xxxxx	XXXXXX	3/M/GBR	Screening	-x	x.xx	x.xx	x.xx	xxx.xx	xx.xx	x.xx	x.xx	xxx.xx	x.xx	xx.xx	xx.xx	x.xx	x.xx	xx.xx	x.xx
			Day 0	-x	x.xx	x.xx	x.xx	xxx.xx	xx.xx	x.xx	x.xx	xxx.xx	x.xx	xx.xx	xx.xx	x.xx	x.xx	xx.xx	x.xx
			Week 2	xx	x.xx	x.xx	x.xx	xxx.xx	xx.xx	x.xx	x.xx	xxx.xx	x.xx	xx.xx	xx.xx	x.xx	x.xx	xx.xx	x.xx

(Continue for all clinic visits)

Abbreviations: ARG = Argentina; AUT = Austria; BEL = Belgium; BRA = Brazil; CAN = Canada; COL = Columbia; DEU = Germany; FRA = France; GBR = United Kingdom; ITA = Italy; LBN = Lebanon; MEX = Mexico; POL = Poland; SGP = Singapore; TUR = Turkey; USA = United States; CDCA = Chenodeoxycholic Acid; CHA = Cholic Acid; DCA = Deoxycholic Acid; GCA = Glycocholic Acid; GCDCA = Glycochenodeoxycholic Acid; GDCA = Glycodeoxycholic Acid; GLCA = Glycolithocholic Acid; GUDCA = Glycoursodeoxycholic Acid; LCA = Lithocholic Acid; TCA = Taurocholic Acid; TCDCA = Taurochenodeoxycholic Acid; TDCA = Taurodeoxycholic Acid; TLCA = Taurolithocholic Acid; TUDCA = Tauroursodeoxycholic Acid; UDCA = Ursodeoxycholic; BQL = below quantification limit

Note: Serum bile acid components are presented in units of umol/L. The lower quantification limit is 0.01 µmol/L for CA, GDCA, TDCA, TLCA, CDCA, GLCA, DCA, and LCA. For GCA, TCA, TUDCA, GUDCA, GCDCA, TCDCA, and UDCA, the lower limit is 0.2 µmol/L.

[1] Age (years) at Baseline.

[2] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: Use data from SDTM.LB. If Clinic Visit = 'Week 0' assign 'Day 0'. Use raw values; for example, <0.10, not analysis value.

Listing 16.7.3
Clinician Scratch Scale Score
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Clinic Visit	Assessment Completed?	Date of Assessment (Study Day) [1]	Clinician Scratch Scale Score	
					Observed [2]	Change from Baseline [3]
xxxxx	XXXXXX	Screening	Yes	DDMMMYYYY (-xx)	X	
		Day 0	Yes	DDMMMYYYY (xx)	X	
		Week 2	No			
		Week 4	Yes	DDMMMYYYY (xx)	X	X
		Week 6	Yes	DDMMMYYYY (xx)	X	X
		Week 10	Yes	DDMMMYYYY (xx)	X	X
		Week 14	Yes	DDMMMYYYY (xx)	X	X
		Week 18	Yes	DDMMMYYYY (xx)	X	X
		Week 22	Yes	DDMMMYYYY (xx)	X	X
		Week 26	Yes	DDMMMYYYY (xx)	X	X

[1] Study Day is calculated relative to the date of the first dose of study drug.
[2] 0 = None; 1 = Rubbing or mild scratching when undistracted; 2 = Active scratching without evident skin abrasions; 3 = Abrasion evident; 4 = Cutaneous mutilation, haemorrhage and scarring evident.
[3] Baseline is Day 0 value (prior to first dose of study drug). If Day 0 value is not available, the last value obtained during Screening is used as the baseline value.

Programming Note: *Use data from SDTM.QS.*

Listing 16.7.4
Itch Reported Outcomes (Subject and Caregiver) Average Morning and Evening Scores
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]	Analysis Visit Period [2]	ItchRO (Pt) [3] Morning Frequency Score	ItchRO (Pt) [3] Morning Frequency CFB	ItchRO (Pt) [3] Morning Severity Score	ItchRO (Pt) [3] Morning Severity CFB	ItchRO (Pt) [3] Evening Frequency Score	ItchRO (Pt) [3] Evening Frequency CFB	ItchRO (Pt) [3] Evening Severity Score	ItchRO (Pt) [3] Evening Severity CFB	ItchRO (Obs) Morning Frequency Score	ItchRO (Obs) Morning Frequency CFB	ItchRO (Obs) Morning Severity Score	ItchRO (Obs) Morning Severity CFB	ItchRO (Obs) Evening Frequency Score	ItchRO (Obs) Evening Frequency CFB	ItchRO (Obs) Evening Severity Score	ItchRO (Obs) Evening Severity CFB
xxxxx	XXXXXX	X	Baseline	x.xx		x.xx		x.xx		x.xx		x.xx		x.xx		x.xx		x.xx	
			Wks 1-6	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 7-10	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 11-14	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 15-18	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 19-22	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 23-26	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
xxxxx	XXXXXX	X	Baseline	--		--		--		--		x.xx		x.xx		x.xx		x.xx	
			Wks 1-6	--	--	--	--	--	--	--	--	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx

(Continue for all analysis visit periods)

Abbreviation: ItchRO = Itch Reported Outcome; CFB = Change from Baseline, defined as post-baseline value minus baseline value; Pt = Patient; Obs = Observer
Note: ItchRO scores have a range from 0 to 4, with the higher score indicating increasing itch frequency/severity.
[1] Age (years) at Screening.
[2] Average scores are calculated for each time period, averaging 7-day weekly averages. For each time period, the average of the 4 weekly scores is presented; or 6 weekly scores for Weeks 1-6. The baseline score is calculated as the average of the 4 weekly average scores before the first dose of study drug.
[3] '--' indicates assessment is not applicable for subject age (i.e., if a subject was < 9 years old).

Programming Note: *Use data from ADAM.ADQS*

Listing 16.7.5
Exploratory Diary Questionnaire (Subject and Caregiver) Average Morning and Evening Scores
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [2]	Analysis Visit Period [3]	EDQ (Pt) [4] Morning Severity		EDQ (Pt) [4] Evening Frequency		EDQ (Pt) [4] Evening Severity		EDQ (Obs) Morning Severity		EDQ (Obs) Evening Severity	
				Score	CFB	Score	CFB	Score	CFB	Score	CFB	Score	CFB
xxxxx	XXXXXX	X	Baseline	x.xx		x.xx		x.xx		x.xx		x.xx	
			Wks 1-6	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 7-10	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 11-14	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 15-18	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 19-22	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
			Wks 23-26	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
xxxxx	XXXXXX	X	Baseline	--		--		--		x.xx		x.xx	
			Wks 1-6	--	--	--	--	--	--	x.xx	x.xx	x.xx	x.xx

Abbreviation: EDQ = Exploratory Diary Questionnaire; CFB = Change from Baseline, defined as post-baseline value minus baseline value; Pt = Patient; Obs = Observer
Note: EDQ scores have a range from 1 to 5, with the higher score indicating increasing itch frequency/severity.
[1] Age (years) at Screening.
[2] Average scores are calculated for each time period, averaging 7-day weekly averages. For each time period, the average of the 4 weekly scores is presented; or 6 weekly scores for Weeks 1-6. The baseline score is calculated as the average of the 4 weekly average scores before the first dose of study drug.
[3] '--' indicates assessment is not applicable for subject age (i.e., if a subject was < 9 years old).

Programming Note: *Use data from ADAM.ADQS*

Listing 16.7.6.1
PIC and CIC
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

			Patient Impression of Change (PIC)			Caregiver Impression of Change (CIC)			
PFIC Type	Subject	Clinic Visit	Completed?	Date of Assessment (Study Day) [1]	Score [2]	Completed?	Date of Assessment (Study Day) [1]	Itch Score [2]	Xanthoma Score [2]
xxxxx	XXXXXX	Week 26 EOT	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X	X
xxxxx	XXXXXX	Week 26 EOT	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X	X
		(Continue for all clinic visits)							

Note: PIC is completed by subjects who are 9 years of age or older.
[1] Study Day is calculated relative to the date of the first dose of study drug.
[2] 1 = Much better; 2 = Better; 3 = A little better; 4 = No change; 5 = A little worse; 6 = Worse; 7 = Much worse

Programming note: *Merge records within a subject together by study visit; remove Visit column if there are visit discrepancies between assessments. Use data from SDTM.QS.*

Listing 16.7.6.2
PIS and CIS
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

			Patient Impression of Severity of Pruritus (PIS)			Caregiver Impression of Severity of Pruritus (CIS)		
PFIC Type	Subject	Clinic Visit	Completed?	Date of Assessment (Study Day) [1]	Score [2]	Completed?	Date of Assessment (Study Day) [1]	Score [3]
xxxxx	XXXXXX	Day 0	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X
		Week 4	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X
		Week 6	No			No		
		Week 10	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X
		Week 14	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X
		Week 18	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X
		Week 22	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X
		Week 26 EOT	Yes	DDMMMYYYY (xx)	X	Yes	DDMMMYYYY (xx)	X

[1] Study Day is calculated relative to the date of the first dose of study drug.
[2] 0 = I didn't feel itchy at all; 1 = I felt a little bit itchy; 2 = I felt pretty itchy; 3 = I felt very itchy; 4 = I felt very, very itchy
[3] 0 = None; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very severe

Programming note: *Merge records within a subject together by study visit; remove Visit column if there are visit discrepancies between assessments. Use data from SDTM.QS.*

Listing 16.7.7
Efficacy Laboratory Tests
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex	Laboratory Test Category	Laboratory Test (units)	Clinic Visit	Analysis Visit	Collection Date (Study Day) [2]	Fasting? [3]	Local Lab?/ Visit [4]	Test Result [5]	Standard Reference Range Low	Standard Reference Range High	Standard Reference Range Flag [6]	Change from Baseline [7]
xxxxx	XXXXXX	xx/M	Cholestasis	Serum Bile Acid (µmol/L)	Week 0	Baseline	DDMMMYYYY (-x)	X	No	xxx				
			Biomarkers											
				7α hydroxyl-4-cholesten-3-one (C4) (ng/mL)	Week 0	Baseline	DDMMMYYYY (-x)	X	No	xxx				
			Liver Enzymes	Alanine aminotransferase (U/L)	xxxxxxx	Baseline	DDMMMYYYY (-x)	X	Yes/Baseline	xxx	xx	xx		
				Bilirubin (mg/dL)	xxxxxxx	Baseline	DDMMMYYYY (-x)	X		xxx	xx	xx		

(Continue for lab categories and lab tests specified in Programming Note)

[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] Y = Yes; N = No; U = Unknown
[4] Were the labs collected for a protocol-related visit in place of central lab collection?/If yes, for which visit?
[5] 'x' indicates a concentration reported as below the minimum quantitation limit. Half of the minimum quantitation limit is used as the analysis value.
[6] H = (High) The result is above the upper limit of the reference range for normal subjects; L = (Low) The result is below the lower limit of the reference range for normal subjects.
[7] Baseline is Day 0 value (prior to first dose of study drug). If Day 0 value is not available, the last value obtained during Screening is used as the baseline value.

Programming Note: *See Appendix 1 of SAP for list of efficacy lab tests (15 lab tests in total); do not include the 15 sBA subspecies since they are in Listing 16.7.2. Round PELD and MELD to integers; round sBA (BILEAC), FIB-4 and APRI to 2 decimal places. Use data from ADaM.ADLB.*

Listing 16.7.8
Height, Weight, and BMI z-Score
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex	Clinic Visit	Analysis Visit	Vital Signs Collected?	Date of Measurement (Study Day) [2]	Height (cm)	Weight (kg)	BMI (kg/m^2)	Height z-Score	Weight z-Score	BMI z-Score
xxxxx	xxxxxx	1/M	Screening	Screening	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
			Week 0	Baseline	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
			xxxxx	Week 2	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
			xxxxxx	Week 4	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
			xxxxxxx	Week 6	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
xxxxx	xxxxxx	x/X	xxxxxxx	Baseline	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
			xxxxxxxx	Week xx	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
			xxxxxxx	Week xx	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx
			xxxxxxxx	Week xx	Yes	DDMMMYYYY (xx)	xxx	xx.x	xx.x	x.xx	x.xx	x.xx

(Continue for all analysis visits)

Abbreviation: BMI = Body Mass Index
Note: Listing includes all records used for analysis purposes. A subject's sex and age (at each analysis visit) are used to derive z-scores.
[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: *Use data from ADAM.ADVS.*

Listing 16.7.9
Exploratory Diary Questionnaire (Caregiver) Average Morning Scores in Sleep Disturbance
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age at Screening (years)	Analysis Visit Period [1]	Sleep Disturbance Score	
				Observed [3]	Change from Baseline
xxxxx	XXXXXX	xx	Baseline	x.xx	
			Wks 1-6	x.xx	x.xx
			Wks 7-10	x.xx	x.xx
			Wks 11-14	x.xx	x.xx
			Wks 15-18	x.xx	x.xx
			Wks 19-22	x.xx	x.xx
			Wks 23-26	x.xx	x.xx

Note: Caregivers for all subjects aged <9 years complete the EDQ(Obs) instrument. Sleep disturbance is scored in the morning, in which the caregiver scores the following question: “Because of itch, my child had trouble staying asleep.”.
[1] Average scores are calculated for each time period, averaging 7-day weekly averages. For each time period, the average of the 4 weekly scores is presented; or 6 weekly scores for Weeks 1-6. The baseline score is calculated as the average of the 4 weekly average scores before the first dose of study drug.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] 1 = Never; 2 = Rarely; 3 = Sometime; 4 = Often; 5 = Almost Always

Programming Note: *Use ADAM.ADQS*

Listing 16.8.1
Adverse Events
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Any AEs?	PFIC Rec [1]	System Organ Class/ Preferred Term/ Verbatim Term	TEAE?	Start Date (Study Day) [2]	End Date (Study Day) [2]	Event Duration (days)	Severity Grade/ Relationship to Study Drug	Med PFIC Rec?/ Outcome/ Study Drug Action Taken	Serious?/ Criteria Met [3]	Hospitalization Start Date- End Date/ Comment
xxxxx	XXXXXX	Yes	xxx	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxx	Yes	DDMMMYYYY (xx)	DDMMMYYYY (xx)	xx	Grade 1 (Mild)/ Not Related	Yes/ Recovered/Resolved/ Dose Not Changed	No/ None	N/A/ None
xxxxx	XXXXXX	Yes	xxx	xxxxxxxxxxxxxxxx xxxxx/ xxxxxxxxxx/ xxxxxxxxxxxxxxx	No	DDMMMYYYY (xx)	DDMMMYYYY (xx)	xx	Grade x (xxxx)/ Related	xxx/ xxxxxxxx/ xxxx xxx xxxxxxx	Yes/ HOSP; LT	DDMMMYYYY-DDMMMYYYY/ xxxxxxxxx xxxxx xxxxxxxx; xxxxx

Abbreviations: TEAE = Treatment-Emergent Adverse Event; Med PFIC Rec? = Medical Treatment Received?
Note: Adverse events coded using MedDRA version 22.1. In determining TEAEs and study day, partial dates were imputed based on the SAP. Treatment-emergent adverse events are AEs with a start date on or after the first dose of study drug and started prior to the last dose of study drug plus 7 days. For any subjects 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, all AEs that occur during the study are considered as TEAEs irrespective of the last dose.
[1] Treatment received at the onset of the event; MRX dose reported in units of µg/kg/day. For AEs that started within 7 days after the last dose of study drug, the last MRX dose received is listed. For AEs that started > 7 days after the last dose of study drug, treatment received is blank. NT = Not Treated (for AEs that started prior to 1st dose of study drug)
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] CONG = Resulted in congenital anomaly or birth defect; DISAB = Resulted in significant incapacity or substantial disruption of normal life functions; FATAL = Resulted in death; HOSP = Required or prolonged hospitalization; LT = Was life-threatening; OTHER = Other medically important event that may jeopardize the subject.

Programming Note: *Sort AEs (within treatment received, cohort and subject) by start date and then by end date; events that are ongoing would be listed after those with end dates (for those events with the same start date). For Comment, concatenate CRF.AE.AENARF1-4 with a '; ' delimiter. Use data from ADAM.ADAE.*

Listing 16.8.2.1
Adverse Events of Clinical Interest: Diarrhoea Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.2.2
Adverse Events of Clinical Interest: Lipid Soluble Vitamin Deficiency Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.2.3
Adverse Events of Clinical Interest: Elevated Transaminases Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.2.4
Adverse Events of Clinical Interest: Elevated Bilirubin Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.3
Treatment Related Adverse Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.4.1
Serious Adverse Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.4.2
Serious Related Adverse Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.5
Adverse Events Leading to Study Drug Discontinuation
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.6
Severe Adverse Events
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.8.7
Adverse Events Resulting in Death
Safety Population

Same shell as Listing 16.8.1, except remove 'Any AEs?' column

Listing 16.9.1
Vital Signs
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]	Clinic Visit	Vital Signs Collected?	Date of Measurement (Study Day) [2]	Heart Rate (beats/min)	Respiratory Rate (rpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Temperature (degrees C)
xxxxx	XXXXXX	xx	Screening	Yes	DDMMMYYYY (-xx)	XX	XX	XXX	XX	XX.X
			Day 0	Yes	DDMMMYYYY (xx)	XX	XX	XXX	XX	XX.X
			Week 2	Yes	DDMMMYYYY (xx)	XX	XX	XXX	XX	XX.X
			Week 4	No						
			Week 6	Yes	DDMMMYYYY (xx)	XX	XX	XXX	XX	XX.X

(Continue for all clinic visits)

Abbreviations: H = High: The result is above the upper limit of the reference range for normal subjects; L = Low: The result is below the lower limit of the reference range for normal subjects
Note: Normal reference ranges for heart rate, respiratory rate and blood pressure are based on the subject's age at time of the measurement.
[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: *Use data from SDTM.VS. If Clinic Visit = 'WEEK 0' assign 'Day 0'.*

Listing 16.9.2
Physical Examination
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Clinic Visit	Examination Performed?	Examination Date (Study Day) [1]	Any/Changed Abnormalities? [2]	Body System	Result	Abnormal Finding	Clinically Significant?
xxxxx	XXXXXX	Screening	Yes	DDMMMYYYY (-xx)	Yes	System 1	Abnormal	XXXXXXXXXXXXXXXXX; XXXXXXXXXXXXXXXXXX	Yes
						System 2	Normal		
						System 3	Normal		
		Day 0	Yes	DDMMMYYYY (xx)	No				
		Week 2	Yes	DDMMMYYYY (xx)	No				
		Week 4	Yes	DDMMMYYYY (xx)	Yes	System 6		XXXXXXXXXXXX	
		Week 6	Yes	DDMMMYYYY (xx)	Yes	System 6		XXXXXXXXXXXXXXXXX	
		Week 10	Yes	DDMMMYYYY (xx)	No				
xxxxx	XXXXXX	Screening	Yes	DDMMMYYYY (-xx)	No				
		Day 0	Yes	DDMMMYYYY (xx)	No				
		Week 2	Yes	DDMMMYYYY (xx)	No				
		Week 4	Yes	DDMMMYYYY (xx)	No				
		(Continue for all clinic visits)							

[1] Study Day is calculated relative to the date of the first dose of study drug.
[2] For Screening Visit, any abnormal findings are presented; for other visits, newly diagnosed or worsened clinically significant findings since previous visit are indicated.

Programming Note: *For multiple Abnormal Findings within a Body System, separate text using a ";". Use data from SDTM.PE. If Clinic Visit = 'WEEK 0' assign 'Day 0'.*

Listing 16.9.3
12-Lead Safety ECG
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Clinic Visit	ECG Performed?	Date/Time Performed	Heart Rate (bpm)	RR Interval (ms)	PR Interval (ms)	QRS Duration (ms)	Uncorrected QT Interval (ms)	QTcB (ms)	QTcF (ms)	Investigator Interpretation: Abnormality [1]	Comments
xxxxx	XXXXXX	Screening	Yes	DDMMMYYYY:hh:mm	99	508	120	72	294	438	376	Normal	
		Day 0	Yes	DDMMMYYYY:hh:mm	xxx	xxx	xxx	xx	xxx	xxx	xxx	A-NCS: xxxxxxxxx	xxxxxxxxxxxxxx
		Week 10	No										
		Week 26	Yes	DDMMMYYYY:hh:mm	xx	xxx	xxx	xxx	xxx	xxx	xxx	xxxxxxxxx	xxxxxxxxxxxxxx
xxxxx	XXXXXX	Screening	Yes	DDMMMYYYY:hh:mm	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx: xxxxxxxxxx	
		Day 0	Yes	DDMMMYYYY:hh:mm	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxxxxxxxx	
		Week 10	Yes	DDMMMYYYY:hh:mm	xx	xxx	xxx	xxx	xxx	xxx	xxx	xxxxxxxxx	
		Week 26 EOT	Yes	DDMMMYYYY:hh:mm	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxxxxxxxx	

Abbreviations: QTcB = QT interval corrected using Bazett's formula; QTcF = QT interval corrected using Fridericia's formula
[1] A-NCS = Abnormal-Not Clinically Significant; A-CS = Abnormal-Clinically Significant

Programming Note: *Use data from CRF.EG.*

Listing 16.10.1
Clinical Laboratory Tests: Clinical Chemistry
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex	Laboratory Test	Clinic Visit	Collection Date (Study Day) [2]	Local Lab?/ Visit [3]	Fasting? [4]	Test Result [5]	Units	Standard Reference Range Low	Standard Reference Range High	Standard Reference Range [6]
xxxxx	XXXXXX	xx/M	xxxxxxxxxxxxxxx	Screening	DDMMMYYYY (-x)	No	Y	xxx	xxx	xx	xx	
				Day 0	DDMMMYYYY (x)	No	Y	xxx	xxx	xx	xx	x
				Week 2	DDMMMYYYY (xx)	Yes/Week 2	Y	xxx	xxx	xx	xx	
				Week 6	DDMMMYYYY (xx)	xx	Y	xxx	xxx	xx	xx	
				Week 10	DDMMMYYYY (xx)	xx	Y	xxx	xxx	xx	xx	
				Week 14	DDMMMYYYY (xxx)	xx	Y	xxx	xxx	xx	xx	
				Week 18	DDMMMYYYY (xxx)	xx	Y	xxx	xxx	xx	xx	
				Week 22	DDMMMYYYY (xxx)	xx	U	xxx	xxx	xx	xx	
				Week 26	DDMMMYYYY (xxx)	xx	Y	xxx	xxx	xx	xx	x

(Continue for all clinic visits)

[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] Were the labs collected for a protocol-related visit in place of central lab collection?/If yes, for which visit?
[4] Y = Yes; N = No; U = Unknown
[5] 'x' indicates a concentration reported as below the minimum quantitation limit. Half of the minimum quantitation limit is used as the analysis value. '+' indicates a concentration reported as above the maximum quantitation limit. The maximum quantitation limit is used as the analysis value. UNL = Unlabeled; SNS = Sample Not Submitted; QNS = Quantity Not Sufficient; NSA = Not Suitable for Analysis; NCAL = Not Calculated
[6] H = (High) The result is above the upper limit of the reference range for normal subjects; L = (Low) The result is below the lower limit of the reference range for normal subjects.

Programming Note: *Sort lab records (within subject) by laboratory test and then by collection date. See Appendix 1 of SAP for listing of safety lab tests. Use data from SDTM.LB since labs from all vendors will be consolidated there.*

Listing 16.10.2
Clinical Laboratory Tests: Hematology
Safety Population

Same shell as Listing 16.10.1

Listing 16.10.3
Clinical Laboratory Tests: Urinalysis
Safety Population

Same shell as Listing 16.10.1 except remove Local Lab?/Visit column and adjust footnotes accordingly.

Listing 16.10.4
Clinical Laboratory Tests: Lipid Soluble Vitamins
Safety Population

Same shell as Listing 16.10.1

Listing 16.10.5
Clinical Laboratory Tests: Lipid Panel
Safety Population

Same shell as Listing 16.10.1

Listing 16.10.6
Clinical Laboratory Tests: Hepatocellular Carcinoma Marker – Alpha-Fetoprotein (AFP)
Safety Population

Same shell as Listing 16.10.1 except remove Local Lab?/Visit column and adjust footnotes accordingly

Listing 16.10.7
Clinical Laboratory Tests: Timing of Sample Collection and Last Meal
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex	Clinic Visit	Date of Sample Collection (Study Day) [2]	Date/Time of Last Meal Prior to Sample Collection [3]
xxxxx	XXXXXX	xx/M	Screening	DDMMMYYYY (-x)	
			Day 0	DDMMMYYYY (x)	
			Week 2	DDMMMYYYY (xx)	DDMMMYYYY:hh:mm
			Week 6	DDMMMYYYY (xx)	DDMMMYYYY:hh:mm
			Week 10	DDMMMYYYY (xx)	DDMMMYYYY:hh:mm
			Week 14	DDMMMYYYY (xx)	DDMMMYYYY:hh:mm
			Week 18	DDMMMYYYY (xxx)	DDMMMYYYY:hh:mm
			Week 22	DDMMMYYYY (xxx)	DDMMMYYYY:hh:mm
			(Continue for all clinic visits)		

[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] Date/time of last meal prior to sample collection is collected on the Case Report Form. In cases where an unscheduled visit has the same date/time as a scheduled visit, the Date/Time of Last Meal Prior to Sample Collection were merged in by Sample Collection Date.

Programming Note: *For Date/Time columns, may not need to add footnote. For example, "Date/Time of Last Meal Prior to Sample Collection data is collected on the Case Report Form. In cases where an unscheduled visit has the same date/time as a scheduled visit, the Date/Time of Last Meal Prior to Sample Collection was merged in by Sample Collection Date." Use data from CRF.LB.*

Listing 16.10.8
Microbiology Tests
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Sex	Clinic Visit	Collection Date (Study Day) [2]	Microbiology Test	Test Result [3]	Units
xxxxx	XXXXXX	xx/M	Screening	DDMMMYYYY (-x)	xxxxxxxxxxxxxxx	xxx	xxx
			Day 0	DDMMMYYYY (x)		xxx	xxx
			Week 2	DDMMMYYYY (xx)		xxx	xxx
			Week 6	DDMMMYYYY (xx)		xxx	xxx
			Week 10	DDMMMYYYY (xx)		xxx	xxx
			Week 14	DDMMMYYYY (xxx)		xxx	xxx
			Week 18	DDMMMYYYY (xxx)		xxx	xxx
			Week 22	DDMMMYYYY (xxx)		xxx	xxx
			Week 26	DDMMMYYYY (xxx)		xxx	xxx

(Continue for all clinic visits)

[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] UNL = Unlabeled; SNS = Sample Not Submitted; QNS = Quantity Not Sufficient; NSA = Not Suitable for Analysis; NCAL = Not Calculated

Programming Note: *Sort microbiology records (within subject) by microbiology test and then by collection date. Include LBCAT = 'EBV PANEL', 'HCV RNA (PCR)', HEP B SURFACE AG', 'HEP C ANTIBODY', 'HEPATITIS A AB, IGM'. Use data from SDTM.MB.*

Listing 16.10.9
Pregnancy Tests
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Age [1]/ Childbearing Potential	Clinic Visit	Sample Collected?/ Reason Not Collected?	Collection Date/Time (Study Day) [2]	Fasting? [3]	Sample Type	Test Result	Units
xxxxx	XXXXXX	XX/Yes	Screening	Yes	DDMMMYYYY:hh:mm (-x)	X	Serum	xxx	xxx
			Day 0	Yes	DDMMMYYYY:hh:mm (x)	X	Urine	NEGATIVE	
			Week 4	No/xxxxxxx					
			Week 10	Yes	DDMMMYYYY:hh:mm (xx)	X	Urine	NEGATIVE	
			Week 18	Yes	DDMMMYYYY:hh:mm (xx)	X	Urine	NEGATIVE	
			Week 26	Yes	DDMMMYYYY:hh:mm (xxx)	X	Urine	NEGATIVE	
xxxxx	XXXXXX	XX/xxx	Screening	NA					
			Day 0	NA					
			Week 4	Yes	DDMMMYYYY:hh:mm (xx)	X	Urine	NEGATIVE	
			Week 26 EOT	NA					
			(Continue for all clinic visits)						

Abbreviation: NA = not applicable
Note: Listing for female subjects only; only females with at least 1 pregnancy test sample are included in the listing.
[1] Age (years) at Baseline.
[2] Study Day is calculated relative to the date of the first dose of study drug.
[3] Y = Yes; N = No; U = Unknown

Programming Note: *Listing should only include female subjects for which at least 1 pregnancy sample was collected. For these subjects, include each clinic visit. Use data from SDTM.LB.*

Listing 16.10.10
Plasma Sample Maralixibat Concentrations
Safety Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Clinic Visit	Time Point	Sample Collected?	Reason Not Collected	Collection Date/Time	Date/Time of Last Meal Prior to Sample Collection	Maralixibat Concentration (ng/mL)
xxxx	XXXXXX	Week 10	PRE-DOSE	Yes		DDMMMYYYY:hh:mm		BLQ
			+2.5H	Yes		DDMMMYYYY:hh:mm	DDMMMYYYY:hh:mm	XX.XX
		Week 26	PRE-DOSE	Yes		DDMMMYYYY:hh:mm	DDMMMYYYY:hh:mm	XX.XX
			+2.5H	No	xxxxxxx xxxx xxx			
xxxx	XXXXXX	Week 10	PRE-DOSE			DDMMMYYYY:hh:mm	DDMMMYYYY:hh:mm	BLQ
			+2.5H			DDMMMYYYY:hh:mm	DDMMMYYYY:hh:mm	BLQ
		Week 26 EOT	PRE-DOSE			DDMMMYYYY:hh:mm	DDMMMYYYY:hh:mm	BLQ
			+2.5H			DDMMMYYYY:hh:mm	DDMMMYYYY:hh:mm	BLQ

(Continue for all clinic visits)

Abbreviations: LLOQ = lower limit of quantitation; BLQ = below quantification limit
Note: LLOQ is 0.250 ng/mL. Any concentration below the LLOQ is reported as BLQ.

Programming Note: *Use data from CRF.PK.*

Listing 16.11
Telephone Contact Log
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Time Point	Subject/ Caregiver Contacted?	Reason Not Contacted	Telephone/Email Contact Date (Study Day) [1]	Any New/ Worsening AEs/SAEs?	Report new Concomitant Medications?
xxxxx	XXXXXX	Week 1	Yes		DDMMMYYYY (x)	No	No
		Week 3	Yes		DDMMMYYYY (xx)	No	No
		Week 5	No	xxxxxxxxx xxxxx			
		Week 8	Yes		DDMMMYYYY (xx)	No	No
		Week 12	Yes		DDMMMYYYY (xx)	No	No
		Week 16	No	xxxxxx xxxx			
		Week 20	Yes		DDMMMYYYY (xx)	No	No
		Week 24	Yes		DDMMMYYYY (xx)	Yes	Yes
		Follow-up	Yes		DDMMMYYYY (NT)	No	No

(Continue for all time points)

Abbreviation: AEs = Adverse Events; SAEs = Serious Adverse Events
[1] Study Day is calculated relative to the date of the first dose of study drug

Programming Note: *If subject was never dosed, Study Day will be reported as "(NT)". Use data from CRF.TC1.*

Listing 16.12
Visit Dates and Type
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Time Point	Visit Date (Study Day) [1]	Type of Visit	Homecare Used?/If No, Explain	Date of Call	Continuing to Next Visit
xxxxx	XXXXXX	Screening	DDMMMYYYY (x)	In Clinic		DDMMMYYYY	Yes
		Baseline (Week 0)	DDMMMYYYY (x)	In Clinic			Yes
		Subject Contact (Week 1)	DDMMMYYYY (x)	Telephone			xxx
		Visit 2 (Week 2)	DDMMMYYYY (x)	Remote	Yes		xxx
		Subject Contact (Week 3)	DDMMMYYYY (x)	xxx			xxx
		Visit 3 (Week 4)	DDMMMYYYY (x)	xxxxxx			
		…	DDMMMYYYY (x)	xxxxxx			
xxxxx	XXXXXX	Screening	DDMMMYYYY (x)	xxxxxxxx			xxx
		Baseline (Week 0)	DDMMMYYYY (x)	xxxxx			xxx
		Subject Contact (Week 1)	DDMMMYYYY (x)	xxxxxx			xxx
		Visit 2 (Week 2)	DDMMMYYYY (x)	xxxxxx			No
		Early Termination	DDMMMYYYY (x)				

[1] Study Day is calculated relative to the date of the first dose of study drug.

Programming Note: *Use data from CRF.SV, CONT.*

Listing 16.13
Healthcare Utilization
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Any Medical Visits?	Type of Visit	Reason for Visit	Admitted to Hospital?	Date of Admission	Date of Surgery/ Procedure	Date of Discharge	Discharge Status	Number of Work Days Caregiver Missed
xxxxx	XXXXXX	No								
xxxxx	XXXXXX	Yes	OUTPATIENT	XXXXXXXXXXXXX	Yes	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	OTHER: xxxxxxxxxxx	xx
		Yes	XXXXXXXXXX	XXXXXXXXXXXXX	xxx	DDMMMYYYY		DDMMMYYYY		xx

Programming Note: *Use data from CRF.HU.*

Listing 16.14
COVID-19 Impact
Intent-to-Treat Population

Treatment: <Maralixibat or Placebo>

PFIC Type	Subject	Subject Affected by/ Visit Impacted by COVID-19?	Type of Visit Adjustment	Time Point	Missed Assessments? Efficacy/ Safety	ET Reason/ Comments	How IP Impacted	Start Date/ End Date	Study Drug Dispensation Change	Study Drug Administration Change	Additional Comments
xxxxx	XXXXXX	Yes/Week 14	Missed	DDMMMYYYY	Yes/Yes						xxxxxxxxxxxx
		Yes/Week 18	Performed via telephone	DDMMMYYYY	No/No		Dispensation Change	DDMMMYYYY/ DDMMMYYYY	Delivered to subject offsite		
		Yes/Week 26	Other: xxxxxxxxxx	DDMMMYYYY	xx/xxx			DDMMMYYYY/ DDMMMYYYY	XXXXXX		
	XXXXXX	No									
xxxxx	XXXXXX	Yes/Week 10	Missed	DDMMMYYYY	Yes/Yes	Subject Decision/ XXXXXXXXXXX	Dosing Interruption	DDMMMYYYY/ DDMMMYYYY			xxxxxxxxxxx

Abbreviations: ET = early termination; IP = investigational product

Programming Note: *If Other, specify is present in data, concatenate Other with specify data (e.g., Other: xxxxxx). Use data from CRF.COVID.*