Sponsor	*Mirum Pharmaceuticals, Inc.*
Protocol Title:	*Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome*
Protocol Number:	*LUM001-304*
Premier Research PCN:	*LUME3296*
Document Version:	*FINAL Version 1.0*
Document Date:	*17 Mar 2020*

Approvals

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1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Mirum Pharmaceuticals Inc. (Mirum) protocol LUM001-304, Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome, dated 08 Feb2019 (Amendment 5.1).

The original LUM001-304 protocol, dated 20 Mar 2014, planned for a 48-week treatment period. This treatment period included 4 parts: a 6-week open-label (OL) dose escalation period at doses up to 400 µg/kg/day; a 12 week OL stable dosing period; a 4-week randomized, double-blind, placebo-controlled drug withdrawal period; and a 26-week long-term stable dosing period at doses up to 400 µg/kg/day.

There have been 6 protocol amendments to date. The summary list of changes to each of the protocol amendments are described in the final amendment, Protocol Amendment 5.1. Several of the protocol amendments included optional long-term treatment extensions and one of the later amendments added a twice-a-day (BID) dosing regimen.

Protocol Amendment 3, dated 13 Nov 2015, provided for an optional 52-week treatment period. At Week 48, all subjects were to be assessed by the investigator to determine the subject's willingness and eligibility to roll over into the 52-week, follow-up treatment period.

Protocol Amendment 4, dated 28 Mar 2017, allowed continued participation in the long-term optional follow-up treatment period, beyond what was previously described in Protocol Amendment 3. During this long-term optional follow-up treatment period, subjects may have their dose of LUM001 increased to a maximum of 800 µg/kg/day (400 µg/kg BID) based on efficacy and safety assessments. Study treatment in the long-term optional follow-up treatment period was to continue until the first of the following occurred: (i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) Mirum Pharmaceuticals stops the program or development in the indication of Alagille syndrome (ALGS).

Protocol Amendment 5, dated 06 Nov 2017, primarily changed the study design going forward to an open-label study.

The final protocol amendment, Amendment 5.1, amended Protocol Amendment 5 to reflect the change of sponsorship from Lumena Pharmaceuticals LLC (Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc.) to Mirum Pharmaceuticals, Inc.

The enrollment of siblings was allowed, however, no siblings enrolled in the study. Thus, the analysis plan does not address the handling of siblings.

A subject may have been off study drug for an extended period of time during the course of their study treatment. The reasons for being off study drug include drug interruption (e.g., as directed by an investigator due to an AE), study drug compliance issues (e.g., missed consecutive doses), and dosing gaps due to being off study between protocol amendments. For example, a subject

could complete study drug treatment through Week 48 under the original protocol before implementation of Protocol Amendment 3 that extended treatment through Week 100. The subject could subsequently provide informed consent under the amendment and be re-initiated on study drug.

Subjects with a drug interruption of at least 7 days had their study drug dose re-escalated beginning at 35 µg/kg/day. Subjects were escalated up to a maximum of 400 µg/kg/day or highest tolerated dose.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analysis 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, and the results of these post-hoc analyses may be referred in the CSR and will be available for review in CSR Section 14.2.

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[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The active study drug LUM001 is now named maralixibat chloride (MRX) and that label will be used hereinafter.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

The objectives of this study (up to and including Week 48) are:

- To evaluate the long-term safety and tolerability of MRX in children with ALGS.
- To evaluate the effect of MRX on serum bile acid levels in children with ALGS.
- To evaluate the effect of MRX on biochemical markers of cholestasis and liver disease in children with ALGS.
- To evaluate the effect of MRX on pruritus in children with ALGS.
- To evaluate the long-term effect of MRX in children with ALGS during 48 weeks of treatment.

The objectives of the long-term optional follow-up treatment period (after Week 48) are:

- To offer eligible subjects treated in the LUM001-304 study continued study treatment at Week 48 until the first of the following occurs: (i) the subjects are eligible to enter another MRX study (ii) MRX is available commercially, or (iii) Mirum Pharmaceuticals stops the program or development in this indication.
- To explore twice a day (BID) dosing regimen and higher daily dosing of MRX.
- To obtain safety and efficacy data in subjects treated long term on MRX including genotyping characteristics.
- To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma.
- To assess palatability of the MRX formulation.

2.2. Study Endpoints

Safety and efficacy endpoints are examined for each of the 3 treatment phases:

- Open-label (OL) Phase (Day 1 – Week 18),
- Randomized Withdrawal (RW) Phase (Weeks 19 - 22), and
- After Randomized Withdrawal (ARW) Phase (Week > 22).

Subjects who withdrew early during the OL Phase will not be included in the RW or ARW analyses. Similarly, subjects terminated during the OL or RW phases will not be included in the ARW analyses.

For select analyses, the 3rd treatment phase will be presented as 2 separate treatment phases: ARW (Week > 22 – Week 48) and ARW (Week > 48). Unless otherwise specified, summaries will be provided by treatment phase and treatment group/sequence.

2.2.1. Safety Endpoints

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

- Incidence of adverse events (AEs) including serious, related to study medication, leading to withdrawal, special interest AEs, along with AEs by severity and by relationship to study medication
- Change from baseline (Day 0) in clinical safety laboratory values at each clinic visit (if applicable).
- Change from Week 18 in clinical safety laboratory values at Week 22 (if applicable).
- Observed AFP values over time.
- Change from baseline (Day 0) in physical examination findings and vital signs at each clinic visit.
- Change from Week 18 in physical examination findings and vital signs at Week 22.
- Concomitant medication usage.

Physical examination findings include body mass index (BMI). 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 2. Note that bilirubin (total and direct), alanine phosphatase (ALP), and alanine aminotransferase (ALT) are considered as both safety and efficacy laboratory tests. For select fat soluble vitamins (FSVs), including 25-hydroxyvitamin D, ratio of alpha tocopherol to estimated total lipids, corrected sodium, INR, retinol:RBP molar ratio, and vitamin A, a summary of abnormalities will be presented at baseline, Week 18, Week 22 (by treatment group), and Week 48. For these FSVs, categories may include normal, sufficient, insufficient, possibly insufficient, indeterminate, and excess (see Section 6.1.9 for specific definitions).

Serum samples for AFP, a marker of hepatocellular carcinoma, are only drawn during the optional follow-up treatment period at every other 12-week repeating period clinic visit (i.e., every 6 months) and at the end-of-treatment (EOT)/early termination (ET) visit.

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the mean change from Week 18 to Week 22 of fasting serum bile acid (sBA) levels in subjects who previously responded to MRX treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 (i.e., Modified Intent-to-Treat [MITT] Population).

2.2.2.2. Secondary Endpoints

Secondary efficacy endpoints include mean change from Week 18 to Week 22 in liver enzymes (ALP, ALT, and bilirubin [total and direct]) and pruritus as measured by ItchRO Observer (ItchRO[Obs]) and ItchRO Patient (ItchRO[Pt]), in subjects who previously responded to MRX treatment, as defined by a reduction in ItchRO scale ≥1 point from baseline to Week 12 or Week 18. The ItchRO(Obs) weekly average morning score is used in defining an ItchRO responder.

Secondary efficacy endpoints also include mean change from baseline to Week 18 in fasting serum bile acid levels, liver enzymes (ALP, ALT, and bilirubin [total and direct]) and pruritus as measured by ItchRO (Observer ItchRO/Patient ItchRO).

For secondary ItchRO variables, the weekly average severity score is used, where the daily score is defined as the higher of the scores from the morning and evening ItchRO score.

The secondary efficacy endpoints for this study are summarized in Table 1.

Table 1 Secondary Efficacy Endpoints

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From Week	To Week
ItchRO(Obs), ItchRO(Pt)	Weekly average severity score (based on daily maximum of morning and evening scores) [1]	0	18
		18	22
sBA	Laboratory test level	0	18
Liver enzymes (ALP, ALT, total bilirubin, direct bilirubin)	Laboratory test level	0	18
		18	22

[1] For change from Week 18 to Week 22, analysis is performed in subjects who previously responded to MRX treatment, as defined by a reduction in ItchRO(Obs) weekly average morning score ≥1 point from baseline to Week 12 or Week 18.

2.2.2.3. Additional Efficacy Endpoints

The following additional efficacy evaluations will be assessed:

- Change from baseline to Weeks 18, 22, 48 and then every 12 weeks in:
  - Fasting serum bile acid levels
  - Liver enzymes (ALT, ALP) and bilirubin (total and direct)
  - Pruritus as measured by the average daily ItchRO (ItchRO[Obs]/ItchRO[Pt])
  - Other biochemical markers of cholestasis (total cholesterol, low-density lipoprotein cholesterol [LDL-C])
  - Bile acid synthesis (serum 7α-hydroxy-4-cholesten-3-one [C4])
- Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 in:
  - Pruritus response rates as measured by ItchRO (ItchRO[Obs]/ItchRO[Pt])
  - Clinician scratch scale
- Change from baseline for PedsQL at Week 18, 22, 48, 60, 72, 84, 96, and 100 and change from Week 18 to Week 22
- PIC at Week 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- CIC at Week 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- CGTB assessment at Weeks 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- Change from Baseline (Day 0) to Week 48 in xanthomas, as measured by Clinician Xanthoma Scale score

2.2.2.4. Sensitivity Endpoints

The definition of the pruritus endpoint used to assess efficacy was not pre-specified in the LUM001-304 study protocol or the Week 48 Statistical Interim Analysis Plan (SIAP). Because there is no single primary pruritus endpoint or statistical analysis approach pre-specified for this study, the pruritus data should be robust to various endpoint definitions and analysis methods that are considered reasonable a priori.

All efficacy endpoints for this study, including non-protocol defined pruritus endpoints based on ItchRO scores and other sensitivity endpoints (e.g., body height and weight z-scores), are described in Table 2 and Table 3, for continuous and categorical endpoints, respectively. Note that data for subjects who early terminated from the study prior to Week 100 or are otherwise missing Week 18, Week 22, Week 48, and/or Week 100 data will be imputed in a last-observation-carried-forward (LOCF) sensitivity analysis approach (see Section 6.1.5.3).

Table 2 Analysis of Continuous Efficacy Endpoints (including Sensitivity)

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From Week	To Week
ItchRO(Obs)	Weekly average morning severity score [1]; Weekly average evening severity score [1]; Weekly average morning frequency score [1]; Weekly average evening frequency score [1]; Weekly average severity score (based on daily maximum of morning and evening scores); Weekly average severity score (based on daily average of morning and evening scores)	0	3, 6, 12, 18*, 18/LOCF, 19, 20, 21, 22, 22/LOCF, 28, 38, 48, 48/LOCF, 62, 74, 86, 98, and 100/LOCF, and each 12-week repeating period (i.e., Week 120, 132, 144, 156, etc.)
		18	19, 20, 21, 22*, 22/LOCF
	4-Week average morning severity score [1]; 4-Week average evening severity score [1]; 4-Week average morning frequency score [1]; 4-Week average evening frequency score [1]	0	6, 12, 18*, 18/LOCF, 22, 28, 38, 48, 48/LOCF
		18	22*

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From Week	To Week
ItchRO(Pt)	Weekly average morning severity score [1]; Weekly average evening severity score [1]; Weekly average severity score (based on daily maximum of morning and evening scores) Weekly average severity score (based on daily average of morning and evening scores)	0	3, 6, 12, 18*, 18/LOCF, 19, 20, 21, 22, 28, 38, 48, 48/LOCF, 62, 74, 86, 98, 100/LOCF, and each 12-week repeating period
		18	19, 20, 21, 22*
	4-Week average morning severity score [1]; 4-Week average evening severity score [1]	0	6, 12, 18*, 18/LOCF, 22, 28, 38, 48, 48/LOCF
		18	22*
sBA	Laboratory test level	0	12, 18*, 18/LOCF, 22, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
		18	22*
Liver enzymes (ALP, ALT, total bilirubin, direct bilirubin)	Laboratory test level	0	3, 6, 12, 18*, 18/LOCF, 22, 28, 38, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
		18	22*
Lipid panel and cholestasis biomarkers (cholesterol, LDL-C, C4)	Laboratory test level	0	12, 18, 18/LOCF, 22, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
		18	22
Clinician Scratch Score (CSS)	Score for CSS	0	3, 6, 12, 18, 18/LOCF, 22, 28, 38, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
		18	22

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From Week	To Week
Body Height Body Weight	z-score	0	3, 6, 12, 18, 18/LOCF, 22, 28, 38, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
Clinician Xanthoma Scale	Score	0	18, 18/LOCF, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
PedsQL	Total Scale Score (Parent); Multidimensional Fatigue Scale Score (Parent); Family Impact Total Scale Score; Psychosocial Health Summary Score (Parent); Total Scale Score (Child); Multidimensional Fatigue Scale Score (Child)	0	18, 18/LOCF, 22, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
		18	22
Caregiver Impression of Change – Itch Related Symptoms (CIC-Itch), Caregiver Impression of Change – Xanthoma Severity (CIC-Xan), Patient Impression of Change (PIC) Caregiver Global Therapeutic Benefit (CGTB)	Score	--	Summary statistics at Week: 18, 18/LOCF, 22, 48, 48/LOCF, 84, 96, 100/LOCF
		18	22

* Indicates endpoint defined as primary, secondary, or exploratory; BID = twice-a-day dosing regimen

[1] Sensitivity pruritus endpoint not pre-defined in the study protocol. See Sections 2.2.2.5 and 6.1.9.

Table 3 Categorical Analyses of Efficacy Endpoints (including Sensitivity)

Efficacy Parameter(s)	Scale and Responder Criteria or Variables	Endpoint
Clinician Scratch Score (CSS)	5-point scale: 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 Responder Definitions: Decrease from baseline score ≥ 1 Decrease from baseline score ≥ 2	Change from baseline (Day 0) at Week: 3, 6, 12, 18, 18/LOCF, 22, 28, 38, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, 156 (3 years), and 204 (4 years)
Caregiver Impression of Change – Itch Related Symptoms (CIC-Itch), Caregiver Impression of Change – Xanthoma Severity (CIC-Xan), Patient Impression of Change (PIC)	7-point scale: 1 = much better 2 = better 3 = a little better 4 = no change 5 = a little worse 6 = worse 7 = much worse Responder: ≤ 3 score	Number and % of Subjects at Week: 18, 18/LOCF, 22, 48, 48/LOCF, 84, 96, 100/LOCF
Caregiver Global Therapeutic Benefit (CGTB)	5-point scale: 1 = definitely 2 = somewhat 3 = about the same 4 = maybe not 5 = definitely not Responder: ≤ 2 score	Number and % of Subjects at Week: 18, 18/LOCF, 22, 48, 48/LOCF, 84, 96, 100/LOCF

Efficacy Parameter(s)	Scale and Responder Criteria or Variables	Endpoint
ItchRO(Obs), ItchRO(Pt)	ItchRO(Obs) morning severity score [1]; ItchRO(Pt) morning severity score [1]	Number and % of Days Scores are ≤ 1 Point During each of the following Time Periods: Day 1 – Week 6, Weeks > 6 - 12, Weeks > 12 - 18, Weeks > 18 - 22, Weeks > 22 - 48, Weeks > 48 - 108, Weeks > 108 - 156 (> 2 - 3 years), Weeks > 156 - 204 (> 3 - 4 years), Weeks > 204 (> 4 years)

[1] Sensitivity pruritus endpoint not pre-defined in the study protocol. See Sections 2.2.2.5 and 6.1.9.for endpoint descriptions and derivations, respectively.

2.2.2.5. Efficacy Parameter Descriptions

Itch Reported Outcome (ItchRO)

The primary efficacy assessment in this study is pruritus severity as measured by the itch reported outcome measures (ItchRO) administered as a twice daily electronic diary (eDiary) completed by caregivers (ItchRO[Obs]). Subjects 9 years of age or older independently complete the patient instrument: ItchRO(Pt). Subjects between 5 and 8 years of age, or where the investigator has expressed concern about the subject's ability to reliably complete the data (e.g., due to developmental delay) complete the patient instrument with the assistance of their caregiver, if needed. There is no ItchRO(Pt) report for subjects under the age of 5 years.

Age at screening will be used as the age for the determination of the appropriate ItchRO instrument to be used for the study and this same instrument will be used for the duration of the study (regardless of subsequent birthdays after the screening visit).

Given the age range of the study population and the small sample size, the primary ItchRO score will be derived from the ItchRO(Obs) instrument. The itch score from the ItchRO(Pt) will be analyzed separately.

For the ItchRO instrument, the caregiver and/or subject indicate the itch severity (Item 1) in the morning and in the evening each day during the following periods:

- Screening through first 48 weeks of the treatment period
- 2 consecutive weeks that follow the Week 60, Week 72, Week 84, and Week 96 clinic visits
- 2 consecutive weeks that follow each recurring 12-week clinic visit during the optional extension follow-up treatment period.

Completion of the ItchRO instrument occurs as outlined in the Schedule of Procedures in Section 3.7. For the ItchRO(Obs) instrument, caregivers also indicate the frequency of itch (Item 3).

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) or more frequent (Item 3) itching. The following 10 ItchRO summary scores are calculated and used in the analysis of pruritus:

- *Weekly average morning severity score*
- *Weekly average evening severity score*
- *4-Week average morning severity score*
- *4-Week average evening severity score*
- *Weekly average morning frequency score (ItchRO[Obs] only)*
- *Weekly average evening frequency score (ItchRO[Obs] only)*
- *4-week average morning frequency score (ItchRO[Obs] only)*
- *4-week average evening frequency score (ItchRO[Obs] only)*
- *Weekly average severity score (based on daily average of morning and evening scores) (ItchRO[Obs] only)*
- *Weekly average severity score (based on daily maximum of morning and evening scores) (ItchRO[Obs] only)*

Weekly average scores for Baseline (Day 0) and Weeks 3, 6, 12, 18, 22, 28, 38, and 48 are calculated as the average of the daily scores over a defined study week consisting of the 7 days before the scheduled visit. Starting with Week 62 (i.e., Weeks 62, 74, 86, 98, and every three months thereafter), the previous study visit date plus 2 weeks is used as the anchor (e.g., the date for Week 62 is based on the Week 60 study visit date plus 2 weeks) in deriving weekly average scores. During the randomized withdrawal period, weekly average scores are also calculated at Weeks 19, 20, and 21, using the Week 22 scheduled visit date as the anchor. For the change from baseline calculations in weekly average ItchRO scores, baseline is defined in Section 6.1.1. Post-baseline weekly average ItchRO scores are only computed if at least 4 of the 7 daily ItchRO scores for the 7-day period are available.

4-week average scores are calculated as the average of the evening/morning scores over a defined period consisting of the 28 days before the scheduled visit (i.e., Baseline [Day 0], Weeks 6, 12, 18, 22, 28, 38, 48, 22, 28, 38, and 48). For the change from baseline calculation in 4-week average ItchRO scores, baseline is defined in Section 6.1.1. Post-baseline 4-week average ItchRO scores are only computed if at least 20 of the 28 daily ItchRO scores for the 28-day period are available.

In deriving weekly or 4-week (where applicable) average post-baseline ItchRO scores, each visit date will be determined based on the varying eDiary collection periods (as applicable): (A) Week

3, 6, 12, 18, 22, 28, 38, and 48, (B) Week 19, 20, and 21, (C) Week 62, 74, 86, 98, and, recurring 12-week periods during the optional extension follow-up treatment period.

A. Week 3, 6, 12, 18, 22, 28, 38, and 48: The scheduled visit date is used.
B. Week 19, 20, and 21: The Week 22 scheduled visit date will be used as the anchor point, where: the Week 21 average score will be based on the 7-day period immediately before the Week 22 date; and the Week 19 and Week 20 average scores will be based on the 7-day periods immediately before the 7-day period used in determining the previous week's average score.
C. Week 62, 74, 86, 98, and recurring 12-week periods: Each scheduled visit date will be determined based on the date of the associated scheduled clinic visit (i.e., Week 60, 72, 84, and 96) plus 14 days.

In general, scheduled visit dates will be determined based on the date of the vital signs assessment. If the date of vital signs is missing, then the date of the physical examination will be used. If both of these dates are missing for a specific scheduled visit then the start date from the subject visits derived dataset will be used. Further, for missing but expected dates (where ItchRO data exists), the last visit past the missing date is used and the appropriate amount of days is subtracted.

Clinician Scratch Score

The CSS provides an assessment of itch severity. The clinician's assessment of the subject's pruritus is focused on scratching and visible damage to the skin as a result of scratching as observed by the physician. The clinician scratch score uses a 5-point scale, in which 0 designates no evidence of scratching, and 4 designates cutaneous mutilation with bleeding, haemorrhage and scarring (see Table 3 for complete scale descriptions).

Clinician Xanthoma Scale Score

The clinician's assessment of the subject's xanthomatosis is focused on the number of lesions present and the degree to which the subject's lesions interfere or limit his or her activities. The Clinician Xanthoma Scale score uses a 5-point scale, in which 0 represents no evidence of xanthomatosis (none), 1 represents fewer than 20 scattered individual lesions (minimal), 2 represents more than 20 lesions that do not interfere with or limit activities (moderate), 3 represents large numbers of lesions that by their large numbers or size cause distortion of the face or extremities (disfiguring), and 4 represents xanthomas that interfere with function (such as hand use or ability to walk) because of excess size or number (disabling).

Caregiver Impression of Change – Itch Related Symptoms (CIC-Itch)

The CIC-Itch is designed to assess the caregiver's perception of the subject's itch-related symptoms after various points of study drug treatment compared to his/her itch-related symptoms prior to the start of treatment with study drug. The questionnaire is designed for self-administration and uses a 7-point scale in which 1 designates the best outcome and 7 designates the worst outcome (see Table 3 for complete scale descriptions).

Caregiver Impression of Change – Xanthoma Severity (CIC-Xan)

The CIC-Xan is designed to assess the caregiver's perception of the subject's xanthoma severity after various points of study drug treatment compared to his/her xanthoma severity prior to the start of treatment with study drug. The questionnaire is designed for self-administration and uses a 7-point scale in which 1 designates the best outcome and 7 designates the worst outcome (see Table 3 for complete scale descriptions).

Patient Impression of Change (PIC)

The PIC is designed to assess the subject's perception of his/her itching after various points of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The PIC is completed by subjects who were 9 years of age or older at clinic visits as outlined in the Schedule of Procedures in Section 3.7. The questionnaire is designed for self-administration and uses a 7-point scale in which 1 designates the best outcome and 7 designates the worst outcome (see Table 3 for complete scale descriptions).

Caregiver Global Therapeutic Benefit (CGTB)

The CGTB questionnaire is designed to assess the caregiver's perception of the treatment benefits on the subject's itching compared to the side effects experienced with study drug. The questionnaire is designed for self-administration and uses a 5-point scale in which 1 designates the best outcome and 5 designates the worst outcome (see Table 3 for complete scale descriptions).

Pediatric Quality of Life (PedsQL)

The PedsQL[13] is a validated, modular instrument designed to measure health-related quality of life (HRQoL) in infants, children and adolescents. The PedsQL questionnaire is administered to subjects and/or caregivers depending on age using age-appropriate PedsQL modules. The PedsQL consists of developmentally appropriate forms for infants/children ages 1 - 12 months, 13 - 24 months, 2 - 4, 5 - 7, 8 - 12, and 13 - 18 years.

Pediatric self-report is measured in children and adolescents ages 5 - 18 years, and parent proxy-report of child HRQoL is measured for children and adolescents ages 12 months to 18 years.

In addition to the core generic PedsQL module, the multidimensional fatigue and family impact questionnaires are also administered using the age-appropriate module.

Age at baseline will be used as the age for the determination of the appropriate module to be used for the study, and this same module will be used for the duration of the study (regardless of subsequent birthdays after the baseline visit).

With the exception of the 5 - 7 year age group (Young Child) subject report, each item of the PedsQL consists of a 5-level Likert-type item survey (0 - 4), where 0 = Never, 1 = Almost never, 2 = Sometimes, 3 = Often, and 4 = Almost always. Items of the PedsQL Young Child subject report are scored on a 3-point scale, where 0 = Not at all, 2 = Sometimes, and 4 = A lot.

The PedsQL Generic Core Scale is composed of items to assess pediatric HRQoL measurements across 6 subscales: Physical Functioning, Physical Symptoms (only applicable for infants, 1 - 24 months), Emotional Functioning, Social Functioning, Cognitive Functioning [only applicable for infants, 1 - 24 months], and School Functioning (only applicable for children, 2 - 18 years).

The Total Scale Score, Physical Health Summary Score and Psychosocial Health Summary Score are computed individually for both the parent and subject reports of the PedsQL Generic Core Scale. The Total Scale Score is computed from all items. The Physical Health Summary Score is computed from the items of the Physical Functioning domain, and the Physical Symptoms domain (infants only). The Psychosocial Health Summary Score is computed from items of the Emotional, Social, and School Functioning domains, and the Cognitive Functioning domain (infants only).

The PedsQL Multidimensional Fatigue Scale is composed of items across 3 subscales: General Fatigue, Sleep/Rest Fatigue, and Mental Fatigue. Respondents use the scale to indicate how frequently certain fatigue-related symptoms and complaints trouble them. The Multidimensional Fatigue Scale Score is computed from all items of the PedsQL Multidimensional Fatigue Scale.

The PedsQL Family Impact Scale is composed of items encompassing 6 subscales measuring parent self-reported functioning: Physical Functioning, Emotional Functioning, Social Functioning, Cognitive Functioning, Communication, and Worry, and 2 subscales measuring parent-reported family functioning: Daily Activities and Family Relationships. The Family Impact module assesses the impact of pediatric chronic health conditions on parents and the family. The Family Impact Total Scale Score is computed from all items of the PedsQL Family Impact Scale. The Parent Functioning Summary Score is computed from the items of the Physical, Emotional, Social, and Cognitive Functioning domains. The Family Impact Summary Score is computed from the items of the Daily Activities and Family Relationships domains.

The scoring algorithms for the PedsQL summary and total scores are presented in Section 6.1.9.

2.2.3. Other Endpoints

Other endpoints of this study include the following:

- Palatability of the MRX formulation over time.
- Plasma levels of MRX at baseline (pre-dose) and over time.

2.2.3.1. Palatability

Palatability of the MRX formulation is assessed in all subjects, by caregiver-proxy in non-collaborating subjects (generally subjects < 4 years of age) and by subject questionnaire in subjects > 8 years of age or caregiver and collaborating child if 4 to 8 years of age. Palatability assessments are obtained at each clinic visit in the optional follow-up treatment period, with the exception of the DE, PA4 DE, and ADE visits.

2.2.3.2. Pharmacokinetics

Due to poor absorption of MRX, very low systemic exposure and plasma drug levels are expected. Pharmacokinetic blood samples are collected at baseline and then approximately 4 hours post-dosing at one additional time point – at Week 12, 18, 38, or 48, as selected by the site/investigator. Plasma samples will additionally be collected at the ADE-Day 0, ADE-Week 4, and ADE-Week 8, and at the 3 scheduled clinic visits following completion of the ADE period.

2.2.3.3. Genotyping Characteristics

All subjects enrolled to the LUM001-304 study have documented JAGGED-1 mutation.

3. OVERALL STUDY DESIGN AND PLAN

3.1. Overall Design

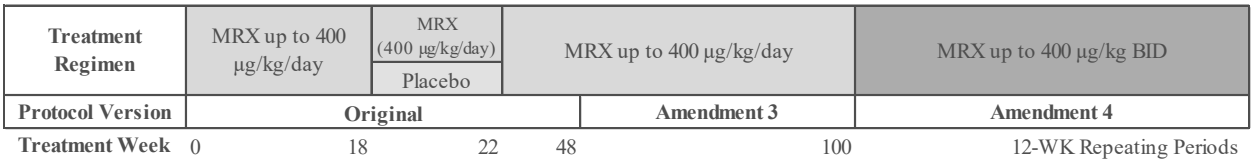
This is a long-term open-label study with a 4-week double-blind, placebo-controlled, randomized drug withdrawal period in children with ALGS designed to evaluate the safety and efficacy of MRX. The study is divided into 6 parts:

- 6-week open-label, dose escalation period at doses up to 400 µg/kg/day
- 12-week open-label stable dosing period
- 4-week randomized, double-blind, placebo-controlled drug withdrawal period
- 26-week long-term stable dosing period at doses up to 400 µg/kg/day
- 52-week optional follow-up treatment period (protocol amendment 3)
- Long-term optional follow-up treatment period for eligible subjects who choose to stay on treatment with MRX (protocol amendment 4)

During the long-term optional follow-up period, subjects may have their dose of MRX increased to a maximum of 800 µg/kg/day (400 µg/kg BID), based on efficacy (sBA level and ItchRO [Obs] score) and safety assessment. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occurs: i) the subjects are eligible to enter another MRX study, ii) MRX is available commercially, or (iii) Mirum Pharmaceuticals stops the program or development in this indication.

Figure 1 depicts an overview of the treatment regimens across the study duration.

Figure 1 Treatment Regimens



3.2. Sample Size and Power

ALGS is a rare disease. The planned sample size of 30 evaluable ALGS subjects is based on practical considerations, rather than a desired power for a pre-specified difference.

3.3. Study Population

The study population is males and females, between the ages of 12 months and 18 years (inclusive), diagnosed with ALGS.

3.4. Treatments Administered

All subjects receive MRX, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day, during the initial open-label treatment period of the study. After completion of the 12-week stable dosing period, subjects were randomized 1:1 to either continue receiving MRX or a corresponding placebo (PBO) for a 4-week double-blind study drug withdrawal period. The randomization was stratified by response criteria where response was defined as a ≥50% reduction in serum bile acids between Baseline and Week 12. Subjects then entered a 26-week long-term stable dosing period, and all subjects received MRX, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day.

Subjects were considered for a 52-week optional treatment period, if eligible, receiving up to 400 µg/kg/day, or the highest tolerated dose below the 400 µg/kg/day dose. Subjects were then considered for the long-term optional follow-up treatment, if eligible, receiving up to 800 µg/kg/day (given as twice daily doses of 400 µg/kg), or a maximum possible daily dose of 50 mg/day.

During the study, the study drug may be adjusted if there is a change of ≥10% in body weight since the screening visit or if there is a change of ≥10% in weight since the last weight-based medication adjustment to maintain the target dose.

3.4.1. Dose Escalation Period

Initially, the MRX dose was administered as a daily morning dose in either a 1.0 mL or 0.5 mL solution. The dose was increased weekly over a 6-week period up to 400 µg/kg/day QD or a maximum daily dose of 20 mg/day QD as follows:

Week 1 Dose: 14 µg/kg/day QD
Week 2 Dose: 35 µg/kg/day QD
Week 3 Dose: 70 µg/kg/day QD
Week 4 Dose: 140 µg/kg/day QD
Week 5 Dose: 280 µg/kg/day QD
Week 6 Dose: 400 µg/kg/day QD (maximum daily dose of 20 mg QD)

If a subject experiences intolerance due to gastrointestinal symptoms (e.g., diarrhoea, abdominal pain, cramping) at any time during the study, the physician investigator in consultation with the

medical monitor may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose.

3.4.2. Stable Dosing Period

Subjects continued dosing for another 12 weeks using the dose administered at Week 6, which may be 400 µg/kg/day or the highest tolerated dose below 400 µg/kg/day.

3.4.3. Double-Blind Placebo-Controlled Study Drug Withdrawal Period

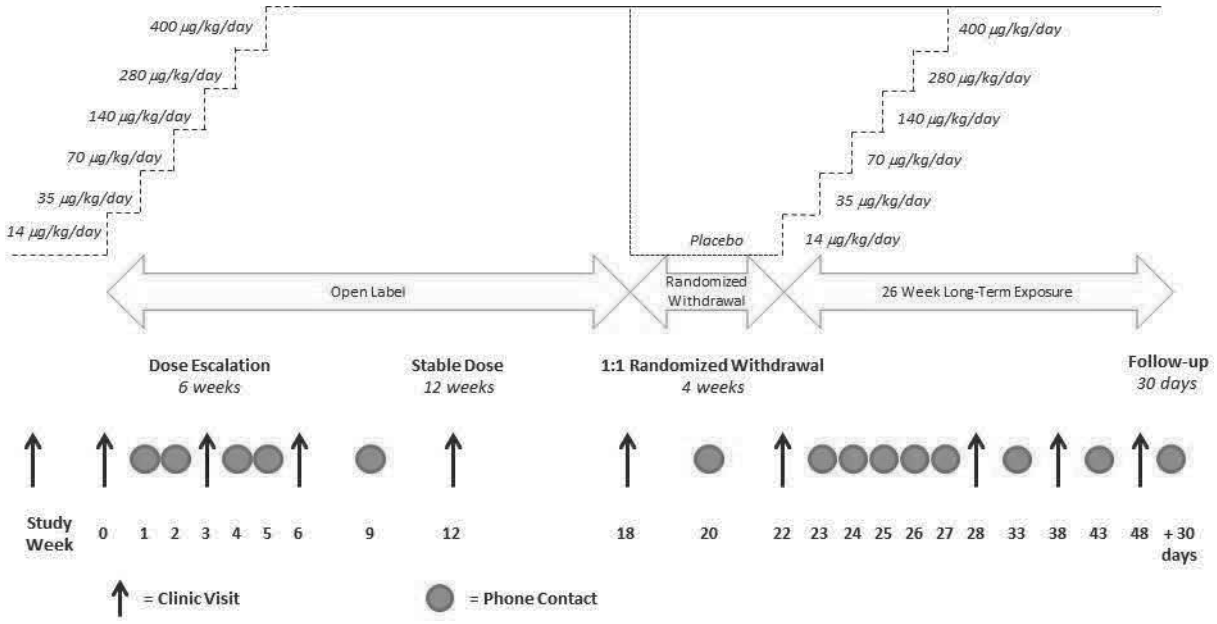
At the Week 18 visit, eligible subjects were randomized to continue to receive study drug or a corresponding placebo for 4 weeks.

3.4.4. Long-Term Exposure Period

Following the 4-week study drug randomized withdrawal period, subjects who received placebo receive MRX dosed according to a dose escalation schedule that mirrors the initial escalation. Subjects who were randomized to receive MRX during this period will continue to receive the same dose of MRX and, following Week 22, a simulated dose escalation will occur to maintain the blind in the randomized withdrawal period. Dosing with MRX will continue in a 26-week long-term exposure period to complete 48 weeks of treatment (see Figure 2).

During the long-term exposure period, the dose may be adjusted to account for a change of ≥10% in weight since the screening visit (e.g., the amount of drug dosed may be increased to reflect the subject's weight increase).

Figure 2 Study Design for Original Protocol (Day 0 – Week 48)



3.4.5. 52-Week Optional Follow-up Treatment Period

At Week 48, all subjects were assessed by the investigator to determine their willingness and eligibility to roll-over into the 52-week optional follow-up treatment period. The 3 following possible scenarios may have occurred:

- Subjects who were eligible to roll over into the optional follow-up treatment period with no MRX dosing interruption or an interruption of < 7 days were maintained at the same dose level (see Figure 3).
- Subjects who were eligible to roll over into the optional follow-up treatment period with a MRX dosing interruption of ≥ 7 days were dose escalated beginning at 35 µg/kg/day and up to a maximum of 400 µg/kg/day or highest tolerated dose (see Figure 4, where DE=dose escalation, FTP=follow-up treatment period).
- Subjects who did not wish to enter the follow-up treatment period were contacted via telephone by the study site approximately 30 days after the last dose of study drug.

Figure 3 Study Design for 52-Week Optional Follow-up Treatment Scheme for Subjects Who Experienced No Interruption in MRX or Interruption < 7 Days Between Protocol Amendment 2 and Protocol Amendment 3

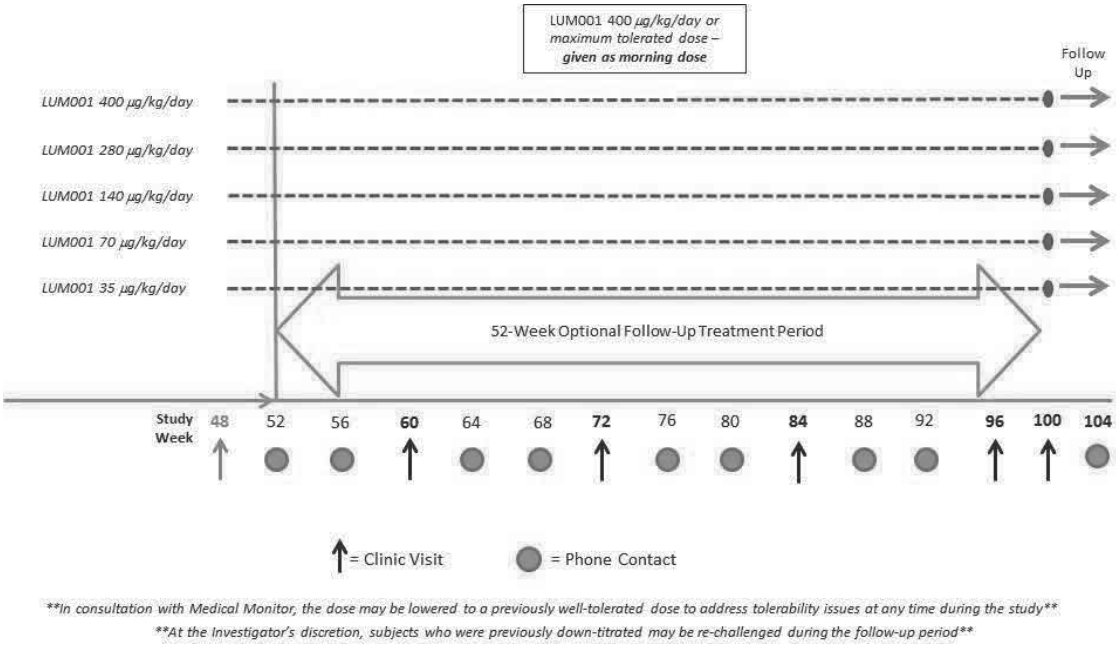
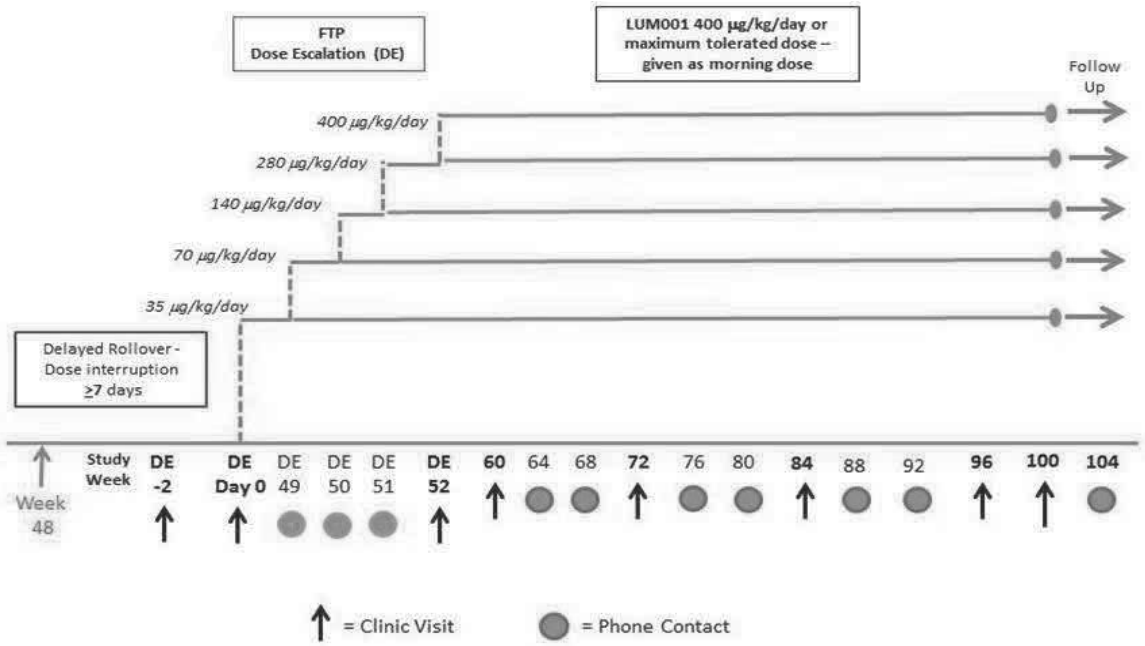


Figure 4 Study Design for 52-Week Optional Follow-up Treatment Scheme for Subjects Who Experienced an Interruption in MRX ≥ 7 Days Between Protocol Amendment 2 and Protocol Amendment 3



3.4.6. Long-Term Optional Follow-up Treatment Period

Upon completion of the 52-week optional follow-up treatment period, and/or implementation of protocol amendment 4, whichever occurred first, subjects were assessed by the investigator to determine their willingness and eligibility to roll-over (or enter) the long-term optional treatment period.

- Subjects who are eligible to roll over from the 52-week follow up treatment period into the long-term optional follow-up treatment period with no MRX dosing interruption or an interruption of < 7 days prior to implementation of PA 4 will be evaluated and either initiate the ADE (Figure 7) or continue receiving the same dose of MRX once a day (Figure 6).
- Subjects with ≥ 7 days since last dose of MRX prior to implementation of PA 4 who are eligible to enter the long-term optional follow-up treatment period will be dose escalated up to 400 µg/kg/day or to the highest tolerated dose beginning with 35 µg/kg/day (Figure 5) prior to being assessed for ADE eligibility and either initiating the ADE (Figure 7) or continue receiving the same dose of MRX once a day (Figure 6).

Note: ADE=afternoon dose escalation, DE=dose escalation, PA=protocol amendment, EOT=end of treatment, ET=early termination, MTD=maximum tolerated dose.

Figure 5 Study Design for Long-Term Optional Follow-up Treatment Scheme for Subjects Who Experienced an Interruption in MRX ≥ 7 Days Between PA 3 and PA 4

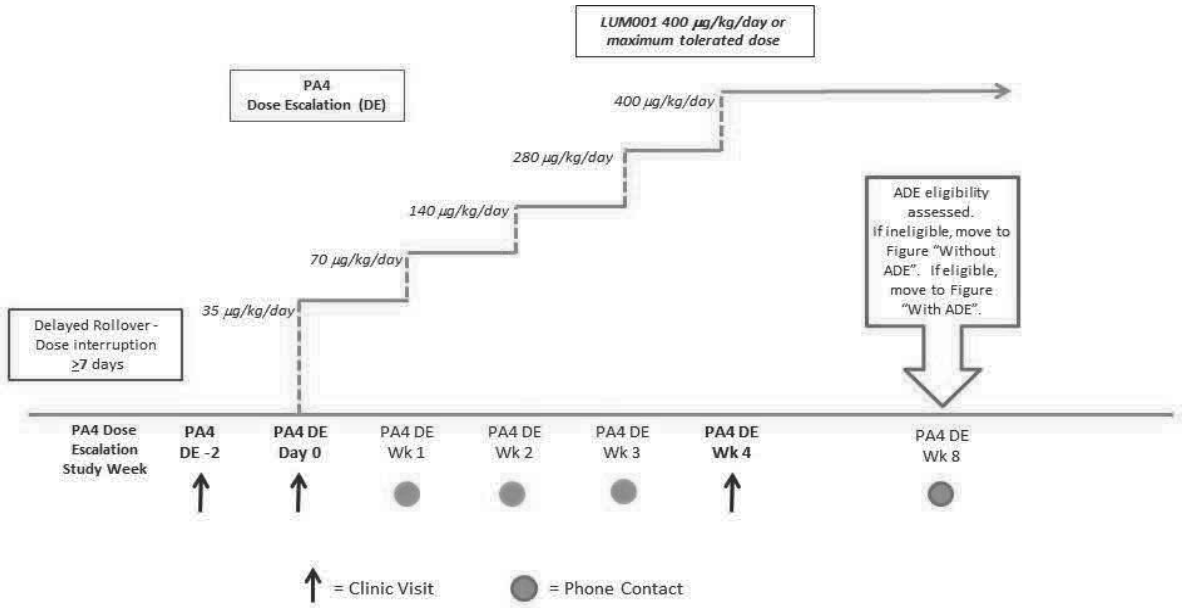


Figure 6 Study Design for Long-Term Optional Follow-up Treatment Scheme, Without Afternoon Dose Escalation (ADE)

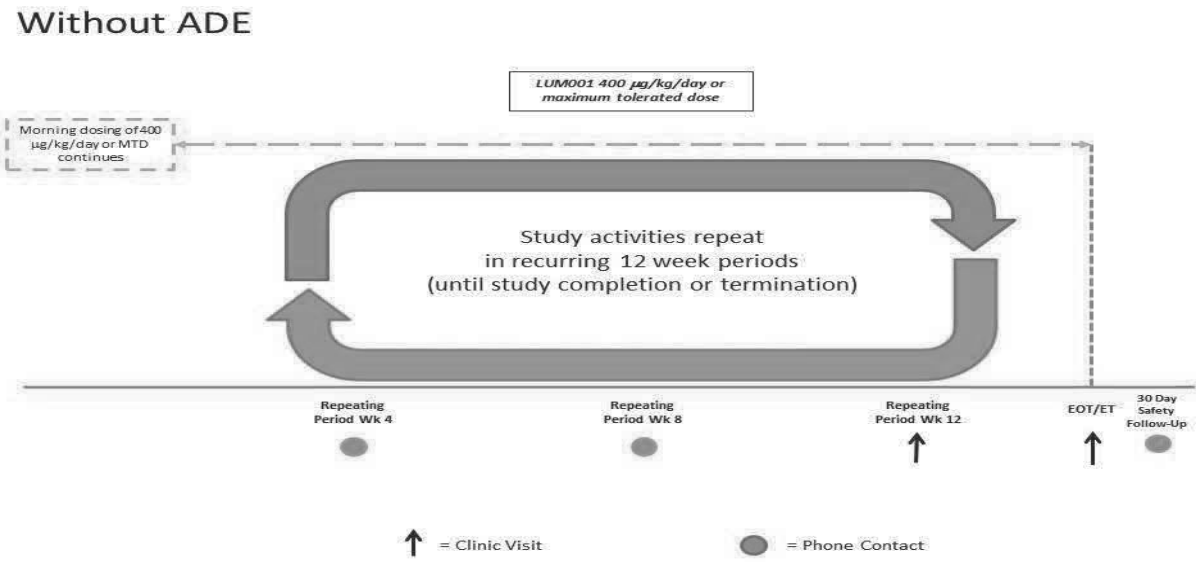
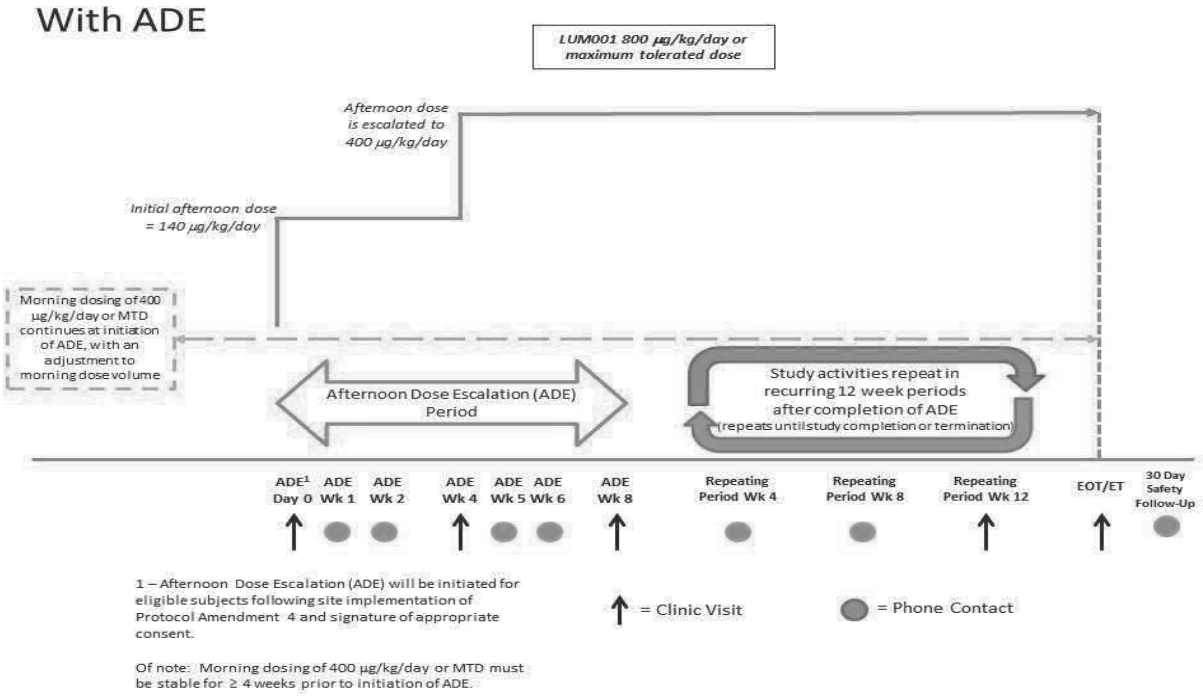


Figure 7 Study Design for Long-Term Optional Follow-up Treatment Scheme, With Afternoon Dose Escalation



3.5. Method of Assigning Subjects to Treatment Groups

At the end of the 12-week stable dosing period, subjects are randomized to treatment using the Interactive Response Technology (IRT) System. The randomization schedule was generated by an independent biostatistician using a permuted block algorithm that was stratified by response criteria where response was defined as a ≥ 50% reduction in serum bile acids between Baseline and Week 12. The method by which the randomization schedule was administered used a central by block randomization process (within IRT), with entire blocks assigned by study site.

Study drug is prepared by a central pharmacy based on the subject's weight at screening. Diluent is added by the central pharmacy pharmacist before shipping study drug to the site. The pharmacist at the central pharmacy is unblinded to treatment group. The study staff including the local site pharmacist (or qualified delegate) will remain blinded to the treatment assignment.

3.6. Blinding and Unblinding

Although subjects are treated in an open-label fashion from Week 1 to Week 18, subjects are randomized 1:1 to continue to receive study drug or a corresponding placebo for 4 weeks between the start of Week 19 and the end of Week 22 (i.e., the double-blind, placebo-controlled study drug withdrawal period). All subjects, monitors, and study center personnel related to the

study, except for the central pharmacist (or qualified designee) who prepares the study drug, will be blinded to study treatment during the randomized withdrawal period (Weeks 19 - 22) and the long-term exposure period (Weeks 23 - 48), and to the subject's study drug withdrawal period treatment assignment. A designated statistician will securely maintain an unblinded randomization schema.

If in the event of an emergency situation when knowledge of the treatment assignment during the double-blind, randomized drug withdrawal period will impact the clinical management of the subject, the investigator will have the ability to unblind the treatment assignment for that subject. If a subject is unblinded by the investigator, Mirum Pharmaceuticals must be informed of the unblinding within 24 hours. If the blinding is prematurely broken, it is the responsibility of the investigator to promptly document and explain any unblinding to Mirum Pharmaceuticals.

Breaking of the blind during the initial 48-week period of the study should not occur before all subjects either discontinue or complete Week 48, except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or when causality must be determined before submitting a regulatory safety report for a serious adverse event (SAE), as defined in the protocol.

Any unblinding event carried out in connection with submission of a regulatory safety report will be conducted by the Sponsor as described in the protocol.

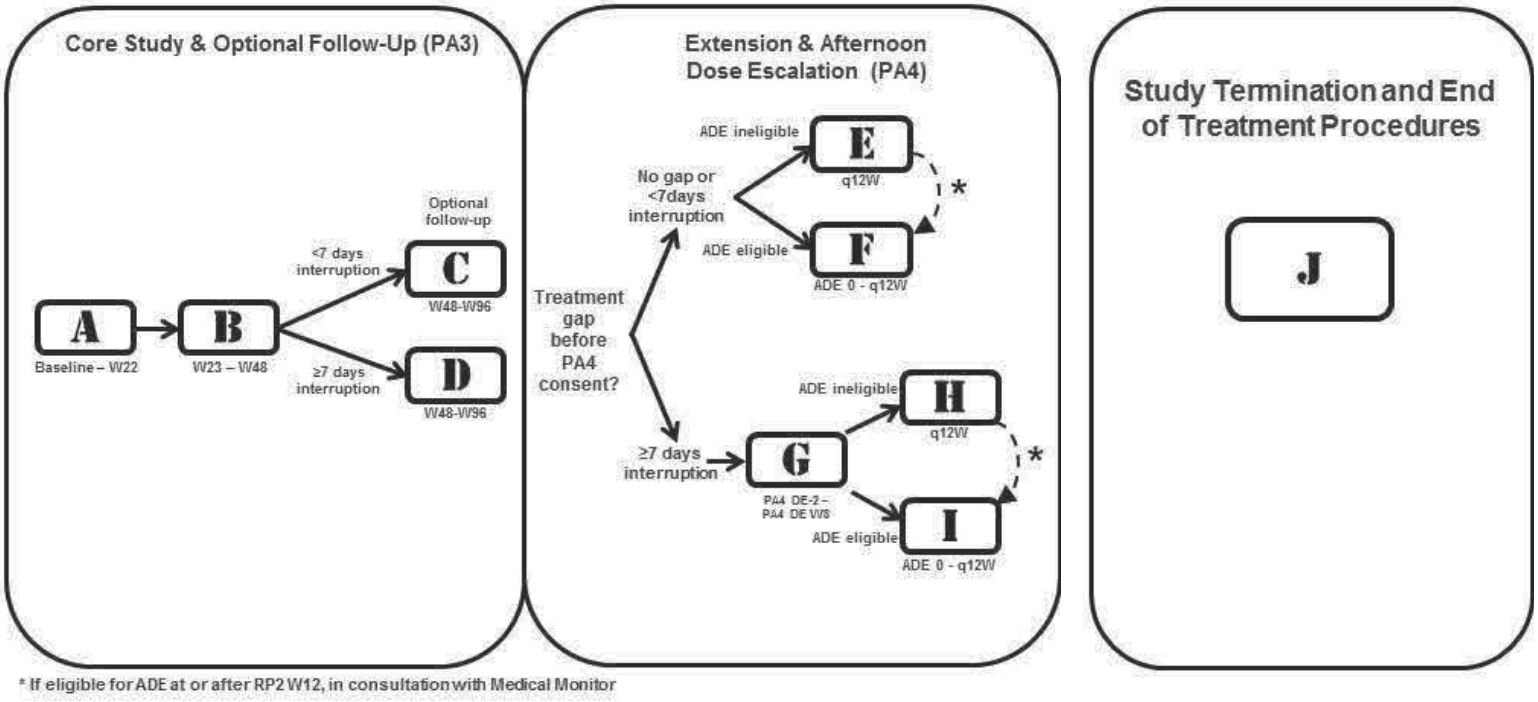
Every reasonable attempt should be made to complete the early termination study procedures and observations (see Schedule of Procedures, Section 3.7) before unblinding, as knowledge of the treatment arm could influence subject assessment.

The study protocol was amended on 06 Nov 2017 (Protocol Amendment 5) to change the study design going forward to an open label study. At that time all subjects had either completed Week 48 or discontinued prior to Week 48. The study was unblinded on 10 Jan 2018 for the interim analysis, as planned in the protocol.

3.7. Schedule of Procedures

A detailed schedule of procedures for the study is provided in the below tables. The following schematic shows the study flow and corresponding Schedule of Procedures (A-I).

Study Termination and End of Treatment Procedures are outlined in Schedule J.



3.7.1. Schedule of Procedures A-D: Study Entry – Week 96

Schedule of Procedures A: Screening – Week 22

Study Period	Screening	Baseline	Treatment Period										
			Dose Escalation[i]						Stable Dose			Randomized Withdrawal	
Study Week			1	2	3	4	5	6	9	12	18	20	22
Study Day	Day -28 to -1	Day 0	7	14	21	28	35	42	63	84	126	140	154
Window (in days)			(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)	(±5)
Informed Consent	X												
Eligibility Assessment/ Medical History	X	X											
Demographics	X												
Physical Exam	X	X			X			X		X	X		X
Body Weight & Height	X	X			X			X		X	X		X
Randomization to Placebo vs. LUM001											X		
Vital Signs[a]	X	X			X			X		X	X		X
CBC with Differential[b]	X	X			X			X		X	X		X
Coagulation[b]	X	X			X			X		X	X		X
Chemistry Panel[b]	X	X			X			X		X	X		X
Lipid Panel[b,c]		X								X	X		X
Cholestasis Biomarkers[b,c]		X								X	X		X
Total Serum bile acids[c]	X[k]	X								X	X		X
Fat Soluble Vitamins[b,c]		X								X	X		X
JAGGED1/NOTCH2 Genotyping[d] (if needed)	X												
Plasma Sample for LUM001		X[j]								X[j]	X[j]		
Urinalysis[b]	X	X[g]			X[g]			X[g]		X	X		X
Serum or Urine Pregnancy Test (if indicated)[e]	X	X			X			X		X	X		X
Subject eDiary/Caregiver eDiary (ItchRO)	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Clinician Scratch Scale	X	X			X			X		X	X		X
Clinician Xanthoma Scale		X									X		
PedsQL		X									X		X
Patient/Caregiver Impression of Change											X		X

Schedule of Procedures A: Screening – Week 22 (cont'd)

Study Period	Screening	Baseline	Treatment Period										
			Dose Escalation[i]						Stable Dose			Randomized Withdrawal	
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**18**	**20**	**22**
Study Day	**Day -28 to -1**	**Day 0**	**7**	**14**	**21**	**28**	**35**	**42**	**63**	**84**	**126**	**140**	**154**
Window (in days)			**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**
Caregiver Global Therapeutic Benefit											X		X
Enrollment		X											
Study Drug Supplied		X			X			X		X	X		X
Review Study Diaries & Assess Compliance		X			X			X		X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[f]			X	X		X	X		X			X	

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[c] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[d] Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation in support of the diagnosis of ALGS.
[e] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Subjects must be available to receive a phone call from study staff.
[g] At the indicated visits during the treatment period, oxalate will be part of the urinalysis.
[h] During screening and throughout the study, the eDiary (ItchRO) will be completed twice daily (AM & PM). Compliance will be assessed at each visit/phone contact.
[i] Subjects should be dosed for at least 7 days at each dose level.
[j] Pharmacokinetic analysis will be done at Baseline, and then approximately 4 hours post-dosing at one additional time point – at Week 12, 18, 38, or 48 (to be selected by site/investigator).
[k] Subjects are NOT required to fast prior to sample collection at the screening visit.

Clinic Visit
Phone Contact

Schedule of Procedures B: Long-term Exposure: Week 23–Week 48

Study Period	Treatment Period (cont'd)										Follow Up
	Long-Term Exposure										
Study Week	23	24	25	26	27	28	33	38	43	Week 48 (or Early Termination[f])	
Study Day	161	168	175	182	189	196	231	266	301	336	30 days after final dose
Window (in days)	(±2)	(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)	(±14)	(±5)
Physical Exam						X		X		X	
Body Weight & Height						X		X		X	
Vital Signs[a]						X		X		X	
CBC with Differential[b]						X		X		X	
Coagulation[b]						X		X		X	
Chemistry Panel[b]						X		X		X	
Lipid Panel[b,c]										X	
Total Serum bile acids[c]										X	
Cholestasis Biomarkers[b,c]										X	
Fat Soluble Vitamins[b,c]						X		X		X	
Plasma sample for MRX								X[i]		X[i]	
Urinalysis[b]						X		X		X[g]	
Urine Pregnancy Test (if indicated)[d]						X		X		X	
Clinician Scratch Scale						X		X		X	
Clinician Xanthoma Scale										X	
Subject eDiary/Caregiver eDiary (ItchRO)	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
PedsQL										X	
Patient & Caregiver Impression of Change										X	
Caregiver Global Therapeutic Benefit										X	
Study Drug Supplied						X		X		X[j]	
Review Study Diaries & Assess Compliance						X		X		X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[e]	X	X	X	X	X		X		X		X

Schedule of Procedures B – Long-term Exposure: Week 23–Week 48 (cont'd)

Study Period	Treatment Period (cont'd)										Follow Up
	Long-Term Exposure										
Study Week	23	24	25	26	27	28	33	38	43	Week 48 (or Early Termination[f])	
Study Day	161	168	175	182	189	196	231	266	301	336	30 days after final dose
Window (in days)	(±2)	(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)	(±14)	(±5)

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[c] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[d] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[e] Subjects must be available to receive a phone call from study staff.
[f] Subjects who withdraw early should complete all evaluations at this visit.
[g] At the indicated visits during the treatment period, oxalate will be part of the urinalysis.
[h] During screening and throughout the study, the eDiary (ItchRO) will be completed twice daily (AM and PM). Compliance will be assessed at each visit/phone contact.
[i] Pharmacokinetic analysis will be done at Baseline, and then approximately 4 hours post-dosing at one additional time point – at Week 12, 18, 38, or 48 (to be selected by site/investigator).
[j] For subjects entering optional Follow-up Treatment Period, once corresponding consent is signed.

☐ Clinic Visit
▒ Phone Contact

Schedule of Procedures C: 52-Week Optional Follow-up Treatment Period (FTP) – Week 48-96 for Those Subjects < 7 Days from the Last Dose of MRX (Includes evaluation of eligibility for BID dosing regimen)

Study Period	52-week FTP											
Study Week	52	56	60	64	68	72	76	80	84	88	92	96
Study Day	364	392	420	448	476	504	532	560	588	616	644	672
Window (in days)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)
Informed Consent/Assent for PA4[g]			X			X			X			X
Afternoon Dose Escalation (ADE) eligibility assessment followed by shift in visit schedule[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Physical Exam			X			X			X			X
Body Weight & Height			X			X			X			X
Vital Signs[a]			X			X			X			X
CBC with Differential[b]			X			X			X			X
Coagulation[b]			X			X			X			X
Chemistry Panel[b]			X			X			X			X
Lipid Panel[b,c]			X			X			X			X
Cholestasis Biomarkers[b,c]			X			X			X			X
Fat Soluble Vitamins[b,c]			X			X			X			X
Optional Genotyping[d]			X									
Urinalysis[b]			X			X			X			X
Urine Pregnancy Test (if indicated)[e]			X			X			X			X
Clinician Scratch Scale			X			X			X			X
Clinician Xanthoma Scale			X			X			X			X
Subject eDiary/Caregiver eDiary (ItchRO)			X[i]	X[i] to Week 62		X[i]	X[i] to Week 74		X[i]	X[i] to Week 86		X[i]
PedsQL			X			X			X			X
Patient & Caregiver Impression of Change									X			X
Caregiver Global Therapeutic Benefit									X			X
Study Drug Supplied			X			X			X			X
Review Study Diaries & Assess Compliance			X			X			X			X

Schedule of Procedures C: 52-Week Optional Follow-up Treatment Period (FTP) – Week 48-96 for Those Subjects < 7 Days from the Last Dose of MRX (cont'd)

Study Period	52-week FTP											
Study Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**
Window (in days)	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Phone contact[f]	X	X		X	X		X	X		X	X	

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[c] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[d] Genotyping sample will be drawn at Week 60 or at the time of re-consent for the optional follow-up treatment period; sample will be used to provide a full characterization and documentation of the mutation type in support of the diagnosis of ALGS.
[e] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Subjects must be available to receive a phone call from study staff.
[g] Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent patient for Protocol Amendment 4 at the next clinic visit.
[h] Once the Protocol Amendment 4 consent/assent has been signed, site will assess subject eligibility for Protocol Amendment 4 and ADE. Depending on the outcome of ADE eligibility assessment, subject will move into either Schedule of Procedures E or F. Of note: It is possible that subject will not necessarily complete up through Week 96 before they move to Schedule of Procedures E or F. ADE eligibility assessments may occur any time between Week 52 and Week 100.
[i] During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 60, Week 72, and Week 84 visits.

Clinic Visit
Phone Contact

Schedule of Procedures D: 52-Week Optional Follow-up Treatment Period – DE -2 – Week 96 for Those Subjects ≥ 7 Days from the Last Dose of MRX (Includes evaluation of eligibility for BID dosing regimen)

Study Period	Treatment Period (cont'd)															
	FTP Dose Escalation (DE)						FTP									
FTP Study Week	DE - 2	DE 0	DE 49	DE 50	DE 51	DE 52	60	64	68	72	76	80	84	88	92	96
DE Study Day	-14	0	343 [a]	350 [a]	357 [a]	364 [a]	420 [a]	448 [a]	476 [a]	504 [a]	532 [a]	560 [a]	588 [a]	616 [a]	644 [a]	672 [a]
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)
Informed Consent/Assent for study re-entry under PA3	X															
Eligibility Assessment for study re-entry	X															
Informed Consent/Assent for PA4[h]							X			X			X			X
Afternoon Dose Escalation (ADE) eligibility assessment followed by shift in visit schedule[i]							X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
Physical Exam	X	X				X	X			X			X			X
Body Weight & Height	X	X				X	X			X			X			X
Vital Signs[b]	X	X				X	X			X			X			X
CBC with Differential[c]	X	X				X	X			X			X			X
Coagulation[c]	X	X				X	X			X			X			X
Chemistry Panel[c]	X	X				X	X			X			X			X
Lipid Panel[c,d]	X	X				X	X			X			X			X
Cholestasis Biomarkers[c,d]	X	X				X	X			X			X			X
Fat Soluble Vitamins[c,d]	X	X				X	X			X			X			X
Optional Genotyping[e]	X															
Urinalysis[c]	X	X				X	X			X			X			X
Urine Pregnancy Test[f]	X	X				X	X			X			X			X
Clinician Scratch Scale	X	X				X	X			X			X			X

Schedule of Procedures D: 52-Week Optional Follow-up Treatment Period – DE -2 – Week 96 for Those Subjects ≥ 7 Days from the Last Dose of MRX (cont'd)

Study Period	Treatment Period (cont'd)															
	FTP Dose Escalation (DE)						FTP									
FTP Study Week	DE - 2	DE 0	DE 49	DE 50	DE 51	DE 52	60	64	68	72	76	80	84	88	92	96
DE Study Day	-14	0	343 [a]	350 [a]	357 [a]	364 [a]	420 [a]	448[a]	476 [a]	504 [a]	532 [a]	560 [a]	588 [a]	616 [a]	644 [a]	672 [a]
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)
Clinician Xanthoma Scale		X				X	X			X			X			X
Subject eDiary/Caregiver eDiary							X[j]	X[j] to Week 62		X[j]	X[j] to Week 74		X[a]	X[j] to Week 86		X[a]
PedsQL		X					X			X			X			X
Patient & Caregiver Impression of Change													X			X
Caregiver Global Therapeutic Benefit													X			X
Study Drug Supplied		X				X	X			X			X			
Review Study Diaries & Assess Compliance						X	X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[g]			X	X	X			X	X		X	X		X	X	

[a] Calculation of Study Day includes subject's participation through the first 48 weeks.
[b] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[c] See Appendix 2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin D supplementation.
[d] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[e] Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation type in support of the diagnosis of ALGS. Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[g] Subjects must be available to receive a phone call from study staff.
[h] Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent subject for Protocol Amendment 4 at the next clinic visit.
[i] Once the Protocol Amendment 4 consent/assent has been signed, site will assess subject eligibility for Protocol Amendment 4 and ADE. Depending on the outcome of ADE eligibility assessment, subject will move into either Schedule of Procedures E or F. Of note: It is possible that subject will not necessarily complete up through Week 96 before they move to Schedule of Procedures E or F. ADE eligibility assessments may occur any time between Week 60 and Week 100.
[j] During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 68, Week 96, and Week 120 visits.

Clinic Visit
Phone Contact

AD-ST-33.04 Effective date: 30 Jun 2017

3.7.2. Schedule of Procedures E-F: Rollover under Protocol Amendment 4

Schedule of Procedures E – Extension of Long-term Optional Follow-up Treatment Period, for subjects ineligible for ADE, applicable as follows:

- **Subject did not yet complete the long-term optional follow up treatment period as outlined under Protocol Amendment 3 and is able to consent to Protocol Amendment 4 activities without an interruption in MRX dosing, OR**
- **Subject completed long-term optional follow up treatment period as outlined under PA3 and dosing interruption was < 7 days.**
- **Subject deemed ineligible for ADE.**

	Below study activities repeat in repeating 12-week periods[h]		
Repeating Period Week (RPx)	**RPx Week 4**	**RPx Week 8**	**RPx Week 12**
Scheduling Considerations	**4 weeks after consent under PA4**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
Physical Exam			X
Body Weight & Height			X
Vital Signs[a]			X
CBC with Differential[b]			X
Coagulation[b]			X
Chemistry Panel[b]			X
Lipid Panel[b,c]			X
Cholestasis Biomarkers[b,c]			X
Fat Soluble Vitamins[b,c,d]			X
Urinalysis[b]			X[j]
AFP Sample			X[i]
Serum or Urine Pregnancy Test (if indicated)[e]			X
Clinician Scratch Scale			X
Clinician Xanthoma Scale			X
Caregiver ItchRO/ Patient ItchRO			X (collected for 2 week period following this visit)

Schedule of Procedures E: Extension of Long-term Optional Follow-up Treatment Period, for subjects ineligible for ADE (cont'd)

	Below study activities repeat in repeating 12-week periods[h]		
Repeating Period Week (RPx)	**RPx Week 4**	**RPx Week 8**	**RPx Week 12**
Scheduling Considerations	**4 weeks after consent under PA4**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
PedsQL			X
Palatability Questionnaire			X
Study Drug Supplied[f]			X
Assess Compliance			X
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Follow-up Phone Contact[g]	X	X	

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.
[h] Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study, (ii) MRX is available commercially, or (iii) the sponsor stops the program or development in this indication.
[i] Sample will be drawn at every other clinic visit starting with RP1 Week 12.
[j] At indicated visits during treatment period, oxalate will be part of the urinalysis.

Clinic Visit
Phone Contact

Schedule of Procedures F: Extension of Long-term Optional Follow-up Treatment Period, for subjects eligible for ADE, applicable as follows:

- **Subject did not yet complete the long-term optional follow up treatment period as outlined under Protocol Amendment 3 (PA3) and is able to consent to Protocol Amendment 4 activities without an interruption in MRX dosing OR**
- **Subject completed the long-term optional follow up treatment period as outlined under PA3 and dosing interruption was < 7 days.**
- **Subject deemed eligible for ADE.**

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeat in repeating 12-week periods after completion of the ADE period[h]		
Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±7)	(±7)	(±14)
Physical Exam	X			X			X			X
Body Weight & Height	X			X			X			X
Vital Signs[a]	X			X			X			X
CBC with Differential[b]	X			X			X			X
Coagulation[b]	X			X			X			X
Chemistry Panel[b]	X			X			X			X
Lipid Panel[b,c]	X			X			X			X
Cholestasis Biomarkers[b,c]	X			X			X			X
Fat Soluble Vitamins[b,c,d]	X			X			X			X

Schedule of Procedures F: Extension of Long-term Optional Follow-up Treatment Period, for subjects eligible for ADE (cont'd)

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeat in repeating 12-week periods after completion of the ADE period[h]		
Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±7)	(±7)	(±14)
Urinalysis[b]	X			X			X			X[k]
AFP Sample										X[i]
Plasma sample for MRX[j]	X			X			X			X[j]
Serum or Urine Pregnancy Test (if indicated)[e]	X			X			X			X
Clinician Scratch Scale	X			X			X			X
Clinician Xanthoma Scale	X			X			X			X
Caregiver ItchRO/ Patient ItchRO										X (collected for 2 week period following this visit)
PedsQL	X			X			X			X
Palatability Questionnaire										X
Study Drug Supplied[f]	X			X			X			X
Assess Compliance	X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X

Schedule of Procedures F: Extension of Long-term Optional Follow-up Treatment Period, for subjects eligible for ADE (cont'd)

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeat in repeating 12-week periods after completion of the ADE period[h]		
Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±7)	(±7)	(±14)
Adverse Events	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[g]		X	X		X	X		X	X	

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.
[h] Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study, (ii) MRX is available commercially, or (iii) the sponsor stops the program or development in this indication.
[i] Sample will be drawn at every other clinic visit starting with RP1 Week 12.
[j] Pharmacokinetic sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose escalation period.
[k] At indicated visits during treatment period, oxalate will be part of the UA.

Clinic Visit
Phone Contact

3.7.3. Schedule of Procedures G-I: Subject Re-Entry under Protocol Amendment 4

Schedule of Procedures G: Long-term Optional Follow-up Treatment Period - Re-entry under Protocol Amendment 4, applicable as follows:

- **Subject previously completed (or early terminated from) the long-term optional follow up treatment period as defined under Protocol Amendment 3 and has subsequently experienced an interruption in MRX dosing ≥7days.**
- **Subject is considered eligible for study re-entry under Protocol Amendment 4.**
- **Subject eligibility will be assessed for afternoon dose escalation at Protocol Amendment 4 DE Week 8 shown in the table below.**
  - **If subject is found to be ineligible for ADE, subject will move from Schedule G to Schedule H.**
  - **If subject is found to be eligible for ADE, subject will move from Schedule G to Schedule I.**

Study Period	Protocol Amendment 4 Follow-up Treatment Period Dose Escalation (DE)						
PA4 DE Study Week	PA4 DE -2	PA4 DE Day 0	PA4 DE Week 1	PA4 DE Week 2	PA4 DE Week 3	PA4 DE Week 4	PA4 DE Week 8
Scheduling Considerations	-14	0					
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)
Informed Consent/Assent	X						
Assess Eligibility for study re-entry	X	X					
Assess Eligibility for ADE							X
Physical Exam	X	X				X	
Body Weight & Height	X	X				X	
Vital Signs[a]	X	X				X	
CBC with Differential[b]	X	X				X	
Coagulation[b]	X	X				X	
Chemistry Panel[b]	X	X				X	
Lipid Panel[b,c]	X	X				X	
Cholestasis Biomarkers[b,c]	X	X				X	

Schedule of Procedures G: Long-term Optional Follow-up Treatment Period - Re-entry under Protocol Amendment 4 (cont'd)

Study Period	Protocol Amendment 4 Follow-up Treatment Period Dose Escalation (DE)						
PA4 DE Study Week	PA4 DE -2	PA4 DE Day 0	PA4 DE Week 1	PA4 DE Week 2	PA4 DE Week 3	PA4 DE Week 4	PA4 DE Week 8
Scheduling Considerations	-14	0					
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)
Fat Soluble Vitamins[b,c,d]	X	X				X	
Urinalysis[b]	X	X				X	
Serum or Urine Pregnancy Test (if indicated)[e]	X	X				X	
Clinician Scratch Scale	X	X				X	
Clinician Xanthoma Scale	X	X				X	
Caregiver ItchRO/ Patient ItchRO						X (collected for 2 week period following this visit)	
PedsQL		X					
Study Drug Supplied[f]		X				X	
Assess Compliance						X	
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Follow-up Phone Contact[g]			X	X	X		X

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.

Clinic Visit
Phone Contact

Schedule of Procedures H: Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject ineligible for ADE

	Below study activities repeat in repeating 12-week periods[h]		
Repeating Period Week	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**The Week 4 visit of the first repeating period will take place 4 weeks after PA4 DE Week 8**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
Physical Exam			X
Body Weight & Height			X
Vital Signs[a]			X
CBC with Differential[b]			X
Coagulation[b]			X
Chemistry Panel[b]			X
Lipid Panel[b,c]			X
Cholestasis Biomarkers[b,c]			X
Fat Soluble Vitamins[b,c,d]			X
Urinalysis[b]			X[i]
AFP Sample			X[i]
Serum or Urine Pregnancy Test (if indicated)[e]			X
Clinician Scratch Scale			X
Clinician Xanthoma Scale			X
Caregiver ItchRO/ Patient ItchRO			X (collected for 2 week period following this visit)
PedsQL			X
Palatability Questionnaire			X
Study Drug Supplied[f]			X
Assess Compliance			X
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Follow-up Phone Contact[g]	X	X	

Schedule of Procedures H – Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject ineligible for ADE (cont'd)

	Below study activities repeat in repeating 12-week periods[h]		
Repeating Period Week	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**The Week 4 visit of the first repeating period will take place 4 weeks after PA4 DE Week 8**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.
[h] Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study, (ii) MRX is available commercially, or (iii) the sponsor stops the program or development in this indication.
[i] Sample will be drawn at every other clinic visit starting with RP1 Week 12
[j] At indicated visits during treatment period, oxalate will be part of the UA.

☐ Clinic Visit
▒ Phone Contact

Schedule of Procedures I: Long-term Optional Follow-up Treatment Period - Re-entry under Protocol Amendment 4, subject eligible for ADE

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeating in repeating 12-week periods after completion of the ADE period[h]		
FTP Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)		(±2)	(±2)	(±7)	(±7)	(±14)
Physical Exam	X			X			X			X
Body Weight & Height	X			X			X			X
Vital Signs[a]	X			X			X			X
CBC with Differential[b]	X			X			X			X
Coagulation[b]	X			X			X			X
Chemistry Panel[b]	X			X			X			X
Lipid Panel[b,c]	X			X			X			X
Cholestasis Biomarkers[b,c]	X			X			X			X
Fat Soluble Vitamins[b,c,d]	X			X			X			X
Urinalysis[b]	X			X			X			X[k]
AFP Sample										X[i]
Plasma sample for MRX[j]	X			X			X			X[j]
Serum or Urine Pregnancy Test (if indicated)[e]	X			X			X			X
Clinician Scratch Scale	X			X			X			X

Schedule of Procedures I: Long-term Optional Follow-up Treatment Period - Re-entry under Protocol Amendment 4, subject eligible for ADE (cont'd)

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeating in repeating 12-week periods after completion of the ADE period[h]		
FTP Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)		(±2)	(±2)	(±7)	(±7)	(±14)
Clinician Xanthoma Scale	X			X			X			X
Caregiver ItchRO/ Patient ItchRO										X (collected for 2 week period following this visit)
PedsQL	X			X			X			X
Palatability Questionnaire										X
Study Drug Supplied[f]	X			X			X			X
Assess Compliance	X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[g]		X	X		X	X		X	X	

Schedule of Procedures I: Long-term Optional Follow-up Treatment Period - Re-entry under Protocol Amendment 4, subject eligible for ADE (cont'd)

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeating in repeating 12-week periods after completion of the ADE period[h]		
FTP Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)		(±2)	(±2)	(±7)	(±7)	(±14)

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.
[h] Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study, or (ii) MRX is available commercially, or (iii) the sponsor stops the program or development in this indication.
[i] Sample will be drawn at every other clinic visit starting with RP1 Week 129.
[j] Pharmacokinetic sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose escalation period.
[k] At indicated visits during treatment period, oxalate will be part of the UA.

☐ Clinic Visit
▒ Phone Contact

3.7.4. Schedule of Procedures J: Study Termination and End of Treatment Procedures

Schedule of Procedures J: End of Treatment (EOT) / Early Termination (ET) Visit and Post-Treatment Safety Follow Up

	EOT / ET	Safety Follow Up
Scheduling Considerations	**To take place upon completion of study[g] or at the time of early withdrawal**	**Minimum of 30 days after final dose**
Physical Exam	X	
Body Weight & Height	X	
Vital Signs[a]	X	
CBC with Differential[b]	X	
Coagulation[b]	X	
Chemistry Panel[b]	X	
Lipid Panel[b,c]	X	
Cholestasis Biomarkers[b,c]	X	
Fat Soluble Vitamins[b,c,d]	X	
Urinalysis[b]	X[h]	
AFP Sample	X	
Serum or Urine Pregnancy Test (if indicated)[e]	X	
Clinician Scratch Scale	X	
Clinician Xanthoma Scale	X	
PedsQL	X	
Patient/Caregiver Impression of Change	X	
Caregiver Global Therapeutic Benefit	X	
Palatability Questionnaire	X	
Assess Compliance	X	
Concomitant Medications	X	X
Adverse Events	X	X
Follow-up Phone Contact[f]		X

Schedule of Procedures J: End of Treatment (EOT) / Early Termination (ET) Visit and Post-Treatment Safety Follow Up

	EOT / ET	Safety Follow Up
Scheduling Considerations	**To take place upon completion of study[g] or at the time of early withdrawal**	**Minimum of 30 days after final dose**

[a] Blood pressure (BP), heart rate (HR), temperature, respiratory rate.
[b] See Appendix 2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential.
[f] Subjects must be available to receive a phone call from study staff.
[g] Will take place when the first of the following occur: (i) subjects are eligible to enter another MRX study, (ii) MRX is available commercially, or (iii) or the sponsor stops the program or development in this indication.
[h] At indicated visits during treatment period, oxalate will be part of the urinalysis.

☐ Clinic Visit
▒ Phone Contact

4. STATISTICAL ANALYSIS AND REPORTING

Statistical analysis will be performed following Premier Research's Standard Operating Procedures (SOPs).

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).

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, 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 number and percentage of subjects who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis population for the treatment phase and/or treatment group/sequence, unless otherwise specified.

For purposes of analysis, there will be 3 treatment phases:

- Open-Label Phase (Day 1 – Week 18),
- Randomized Withdrawal Phase (Weeks 19 - 22), and
- After Randomized Withdrawal Phase (Week > 22)

For select analysis, the 3rd treatment phase will be presented as 2 separate treatment phases: ARW (Week > 22 – Week 48) and ARW (Week > 48). Unless otherwise specified, summaries will be provided by treatment phase and treatment group/sequence.

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, unless otherwise specified. Measures of location (mean and median) and measures of spread (standard deviations or errors) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) 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, along with select laboratory values of autotaxin, FGF-19, and FGF-21, will be presented as integers. Derived values for BMI, PedsQL summary and total scale scores, along with select laboratory values of sBA, 25-hydroxyvitamin D, and vitamin A, and pH, will be presented to 1 decimal place. Derived values of height and weight z-scores, and ItchRO average values, along with select laboratory values of creatinine, α-tocopherol, retinol binding protein (RBP), retinol:RBP molar ratio, and ratio of α-tocopherol to the sum of cholesterol and triglycerides will be reported to 2 decimal places.

Percentages will be presented to 1 decimal place, unless otherwise specified. Where the number of subjects in a particular category is 0, a percentage (i.e., 0.0%) will not be displayed.

Statistical tests will be conducted using 2-tailed tests at the 0.05 significance level. P-values will be reported for all statistical tests and will be interpreted as nominal p-values in establishing statistical significance. Where appropriate, corresponding 95% CIs will be presented.

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

4.2. Interim Analysis

A planned unblinded interim analysis (IA) was conducted after all subjects completed the study through Week 48 or discontinued the study before the Week 48 clinic visit. A SIAP, dated 04 Feb 2018, describes the analysis performed on assessments through the Week 48 visit (per Protocol Amendment 4). The final interim analysis for the 48-week treatment period was performed on unblinded (actual) treatment codes. The purpose of this 1st interim analysis was to guide the future of the program.

Since the efficacy analysis comparing treatment arms (MRX versus PBO) will be performed only once on the final efficacy data (i.e., during the randomized placebo-controlled withdrawal period), there will be no statistical penalty.

In preparation for briefing documents for the End-of-Phase 2 meeting with FDA on 21May2019 and the pre-NDA meeting with FDA on 19 Nov 2019, additional interim analyses were performed. In preparation for the NDA submission, currently planned in August 2020, the analysis herein described will be performed using an interim data cut date of 01 Dec 2019.

Additional analyses may be performed to explore both safety and efficacy measures collected in this study. The precise methods and analyses will be determined after the database is locked and the blind is broken. Thus all such analyses will be interpreted cautiously and not used for formal inference, although inferential statistics may be used as part of the data summary

4.3. Data Monitoring

A Data Monitoring Committee (DMC) will review SAE data and other key subject safety and study data at specified intervals for the duration of the study. The DMC will be composed of several members who are otherwise independent from the conduct of the study: two or more physicians and one biostatistician. The DMC's primary responsibility is to review the progress of the study, particularly with regard to safety and risk/benefit, and make recommendations to stop or modify the study if safety concerns are identified. Further details regarding the structure, function and operation of the DMC will be detailed in the DMC charter.

5. ANALYSIS POPULATIONS

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population is defined as all subjects who were enrolled and received at least one dose of the study drug.
- **Intent-To-Treat Population (ITT):** The ITT Population includes all subjects who were enrolled and received at least one dose of the study drug.
- **Modified Intent-To-Treat Population (MITT):** The MITT Population includes all subjects who were enrolled, received study drug through Week 18, and had a reduction from baseline in sBA of ≥50% at the Week 12 or Week 18 measurement (sBA responder).

For each treatment phase, the following subjects will be included in each respective analysis population:

OL Phase: Subjects dosed during the OL phase.

RW Phase: Subjects randomized and dosed during the RW phase.

ARW Phase: Subjects dosed after the RW phase.

The Safety Population will be used for the analyses of safety endpoints. Safety analyses will be conducted according to the treatment received.

The ITT and MITT populations will be used for analyses of efficacy endpoints, as described in Section 8. Efficacy analyses will be conducted according to the assigned treatment (i.e., MRX or PBO) or treatment sequence (i.e., MRX-MRX-MRX or MRX-PBO-MRX), as appropriate.

There are 13 subjects that were off study drug for an extended period of time (i.e., at least 7 weeks) due to the subject being off study between protocol amendments. Of the 13 subjects that were off study (between protocol amendments), 5 had interruptions that occurred between protocol amendments 2 and 3 (after the Week 48 visit), while 8 others had interruptions that occurred between amendments 3 and 4 (after the Week 100 visit). No subject was off study between protocol amendments more than once. For select visit-based safety data, the primary analysis will exclude any safety data collected or assessed after a drug interruption of > 28 days due to a subject being off study. Visit-based data collected after the drug interruption, at the point of study drug re-initiation, will be analyzed separately as a sensitivity analysis.

6. GENERAL ISSUES FOR STATISTICAL ANALYSIS

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

All Efficacy Assessments and Safety Assessments Before Drug Interruption

For all visit-based efficacy analyses, and for visit-based safety data that is collected/assessed before an extended (> 28-day) drug interruption period (between protocol amendments), there are two baselines that will be used for change from baseline values, defined as follows:

- Baseline (Day 0): The observation obtained at Study Day 0 (before first dose of study drug) will be used as the baseline (Day 0) observation for all calculations of change from baseline (Day 0). If Study Day 0 is not available/missing, the last value obtained during the screening period is used as the baseline (Day 0) observation. This baseline is applicable for each of the 3 treatment phases (OL, RW, and ARW).
- Baseline (Week 18): The observation obtained at Week 18 (before the Randomized Withdrawal Phase) will be used as the baseline (Week 18) observation for all calculations of change from baseline (Week 18). If Week 18 is not available/missing, the last value obtained prior to the Randomized Withdrawal Phase will be used as the baseline (Week 18) observation. This baseline is only applicable for the RW treatment phase.

For ItchRO weekly average scores, each of the 2 baselines are defined as the average of daily scores in the week consisting of the 7 days immediately before the associated baseline visit. For ItchRO 4-week average scores, each of the baselines are defined as the average of daily scores in the 4-week period consisting of the 28 days immediately before the associated baseline visit.

Safety Assessments After Drug Interruption

For visit-based analyses on safety data collected/assessed after an extended drug interruption period (between protocol amendments), as described in Section 5, the following baseline definitions will be used for change from baseline values.

- Baseline (Day 0): Same definition as above.
- Baseline (PA Day 0): The last observation obtained before the first re-initiation dose after the drug interruption will be used as the baseline (PA Day 0) observation for all calculations of change from baseline (PA Day 0). *For subjects with a drug interruption between protocol amendments 2 and 3, the PA Day 0 visit is described as "Dose Escalation Day 0" in the database. For subjects with a drug interruption between protocol amendments 3 and 4, the PA Day 0 visit is described as "PA4 Dose Escalation Day 0".*

Because drug interruptions of > 28 days (between protocol amendments) occurred after the randomized withdrawal period, the above baselines are only applicable for the ARW treatment phase.

6.1.2. Study Day

Day 1 is defined as the date of first study drug administration. Study day is calculated relative to the date of Day 1.

6.1.3. Adjustments for Covariates

Analysis of covariance (ANCOVA) on the primary and secondary endpoints, with change from baseline as the dependent variable, will include the stratification variable sBA responder indicator as a covariate. These models will also include an interaction term for the covariate by treatment sequence (i.e., MRX-PBO-MRX or MRX-MRX-MRX).

If there appears to be a relative significant difference among treatment sequences with respect to baseline characteristics, that baseline variable may be added to the statistical model as a blocking factor or covariate to determine the effect on treatment. For this analysis, an interaction term for the covariate by treatment sequence will not be included.

ANCOVA models which only include the baseline value (of the variable of interest) as a single covariate will also be included.

ItchRO weekly morning severity scores, which are assessed over time during the 4-week Randomized Withdrawal phase, will also be analyzed using a mixed-effects model for repeated measures (MMRM). The MMRM model with change from baseline (Week 18) as the dependent variable, will include fixed, categorical effects of treatment group, visit (time point), and treatment group-by-visit interaction as well as the continuous, fixed covariates of baseline ItchRO score and baseline-by-visit interaction.

6.1.4. Multiple Comparisons

No adjustments will be made for multiple comparisons.

Because the definition of the pruritus endpoint used to assess efficacy was not pre-specified in the protocol (or SIAP) and the Type I error was not specifically controlled for, p-values for the analyses will be treated as nominal. The focus of the efficacy results will be on consistency and robustness of effect across multiple pruritus endpoints and methods of analysis.

6.1.5. Handling of Dropouts or Missing Data

6.1.5.1. General

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

Any subject who withdraws from the study is scheduled to undergo all procedures specified for the EOT/ET visit. Per the protocol, the ET visits should be scheduled within 7 days of the last dose of study drug. However, in the event an ET visit occurs more than 7 days after the date of last dose, prior to the respective ET visit (i.e., Week 48/ET, 100/ET, and EOT/ET), visit-based assessments performed during that visit will not be used in analysis summaries.

For a subject who prematurely discontinues the study, their ET visit data will be assigned to a protocol-specified visit window (for analysis purposes) as described in Section 6.1.7.

The procedures for handling dropouts or missing data, including the handling of missing individual daily ItchRO scores, PedsQL scale score items, and adverse event (AE) severity and relationship to study drug are described in the below subsections.

Rules for handling missing or partial AE or birth dates are described in Section 6.1.10.

6.1.5.2. MMRM Analysis Method

ItchRO weekly average morning severity scores derived for each week over the 4-week RW treatment phase (i.e., Weeks 19, 20, 21, and 22) will be analyzed using a restricted maximum likelihood (REML)-based repeated-measures approach, as the principal sensitivity analysis method. Details on the MMRM model to be used are described in Section 8.

The MMRM method has been demonstrated extensively as an appropriate choice for the primary analysis in confirmatory clinical trials with continuous endpoints. 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 subjects by estimating the covariance between data from different time points (Molenberghs and Kenward, 2007[4]). 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 (Week 22 in this case) are adjusted to reflect both the actual observed data and the projected outcomes from the subjects with missing data (Molenberghs et al., 2004[5], Molenberghs and Kenward, 2007[4]).

As a direct likelihood method, the MMRM method is a preferred approach for handling missing data in such designs. 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[6]). 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 (European Medicines Agency, 2010[7]). For studies of missing data in a controlled clinical trial setting, MAR is usually considered as a plausible underlying missing mechanism (Molenberghs and Kenward, 2007[4]; Siddiqui et al., 2009[8], Mallinckrodt et al., 2013[9]). The assumption of MAR is often reasonable because the observed data and the models used to analyze them can explain much of the missingness (Little and Rubin, 1987[10]).

6.1.5.3. LOCF Imputation

In addition to the time points specified in the protocol, safety and efficacy variables analyzed by time point will also be analyzed (as a sensitivity analysis) at the following LOCF time points: Week 18/LOCF, Week 22/LOCF, Week 48/LOCF, and Week 100/LOCF time points, where appropriate. Week 22/LOCF imputed time points are only applicable for ItchRO(Obs) weekly average score variables during the RW phase; there are no missing Week 22 assessments for ItchRO(Pt).

For subjects who early terminated from the study prior to Week 100 or are otherwise missing Week 18, Week 22, Week 48, and/or Week 100 data will be imputed in a LOCF approach as follows:

- OL Phase: last observation on or before Week 18 imputed as Week 18/LOCF;
- RW Phase: last observation between Week 18 and end of Week 22 imputed as Week 22/LOCF (only applicable for ItchRO[Obs] weekly average score variables);
- ARW Phase: last observation between Week 22 and end of Week 48 imputed as Week 48/LOCF and last observation after Week 22 and end of Week 100 imputed as Week 100/LOCF

For subjects that discontinue early, these time points are defined as the last post-baseline value obtained on or before the date of last dose plus 7 days (prior to the ET visit date). ItchRO assessments that occur more than 7 days after the date of last dose (prior to the ET visit date) will not be used to derive LOCF average scores. In this event, the LOCF average score will include assessments made up to the last 7 days immediately following the date of last dose (see Section 6.1.7).

6.1.5.4. Missing ItchRO Scores

In deriving ItchRO weekly and 4-week average scores, each scheduled visit date will be determined from the date of the vital signs assessment. If the date of vital signs is missing, then the date of the physical examination will be used. If both of these dates are missing for a specific scheduled visit then the start date from the subject visits derived dataset will be used. Further, for missing but expected dates (where ItchRO data exists), the last visit past the missing date is used and the appropriate amount of days is subtracted.

In the event that a subject/caregiver failed to complete the morning/evening report, the morning/evening score for that day will be treated as missing data.

On-study compliance for post-baseline ItchRO is defined as having at least 4 of the 7 daily scores for a 7-day period and at least 20 of the 28 daily scores for a 28-day period. Compliance restrictions are not set for baseline ItchRO average scores.

If a subject/caregiver is not compliant with reporting ItchRO assessments during the 7-day period before a study visit, the weekly average score from the most recent, previous compliant 7-day period will be used in a LOCF format. For non-compliant 4-week ItchRO assessments, the most recent compliant 28-day period will be used, where the 28 days minus the 7 days immediately prior to the study visit will be used. This process will be repeated as necessary. For example, if the 28-day period before the Week 6 visit (e.g., Study Days 15-42) is non-compliant, then Study Days 8-35 would be used. If that 4-week period is non-compliant then Study Days 1-28 would be used. If that 4-week period is non-compliant then the 4-week ItchRO score would be missing. Additionally, the same ItchRO assessment day (morning/evening daily score) will not be used across different weekly/4-week time periods (i.e., no overlap).

6.1.5.5. Missing PedsQL Scores

For PedsQL scale scores, if more than 50% of the items in the scale are missing, the scale score is not computed (see Section 6.1.9).

6.1.5.6. Responder Definitions

If a subject has a missing sBA, ItchRO, or CSS value at a week required in determining responder status, then the missing change from baseline value will be considered as not meeting the criteria for a responder.

6.1.5.7. Missing Last Dose

For subjects 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 and study drug exposure.

6.1.5.8. Missing Adverse Event Severity/Relationship

For analysis purposes, only the following rules will be applied for missing AE severity or relationship to study drug. For an AE that does not have a recorded relationship to study drug, the event will be conservatively considered as “Possibly Related” to study drug. If the severity of an AE is missing, the severity will be reported as “Severity Not Recorded”.

6.1.5.9. Missing Fat Soluble Vitamin (FSV) Data

For analysis purposes, missing FSV lab values will be reported in a “Missing” category in summarizing FSV level abnormalities.

6.1.6. Investigative Sites

An investigative site is defined as a single principal investigator (including sub-investigators) who enrols subjects for the study. If an investigator has multiple practice locations, these locations are considered a single investigative site.

Analyses will be based on data pooled across investigative sites.

There is the potential that a subject could be transferred to a principal investigator that did not enrol the subject. Unless otherwise specified, the investigative site of the enrolling investigator will be used for the unique subject ID.

6.1.7. Analysis Visit Windows

Analyses of all visit-based efficacy and safety variables will be performed using the analysis visit windows as defined in this section. The below tables address scheduled post-baseline assessments; baseline assessments are described in Section 6.1.1. Scheduled visits will be selected over unscheduled visits.

For those subjects who discontinue early from the study, the below tables (as appropriate) will also be used to assign the appropriate analysis visit to the ET visit. For subjects that were dose-escalated after a drug interruption of > 28 days (between protocol amendments), the data collected/assessed during the dose-escalation period (i.e., DE Week -2 and DE Day 0 for both PA3 and PA4) will not be assigned to a post-dose analysis visit. Only the DE Day 0 values will be used as baseline values as described in Section 6.1.1.

The study day will be calculated for each scheduled or ET post-baseline visit (and/or assessment), as described below, and compared to the assessment window presented in Table 4 or Table 5, as appropriate, 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 3 but a specific assessment (e.g., sBA sample or Clinician Xanthoma Scale score) was not scheduled at that visit (see Section 3.7, Schedule of Procedures), then that assessment will not be used for analyses.

Average ItchRO scores, which are derived by anchoring on scheduled in-clinic visit dates, will also be assigned to a study week for analysis according to Table 4. For analysis visits past Week 48, ItchRO average weekly scores are based on the 2-week period following the scheduled in-clinic visit. Thus, the “Analysis Visit” and “Analysis Visit Name” will be adjusted accordingly (e.g., “Week 62” rather than “Week 60”).

If more than 1 visit falls within the same visit window, the data from the visit closest to the target day will be used for the analysis visit. If 2 visits within the same visit window are equidistant from the target day, the data from the later visit will be used for the analysis visit.

Efficacy and Visit-Based Safety Assessments Before Drug Interruption

Analyses of all efficacy variables, regardless of drug interruptions, 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 4. For subjects with an extended drug interruption, efficacy assessments after the interruption are essentially treated as if the subject was on study drug during the period of time that the subject was off study drug.

The analysis visit windows in Table 4 will also be used for all visit-based safety assessments that occurred before a drug interruption (due to a protocol amendment), including those subjects without such a drug interruption.

Table 4 Analysis Visit Windows – Efficacy and Primary Safety Analysis

Analysis Visit	Analysis Visit Name	Target Day of Planned Visit	Assessment Window (Study Days[1])
3	Week 3	21	Post-dose ─ 31
6	Week 6	42	32 ─ 62
12	Week 12	84	63 ─ 105
18	Week 18	126	106 – Week 18 Visit Day[2]
22	Week 22	154	n/a[3]
28	Week 28	196	Week 22 Visit Day[2] (plus 1 day) – 232
38	Week 38	266	233 – 301
48	Week 48	336	302 – 378
60	Week 60	420	379 – 476
72	Week 72	504	477 – 546
84	Week 84	588	547 – 630
96	Week 96	672	631 – 714
108	Week 108	756	715 – 812
120	Week 120	840	813 – 882
132	Week 132	924	883 – 966
144	Week 144	1008	967 – 1054
156	Week 156	1092	1055 – 1148
168	Week 168	1176	1149 – 1218
180	Week 180	1260	1219 – 1302
192	Week 192	1344	1303 – 1385
204	Week 204	1428	1386 – 1470
216	Week 216	1512	1471 – 1554
228	Week 228	1596	1555 – 1638
240	Week 240	1680	1639 – 1722
252	Week 252	1764	1723 – 1806
264	Week 264	1848	1807 – 1890
276	Week 276	1932	1891 – 1974
288	Week 288	2016	1975 – 2058
300	Week 300	2100	2059 – 2142

[1] Study day relative to the date of first dose of study medication, unless otherwise specified.
[2] All 29 subjects in the RW phase completed their Week 18 and Week 22 clinic visits.
[3] For Week 22, the nominal visit or time point as collected in the CRF and/or database.

Visit-Based Safety Assessments After Drug Interruption

For visit-based safety data, the primary analysis will exclude any safety data collected or assessed after a drug interruption > 28 days due to a subject being off study (between protocol amendments). Safety chemistry data for laboratory samples collected after the drug interruption, at the point of study drug re-initiation, will be analyzed separately as a sensitivity analysis. FSV level abnormalities (e.g., sufficient, insufficient, excess) will also be analyzed separately as a sensitivity analysis using laboratory samples collected after the drug interruption. All visit-based safety data collected or assessed after the drug interruption period will be provided separately in subject listings.

For visit-based analyses (and listings) on safety data collected or assessed after a drug interruption period > 28 days (between protocol amendments), as described in Section 5, the analysis visit windows defined in Table 5 will be used. The analysis visit windows below are defined by study day relative to the date of first re-initiation of study drug after the drug interruption (i.e., PA Day 0; see Section 6.1.1).

Table 5 Analysis Visit Windows – Supporting Safety Subgroup Analysis (Data Assessed after an Extended Drug Interruption)

Analysis Visit	Analysis Visit Name	Target Day of Planned Visit	Assessment Window (Study Days[1])
4	Week 4	28	Post-dose ─ 56
12	Week 12	84	57 ─ 98
16	Week 16	112	99 – 129
24	Week 24	168	130 - 196
36	Week 36	252	197 - 283
48	Week 48	336	284 – 367
60	Week 60	420	368 – 451
72	Week 72	504	452 – 535
84	Week 84	588	536 – 619
96	Week 96	672	620 – 703
108	Week 108	756	704 – 787
120	Week 120	840	788 – 871
132	Week 132	924	872 – 955
144	Week 144	1008	956 – 1039
156	Week 156	1092	1040 – 1123
168	Week 168	1176	1124 – 1207
180	Week 180	1260	1208 – 1291
192	Week 192	1344	1292 – 1375
204	Week 204	1428	1376 – 1459

[1] Study day relative to the date of first re-initiation of study drug after the drug interruption.

Because drug interruptions between protocol amendments occurred after the RW phase, all subjects were administered MRX at all post-interruption time points.

6.1.8. Variable Definitions

- "Open-Label Phase" is defined for analysis purposes as the period of time between the first dose of study drug and the end of study Week 18 (i.e., through the Week 18 visit date).
- "Randomized Withdrawal Phase" is defined for analysis purposes as the period of time between the beginning of Week 19 (i.e., Week 18 visit date plus 1 day) and the Week 22 visit (inclusive).
- "After Randomized Withdrawal Phase" is defined for analysis purposes as the period of time between the beginning of Week 23 (i.e., Week 22 visit date plus 1 day) and the EOT visit (inclusive).
- "Week 18/LOCF" (see Section 6.1.5.3)
- "Week 22/LOCF" (see Section 6.1.5.3)
- "Week 48/LOCF" (see Section 6.1.5.3)
- "Week 100/LOCF" (see Section 6.1.5.3)
- "sBA Responder" is defined as a subject with a reduction in sBA ≥50% from baseline (Day 0) to clinic visit Week 12 or Week 18. See Section 6.1.5.6.
- "ItchRO Responder" is defined as a subject with a reduction in ItchRO(Obs) weekly average morning severity score ≥1.0 point from baseline (Day 0) to clinic visit Week 12 or Week 18. See Section 6.1.5.6.

  If a subject has a missing sBA or ItchRO value at a clinic visit required in determining responder status, then the missing change from baseline value would be considered as not meeting the criteria for a responder (non-responder).
- Treatment-emergent adverse events (TEAEs) are defined in Section 6.1.10.
- Concomitant medications are defined in Section 6.1.10.

6.1.9. Derived Variables

- **Age (months) at Baseline**:

  For subjects under 2 years of age, the age in years and months at baseline will be used:
  Age (months) at Baseline = (12 x Age (years) at Baseline) + # of months at Baseline

Otherwise,

Age (months) at Baseline = Integer of (Baseline Visit Date – Date of birth) / 30.44

Partial birth dates are imputed for analysis purposes as described in Section 6.1.10.

- **Age Group at Baseline**: 1 if age (full years) at baseline < 2 years
  2 if age (full years) at baseline is 2 - 4 years
  3 if age (full years) at baseline is 5 - 8 years
  4 if age (full years) at baseline is 9 - 12 years
  5 if age (full years) at baseline is 13 - 18 years

- **Body Mass Index (kg/m^2)** = $\frac{weight\ in\ kilograms}{(height\ in\ meters)^2}$

- **Treatment Duration (days)** = LASTDAY – FIRSTDAY + 1 day – GAP

  Treatment duration is derived overall and for each treatment phase (see below). For the OL and ARW (Week > 22 - 48) treatment phases, treatment duration is derived for the MRX QD dosing regimen. For the RW phase, treatment duration is derived separately for the MRX and PBO (QD) treatment groups. For the ARW (Week > 48) phase, treatment duration is derived separately for the MRX QD and MRX BID dosing regimens. For the overall study, treatment duration is derived for the MRX treatment group, where both QD and BID dosing regimens are considered.

  For the OL Phase (Week 0 - 18): LASTDAY = date of the Week 18 visit OR the date of last dose for subjects that ET before their Week 18 visit, FIRSTDAY = date of first dose, and GAP = 0;

  For the RW Phase (Week > 18 - 22): LASTDAY = date of the Week 22 visit OR the date of last dose for subjects that ET before their Week 22 visit, FIRSTDAY = date of the Week 18 visit plus 1 day, and GAP = 0;

  For the ARW Phase (Week > 22 - 48): LASTDAY = date of the Week 48 visit OR the date of last dose for subjects that ET before their Week 48 visit, FIRSTDAY = date of the Week 22 visit plus 1 day, and GAP = 0;

  For the ARW Phase (Week > 48):

  During the Week > 48 treatment phase, subjects may only receive MRX QD dosing or both QD and BID dosing, and potentially switch between QD to BID to QD dosing (depending upon their safety profile). Thus, treatment duration will be derived separately for MRX QD and MRX BID dosing.

MRX QD Treatment Duration is derived as the sum over the days on which a subject is on a QD dosing regimen minus GAP, where GAP = # days subject was off study between protocol amendments (i.e., PA2 and PA3 or PA3 and PA4).

MRX BID Treatment Duration is derived as the sum over the days on which a subject is on a BID dosing regimen (GAP = 0).

The date of the Week 48 visit plus 1 day would be the earliest date on which treatment duration would be derived during the Week > 48 phase.

For the Overall Study Phase (Week 0 – EOT): LASTDAY = date of the EOT visit OR the date of last dose for subjects that withdrew from the study, FIRSTDAY = date of first dose, and GAP = total # of days subject was off study between protocol amendments.

For ET subjects, the date of last dose is considered, rather than the last visit date during the study phase in which the subject early terminated. For subjects 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 and study drug exposure.

- **% Compliance During QD Dosing** = 100 *x* Number of days at least 1 dose is taken / QD Treatment Duration (days)

  where,

  Number of days at least 1 dose is taken = Treatment Duration (days) – Number of days a dose was missed *[during the specified time period, not including dosing gaps due to the subject being off study between protocol amendments]*

  Compliance is derived overall (Week 0-EOT) and for the following treatment phases: Week 0 - 18, Week > 18 - 22, Week > 22 - 48, and Week > 48. Study drug compliance will not be calculated for those subjects whose date of last dose is unknown.

- **% Compliance During BID Dosing** = 100 *x* Number of days both morning and evening dose is taken / BID Treatment Duration (days)

  where,

  Number of days both morning and evening dose is taken = BID Treatment Duration (days) – Number of days the morning and/or evening dose was missed during the BID treatment period *[not including dosing gaps due to the subject being off study between protocol amendments]*

BID dosing compliance is determined for the Week > 48 study phase, while subjects are on the BID dosing regimen. Only subjects that initiated ADE are included.

- **Total Dose Received (µg/kg)** = Dose (µg/kg/day) x Treatment Duration (days), for a given dose level
- **Total Drug Exposure (µg/kg)** = $\sum$ [Treatment duration (days)$_i$ *x* Total dose received (µg/kg)$_i$)]

  where,

  i = 1 to k, (k = number of days subject is receiving a constant dose)

  Total drug exposure is derived overall (Week 0-EOT) and for each treatment phase: Week 0 - 18, Week > 18 - 22, Week > 22 - 48, and Week > 48. The time periods for which no study drug was administered due to dosing gaps while a subject is off study (between protocol amendments) are not included. For subjects 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 and study drug exposure.

  For the ARW (Week > 48) phase, total drug exposure is derived separately for the MRX QD and MRX BID dosing regimens. For the overall study, total drug exposure is derived for the MRX treatment group, where both QD and BID dosing regimens are considered.

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

  Average daily dose is derived overall (Week 0-EOT) and for each treatment phase: Week 0 - 18, Week > 18 - 22, Week > 22 - 48, and Week > 48. The time periods for which no study drug was administered due to dosing gaps while a subject is off study (between protocol amendments) are not included.

  For the ARW (Week > 48) phase, average daily dose is derived separately for the MRX QD and MRX BID dosing regimens. For the overall study, average daily dose is derived for the MRX treatment group, where both QD and BID dosing regimens are considered.

- **ItchRO Weekly Average Morning Score** = Sum of ItchRO daily morning scores (over a 7-day period) divided by the number of days ItchRO completed

  ItchRO Weekly Average Evening Score = Sum of ItchRO daily evening scores (over a 7-day period) divided by the number of days ItchRO completed

The above definitions apply to both severity (Item 1) and frequency (Item 3, Observer only) weekly average scores. The baseline weekly morning/average evening score is derived using the 7 days immediately before the baseline visit date, according to the baseline definitions described in Section 6.1.1. The derivation for post-baseline weekly morning/average evening scores are described in Section 2.2.2.5.

- **ItchRO 4-Week Average Morning Score** = Sum of ItchRO daily morning scores (over a 28-day period) divided by the number of days ItchRO completed

  ItchRO 4-Week Average Evening Score = Sum of ItchRO daily evening scores (over a 28-day period) divided by the number of days ItchRO completed

  The above definitions apply to both severity (Item 1) and frequency (Item 3, Observer only) 4-week average scores. The baseline 4-week morning/average evening score is derived using the 28 days immediately before the baseline visit date, according to the baseline definitions described in Section 6.1.1. The derivation for post-baseline 4-week morning/average evening scores are described in Section 2.2.2.5.

- **ItchRO(Obs) Weekly Average Severity Score (based on the daily average of morning and evening scores)** = Sum of ItchRO(Obs) daily average of morning and evening scores (over a 7-day period) divided by the number of days ItchRO completed

  ItchRO(Obs) Weekly Average Severity Score (based on the daily maximum of morning and evening scores) = Sum of ItchRO(Obs) daily maximum of morning and evening scores (over a 7-day period) divided by the number of days ItchRO completed

  The baseline weekly average severity scores are derived using the 7 days immediately before the baseline visit date, according to the baseline definitions described in Section 6.1.1. The derivation for post-baseline weekly average severity scores are described in Section 2.2.2.5.

- **Estimated Total Lipids, mg/dL** = cholesterol (mg/dL) + triglycerides (mg/dL)

- **Ratio of Alpha Tocopherol to Estimated Total Lipids (the sum of Cholesterol + Triglycerides), mg/g** = 1000 x alpha tocopherol (mg/dL) / Estimated Total Lipids (mg/dL)

  For alpha tocopherol concentrations reported as below the minimum quantitation limit (i.e., 0.1 mg/dL), half of the minimum quantitation limit is used in the calculation.

- **Corrected Sodium, mmol/L** = sodium (mmol/L) + [0.00216 x Estimated Total Lipids (the sum of cholesterol + triglycerides) (mg/dL)]

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

- **Fat Soluble Vitamin Level Abnormality Definitions:**

  25-Hydroxyvitamin D: Sufficient if level ≥ 20 to 96 ng/mL
  Insufficient if level < 20 ng/mL
  Excess if level > 96 ng/mL

  Ratio of Alpha Tocopherol to Estimated Total Lipids: Sufficient if ratio > 0.8 to < 3.5 mg/g
  Insufficient if ratio ≤ 0.8 mg/g
  Excess if ratio ≥ 3.5 mg/g

  Corrected Sodium: Normal if level ≥ 135 to 148 mmol/L
  Low if level < 135 mmol/L
  High if level > 148 mmol/L

  Prothrombin Intl. Normalized Ratio: Sufficient if ratio < 1.2
  Indeterminate if ratio ≥ 1.2 to 1.5
  Possibly Insufficient if ratio > 1.5

  Retinol:RBP Molar Ratio: Sufficient if ratio ≥ 0.8 mol/mol
  Insufficient if ratio < 0.8 mol/mol

  Vitamin A: Sufficient if level 20 to 77 µg/dL
  Insufficient if level < 20 µg/dL
  Excess if level > 77 µg/dL

  For missing FSV values, a category of "Missing" is used.

- **Baseline Value** = Value obtained at baseline visit

  Change from Baseline = Value at current time point – Value at baseline

  % Change from Baseline = 100 x Change from Baseline / Value at baseline

  Refer to Section 6.1.1 for various baseline definitions. For ItchRO average scores, "Value" is the average score over the specified time period, as defined above. If Change from Baseline = 0 and Baseline Value = 0, then set % Change from Baseline to 0.

- **PedsQL Scoring Algorithm:**

  For each item of the PedsQL instrument (parent and subject), 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 Reference 13 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 age 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 subject reports. Family impact and parent functioning total scale and summary scores are based on parent-reported items.

- **Body Weight and Height z-Scores:**

  Height and weight z-scores are based on a subject's gender and age at each scheduled visit. For subjects less than 24 months of age, the World Health Organization (WHO) growth charts[11] are recommended by the Centers for Disease Control (CDC) and will be used to derive z-scores. For subjects at least 24 months of age, the CDC growth charts[12] will be used to derive z-scores.

- **Responder Definitions**:

  sBA Responder is defined as a subject with a reduction in sBA ≥50% from baseline (Day 0) to clinic visit Week 12 or Week 18.

  sBA Responder at Week 48 is defined as a subject with a reduction in sBA ≥50% from baseline (Day 0) to clinic visit Week 48.

  ItchRO Responder is defined as a subject with a reduction in ItchRO(Obs) weekly average morning severity score ≥1.0 point from baseline (Day 0) to clinic visit Week 12 or Week 18.

  CSS Responder – A responder is defined (separately at each analysis visit) as a:

  - Decrease from baseline ≥ 1
  - Decrease from baseline ≥ 2

  CIC-Itch, CIC-Xan, and PIC, Responders - A responder is defined (separately at each analysis visit) as a score ≤ 3 (i.e., a little better, better, or much better).

  CGTB Responder - A responder is defined (separately at each analysis visit) as a score ≤ 2 (i.e., somewhat, or definitely).

  If a subject has a missing value at a clinic visit required in determining responder status, then the missing observed or decrease from baseline value would be considered as not meeting the criteria for a responder (non-responder).

6.1.10. Data Adjustments/Handling/Conventions

Data not subject to analysis according to this plan will not appear in any tables, listings, or graphs.

Subject Age

Age at screening will be used as the age for the determination of the appropriate ItchRO instrument to be used for the study. The age of a subject at Study Day 0 (baseline) will be used as the age for the determination of the appropriate PedsQL module to be used for the study. The

same age-appropriate instrument will be used for the duration of the study (regardless of subsequent birthdays after the baseline visit).

Adverse Event and Concomitant Medication Coding

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 thesaurus. Prior and concomitant medications will be coded using WHO-DD (Enhanced version Sept 2019), Anatomical Therapeutic Chemical (ATC) level 2 for ATC class and Clinical Substance for preferred term.

Prior and Concomitant Medication Definition and Handling of Data

A concomitant medication is any non-protocol specified drug or substance administered during participation in the study. In general, this period of participation is from the first day of screening through the date of last contact.

Medications that started before the first dose of study drug are considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medication continuing or starting after the first dose of study drug will be considered to be concomitant. If a medication 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.

For subjects with study drug interruptions (for any reason), any concomitant medication that starts > 14 days after the last dose before the drug interruption and ended before the study drug was re-initiated will not be considered (for analysis purposes) as a concomitant medication.

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.

Treatment-Emergent Adverse Event Definition and Handling of Data

In general, TEAEs are defined as AEs with a start date on or after the first dose date of study drug and started before the last dose of study drug plus 14 days. For subjects with > 14 days of study drug interruption/withdrawal, the definition of a TEAE will consider both the date of the last dose before study drug interruption and the actual last dose. For these subjects, AEs that start > 14 days after the last dose (before study drug interruption) and ended before the drug is re-initiated will not be considered as treatment-emergent.

Any event which started before the first dose and worsens in severity or changes from non-serious to serious on or after the first dose date will also be designated as a treatment-emergent event. If an event worsens in severity during the study, the lower grade event is marked as “Not recovered/not resolved” on the AE 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 SAE.

Adverse event severity grades are reported according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. If the CTCAE does not have a grading for a particular AE, the severity of the event is reported by the investigator as mild, moderate, or severe. If CTCAE is not used and the event is reported as life-threatening then the severity of the event is considered as "Life-Threatening (CTCAE Grade 4)" for analysis purposes. Similarly, if CTCAE is not used and the event results in death then, for analysis purposes, the severity of the event is considered as "Fatal (CTCAE Grade 5)".

A treatment-related AE is any AE with a relationship to the study drug of related or possibly related.

An AE that does not have a recorded relationship to study drug will be considered as "Possibly Related" to study drug. If severity of an AE is missing, severity of the event will be reported for analysis purposes as "Severity Not Recorded".

Adverse Events of Special Interest

The following events have been defined as AEs of special interest (AESI) due to the nature of Alagille disease as well as of MRX:

- Diarrhoea events
- FSV deficiency events
- Elevated transaminases events
- Elevated bilirubin events

ALGS is associated with FSV deficiency and fluctuating transaminase elevations. MRX is associated with gastrointestinal disturbances such as diarrhoea.

The list of PTs used to identify FSV deficiency events are provided in Appendix 3. Diarrhoea events include PTs of 'Diarrhoea' and 'Gastroenteritis'. Elevated transaminases events include PTs of 'Alanine aminotransferase increased' and 'Aspartate aminotransferase increased'. Elevated bilirubin events include the PT of 'Blood bilirubin increased'.

Partial Date Imputation

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

Partial ALGS Diagnosis Dates

For partial original ALGS 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 Dates of Birth

Several of the investigative sites are located in countries that do not permit the reporting of complete dates of birth. These sites only report the month and year of date of birth. Complete date of birth is required, however, to derive a subject's weight and height z-scores at each scheduled study visit. For partial birth dates, the convention for replacing missing dates for the purpose of statistical analysis is as follows: the day is assigned the 15th day of the month (15).

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 prior/concomitant medication 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 before 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 before the first dose date, then the day/month are assigned the first day of the year (01 Jan).

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 (31 Dec).

Lower and Upper Limit of Quantification

In general, for quantitative laboratory values reported as "<" or "≤" the lower limit of quantification (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 MRX 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 quantification (ULOQ), the reported value (i.e., ULOQ) will be used for analysis.

Repeat 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.

Dose Used in Safety Analysis

For all safety and tolerability analyses, subjects will be analyzed by the treatment received. For AE summaries, MRX treatment groups are based on the dose received at the onset of the event. For all other safety summaries, treatment groups will be presented as either MRX (or PBO, where applicable).

Treatment Duration and Exposure

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

7. STUDY SUBJECTS AND DEMOGRAPHICS

7.1. Disposition of Subjects and Withdrawals

Subject disposition will be presented overall and by treatment period and assigned treatment group.

Subject disposition will include tabulations of the number and percentage of subjects in each of the analysis populations, dose reduced during the study, completed treatment, and discontinued treatment early (along with reasons for withdrawal). For the overall summary and the Week > 48 treatment period, subjects that did not consent to the optional long-term treatment extensions (PA3 or PA4) are not considered to have completed treatment. Reasons for withdrawal will include those collected on the CRF, along with not consenting to PA3 or PA4 (separately).

For the by study phase and treatment group summaries, the number and percentage of subjects presented will be based on the number of subjects in each treatment period (OL, RW, ARW Week 23 - 48, and ARW Week > 48) and treatment group (i.e., MRX and PBO for the RW phase only).

The subject disposition tabulation will also include the number of subjects screened for eligibility (under the original protocol), the number of screen failures (under the original protocol), and enrolled/randomized/continued, as appropriate for each treatment phase.

For the overall summary, the number and percentage of subjects that were initiated on the BID dosing regimen, and discontinued early during BID dosing regimen (along with reasons for withdrawal) will also be summarized. Percentages will be based on the number of subjects in the Safety Population.

Study drug accountability and compliance listings will be prepared for all subjects, 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 major 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 the Maralixibat program, including:

- ICF process or signature/version issue
- Violation of inclusion/exclusion criteria
- Deviation from study protocol procedures
- Dosing error
- Other deviation from study procedures

Other protocol deviations may be identified during the study.

Protocol deviations will be classified as “Major” or “Minor”. A major deviation poses a significant safety issue or significant impact on the statistical analysis of the clinical data. A minor deviation is identified as any protocol deviation that does not meet the criteria for a major deviation. Major deviations will be reviewed by Mirum Pharmaceuticals and Premier to determine the final classification, however all deviations will be reviewed with the study team at regular intervals.

Major protocol deviations may include:

- Significant and/or persistent dosing error
- Subject did not meet criteria for assignment and does not have a waiver or dispensation by medical monitor
- Error in randomization (i.e., received wrong drug)
- Use of prohibited concomitant treatment during participation in the trial

Major protocol violations/deviations will be presented in a subject listing. Additionally, inclusion and exclusion criteria not met and reasons for screen failures will be listed.

7.3. Demographics and Other Baseline Characteristics

Subject demographics and other baseline characteristics will be presented (1) by treatment period and assigned treatment group, (2) by sBA responder/non-responder and assigned treatment group (overall and during the RW phase), and (3) by ItchRO responder/non-responder and assigned treatment group (overall and during the RW phase).

Summary statistics for age (at baseline), age group, gender, country, mutation type, weight z-score, height z-score, and BMI will be presented. Age group categories are defined as < 2, 2 - 4, 5 - 8, 9 - 12 and 13 - 18 years of age at baseline.

These analyses will be conducted for the Safety Population.

7.4. Disease History and Baseline Disease Characteristics

Disease history and baseline disease characteristics will be presented (1) by treatment period and assigned treatment group, (2) by sBA responder/non-responder and assigned treatment group (overall and during the RW phase), and (3) by ItchRO responder/non-responder and assigned treatment group (overall and during the RW phase).

Summary statistics will be presented for the following baseline variables:

- time since original diagnosis of ALGS
- family history of ALGS *(yes/no)*
- presence of paucity *(yes/no/unknown)*
- mutation present *(JAGGED1/NOTCH2)*
- additional clinical criteria/features of ALGS *(chronic cholestasis, cardiac disease, renal abnormalities, vascular abnormalities, skeletal abnormalities, ocular abnormalities, and characteristic facial features)*
- used anything to treat itch in the past *(yes/no)*
- type of therapy used to treat itch in the past *(topical/oral/other)*
- specific therapy used to treat itch in the past *(reference list on Disease History CRF)*
- baseline pruritus assessments:
  - CSS *(continuous and categorical [0,1,2,3,4])*
  - ItchRO(Obs) weekly average morning severity score
  - ItchRO(Obs) weekly average morning frequency score
  - Clinician Xanthoma Scale score *(continuous and categorical [0,1,2,3,4])*
- baseline levels of select efficacy laboratory tests:
  - serum bile acids (sBA)
  - ALP
  - ALT
  - bilirubin (total and direct)
  - cholesterol
  - LDL-C
  - C4

The analyses of disease history and baseline disease characteristics will be conducted on the Safety Population.

A summary of demographic and baseline disease characteristics for all enrolled subjects will also be provided.

Subject demographics and baseline characteristics, and medical and surgical history information will be presented in subject listings.

7.5. Prior Medications

Prior medications will be summarized descriptively by treatment phase (OL, RW, and ARW), and treatment group for the RW treatment phase, using the number and percent of subjects by ATC class and preferred term (i.e., chemical substance). Summaries will be presented separately for: (1) prior anti-pruritus medications, (2) prior medications (excluding anti-pruritus medications), and (3) therapies to treat pruritus in the past, as collected specifically on the Disease History CRF under categories of topical, oral, and other therapies. Each summary will also include tabulations for the following categories: no medication/therapy, 1 medication/therapy, 2 medications/therapies, and at least 3 medications/therapies. For (1) and (2), medications that treat pruritus are listed in Section 6.1.10.

Prior medications will be presented separately from concomitant medications.

Prior and concomitant medications will also be presented separately in subject listings. A separate listing of prior medications that treat pruritus will also be presented.

7.6. Treatment Compliance

Treatment compliance will be calculated for each subject and summarized descriptively. This analysis will be completed using the Safety Population for each of the following study phases: Weeks 0 - 18, Weeks > 18 - 22, Weeks > 22 - 48, Weeks > 48, and overall (Weeks 0 - EOT). Subjects that withdraw early before any given study phase are not included in the analysis of that study phase.

For the RW treatment phase, treatment compliance will be summarized for both treatment groups (MRX and PBO).

For the ARW Week > 48 treatment period, treatment compliance will be summarized separately for the MRX QD and BID dosing regimens.

During the QD dosing regimen, a subject is considered compliant with treatment (for a given day) if any amount of study drug was administered. During the BID dosing regimen, a subject is considered compliant with treatment (for a given day) if both the morning and evening doses of study drug were administered.

Study drug accountability will be presented in a subject listing.

8. EFFICACY ANALYSIS

The primary analysis population for efficacy analysis will be the MITT Population defined in Section 5. Analyses for the primary and secondary efficacy outcome variables will also be

performed on the ITT Population. All sensitivity analysis will be performed on the ITT Population, unless otherwise specified.

Subjects will be analyzed by assigned treatment group (MRX or PBO during the RW phase) and/or by assigned treatment sequence (e.g., MRX-PBO-MRX, MRX-MRX-MRX). Efficacy data summaries will be provided by treatment phase and treatment group/sequence, unless otherwise specified.

All efficacy data will be presented in subject listings.

8.1. Primary Efficacy Analysis

The change from baseline in serum bile acid will be displayed for each treatment group during the randomized withdrawal phase using summary statistics including a 95% CI on the mean change. For each post-baseline analysis visit, the null hypothesis that the mean change is equal to zero will be tested using the Student's t-test to determine if the mean change is statistically significant.

The difference between treatment groups in change from Week 18 to Week 22 in serum bile acid will be evaluated using an ANCOVA model with treatment group as a factor, and Week 18 serum bile acid as a covariate. An ANCOVA model that includes the stratification variable sBA responder indicator as an additional covariate will also be performed on the ITT Population. This model will also include the sBA responder covariate by treatment sequence interaction term. The LS mean difference between treatment groups (MRX minus PBO) with standard error, 95% CI for the LS mean difference, and p-value for testing if the treatment group LS means are equal will be calculated to determine if the change in sBA levels between the treatment groups are statistically significant.

The primary analysis population will be the MITT Population. Analysis on the ITT Population will also be performed.

8.2. Secondary, Exploratory and Other Efficacy Analyses

Secondary, exploratory, and other efficacy variables that are continuous measures will be analyzed similarly to the primary efficacy analyses, using summary statistics and, with the exception of PIC, CIC, and CGTB, by ANCOVA. For the ItchRO weekly average morning severity scores during the RW treatment phase, treatment effects over the 4-week time period will also be analyzed using a REML-based repeated-measures approach.

Correlation analysis on change from baseline to Week 18, change from baseline to Week 48, and change from Week 18 to Week 22 values will also be performed on ItchRO weekly average scores and CSS scores.

Efficacy measures that are categorical binary responder outcomes will be analyzed using the chi-square or Fisher's Exact test, as appropriate based on sample sizes. Fisher's Exact test will be chosen over the chi-square test if any of the cell counts are less than 5. For ordinal non-binary

outcomes, the Cochran-Mantel-Haenszel (CMH) test will be used to take the ordinal nature of the variable into account.

Analyses specific to each efficacy variable are described below.

8.2.1. Continuous Measures

Efficacy variables that will be analyzed as continuous measures (i.e., ItchRO scores, efficacy lab levels, CSS, Clinician Xanthoma Scale score, CIC, PIC, CGTB, height and weight z-scores, and select PedsQL total/summary scale scores) will be examined by analysis visit for each of the following 3 treatment phases:

OL Phase (Day 1 – Week 18): Observed and change from baseline (Day 0) values.

RW Phase (Weeks 19 - 22): Observed, change from baseline (Day 0), and change from Week 18 values, where applicable (e.g., not applicable for Clinician Xanthoma Scale score or height and weight z-scores).

ARW Phase (Weeks > 22): Observed and change from baseline (Day 0) values.

Efficacy laboratory tests that will be statistically summarized include sBA, ALP, ALT, bilirubin (total and direct), C4, cholesterol, and LDL-C. A complete list of efficacy laboratory tests, and associated units of measure to be used for reporting, are listed in Appendix 2, noting that several efficacy laboratory results will not be statistically summarized, but rather included in subject listings. Bilirubin (total and direct), ALP, and ALT are considered as both safety and efficacy laboratory tests, and will be analyzed as efficacy variables. CSS, CIC-Itch, CIC-Xan, PIC, and CGTB will be examined as continuous and categorical measures.

A complete list of continuous efficacy variables and endpoint definitions (including sensitivity) are provided in Table 2.

Summary statistics, ANCOVA, MMRM, and correlation analyses will be performed as described below.

8.2.1.1. Summary Statistics by Analysis Visit

Summary statistics for all continuous efficacy measures will be presented by analysis visit on the ITT Population as observed and change from baseline values. For the OL and ARW treatment phases, summary statistics will be presented overall and for each treatment group during the RW phase. For the RW phase, summary statistics will be presented by the randomized treatment group. For each post-baseline analysis visit, the null hypothesis that the mean change is equal to zero will be tested using the Student's t-test to determine if the mean change is statistically significant.

For ItchRO(Obs) weekly average morning severity scores and sBA levels, summary statistics by analysis visit will also be presented for the following subgroups:

- Age group (up to 24 months, 2 - 12 years, > 12 years)
- Baseline sBA (< 275 µmol/L, ≥ 275 µmol/L)
- Baseline total bilirubin (< 3.8 mg/dL, ≥ 3.8 mg/dL)
- Baseline ALT (< 90 U/L, ≥ 90 U/L)
- Baseline ItchRO(Obs) weekly average morning severity score (< 3 pts, ≥ 3 pts)

For the subgroup analyses, observed and change from baseline (Day 0) values will be presented for the OL and ARW phases. For the RW phase, observed and change from Week 18 values will be presented for the MRX and PBO treatment groups.

Summary statistics will be presented in the ITT Population.

8.2.1.2. ANCOVA by Analysis Visit

For all continuous efficacy variables that are assessed at the baseline visit, an ANCOVA will be performed for each post-baseline analysis visit. The ANCOVA model will include change from baseline as the dependent variable, treatment sequence (MRX-MRX-MRX or MRX-PBO-MRX) as a fixed effect, and baseline value as a covariate. The ANCOVA will use a REML estimation method for the covariance parameter.

For each analysis visit, least squares (LS) means with SE, 95% CI for the LS means, and p-value for testing if the LS mean is zero will be calculated for each treatment sequence on observed and change from baseline values. For each analysis visit, the LS mean difference between treatment sequences (MRX-MRX-MRX minus MRX-PBO-MRX) with standard error, 95% CI for the LS mean difference, and p-value for testing if the treatment sequence LS means are equal will be presented.

The ANCOVA will be repeated in the following subgroups and/or data treatments as sensitivity analyses:

- Subjects considered to be an ItchRO Responder (see Section 6.1.9). This analysis will be performed on change from baseline in the following variables: ItchRO(Obs) weekly average morning severity score, ItchRO(Obs) and ItchRO(Pt) weekly average severity scores based on the daily maximum of morning and evening scores, ItchRO(Obs) and ItchRO(Pt) weekly average severity scores based on the daily average of morning and evening scores, and each efficacy laboratory test level.
- Subjects considered to be a sBA Responder at Week 48 (see Section 6.1.9). This analysis will be performed on change from baseline in ItchRO(Obs) weekly average morning severity score, and sBA level.
- As a sensitivity analysis, ItchRO(Obs) weekly average morning severity scores are alternatively derived using a minimum of 3 (rather than 4) daily morning scores to determine a “compliant” weekly average score. This analysis will be performed on

change from baseline in ItchRO(Obs) weekly average morning severity score using the alternate definition of a compliant week. *Based on the alternate definition, there are no missing weekly average morning scores for each week of the RW treatment phase.*

- For subject 050007, the 4-week time period immediately after the Week 18 visit date will be used to derive ItchRO weekly scores for Weeks 19, 20, 21, and 22. This sensitivity analysis will be performed on change from baseline in ItchRO(Obs) weekly average morning severity score, and sBA level, for analysis visits during the RW and ARW phases. An sBA sample was not collected in the 4-week time period following the Week 18 visit date for this subject, thus the sensitivity analysis on sBA levels will not include a "true" Week 22 sBA result.

  Subject 050007 was hospitalized during the RW phase for a SAE of polytraumatism/splenic rupture which made it impossible for the subject to comply with in-clinic visits and study drug treatment. It was decided by the Medical Monitors that this subject should discontinue study medication until the SAE resolved and the subject was able to comply with study requirements. The subject was on placebo for the first 5 weeks of the RW phase and then discontinued study drug for 13 weeks before their "Week 22" clinic visit. The primary analysis uses the "Week 22" sBA sample and the clinic visit date as the anchor in deriving Week 22 ItchRO weekly average scores, rather than (i) excluding this subject's sBA data during the RW phase, or (ii) using ItchRO data from the 4 weeks immediately following this subject's Week 18 clinic visit.

- If there appears to be a relative significant difference among treatment sequences with respect to baseline characteristics, that baseline variable may be added to individual ANCOVA models as a blocking factor or covariate to determine the effect on treatment. For this analysis, an interaction term for the covariate by treatment sequence will not be included. These analyses will be performed on change from baseline ItchRO(Obs) weekly average morning severity score.

  The following baseline covariates are currently considered as a covariate for this analysis: presence of paucity, CSS, sBA, total bilirubin, C4, age in months, BMI, ALT, family history of ALGS, cholesterol, GGT, and Clinician Xanthoma Scale score.

An ANCOVA that also includes the stratification variable, sBA responder group, as an additional covariate and the sBA responder group by treatment sequence interaction term in the model will also be performed. This analysis will be performed in change from baseline on the following efficacy variables: ItchRO(Obs) and ItchRO(Pt) weekly average morning severity scores, laboratory test levels, CSS, height and weight z-scores, and the select PedsQL total scale and summary scores.

ANCOVA described above will be performed on the ITT Population.

For the MITT Population (i.e., sBA Responders), the ANCOVA model that includes change from baseline as the dependent variable, treatment sequence as a fixed effect, and baseline value as a covariate will also be used for the following efficacy variables: ItchRO(Obs) weekly average morning severity score, ItchRO(Obs) and ItchRO(Pt) weekly average severity scores based on the daily maximum of morning and evening scores, ItchRO(Obs) and ItchRO(Pt) weekly average severity scores based on the daily average of morning and evening scores, and each efficacy laboratory test level.

8.2.1.3. MMRM Analyses

ItchRO(Obs) and ItchRO(Pt) weekly average morning severity scores derived for each week over the 4-week RW treatment phase (i.e., Weeks 19, 20, 21, and 22) will be analyzed using a REML-based repeated-measures approach, as the principal sensitivity analysis method. The MMRM analysis model, with change from baseline (Week 18) as the dependent variable, will include the fixed, categorical effects of treatment group, visit (time point), and treatment group-by-visit interaction as well as the continuous covariates of baseline and baseline-by-visit interaction.

An unstructured variance/covariance matrix, shared across treatment groups, will be used to model the variances and covariances for the 4 time points included in the model. The unstructured variance/covariance does not impose any restrictions on the pattern of the matrix elements. Every attempt (e.g., relaxing the convergence criteria, increasing the iteration limit, choosing reasonable starting values for the estimates) will be made to ensure convergence using the unstructured modeling of within-subject correlations. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors.

The p-value for testing the statistical significance of each effect in the MMRM model will be presented. For each time point, LS means with SE, 95% CI for the LS means, and p-value for testing if the LS mean is zero will be present for each treatment group on change from baseline (Week 18). For each time point, the LS mean difference between treatment groups (MRX minus PBO) with standard error, 95% CI for the LS mean difference, and p-value for testing if the treatment group LS means are equal will be presented.

The primary comparison will be the contrast (difference in least-squares mean) between treatments at the last visit during the RW phase (Week 22). The overall p-value for the model will also be presented to test the null hypothesis that there is no change at any time point.

For ItchRO(Obs) weekly average morning severity scores, MMRM analyses will be repeated as sensitivity analyses using the below data treatments or added covariates:

- A minimum of 3 (rather than 4) daily morning scores will be used to determine a "compliant" weekly average score. *Based on this alternate definition, there are no missing weekly average morning scores at any of the 4 time points during the RW treatment phase.*

- For subject 050007, the 4-week time period immediately after the Week 18 visit date will be used to derive ItchRO weekly scores for Weeks 19, 20, 21, and 22. *See above for further information regarding this subject.*
- Include the stratification variable, sBA responder group, as an additional covariate in the model.
- Include baseline BMI as an additional covariate in the model.
- Includes gender, age (in months), and baseline BMI as additional covariates in the model.

The MMRM analyses described above will be performed on the ITT Population.

8.2.1.4. Correlation Analyses

Pairwise correlation analysis on change from baseline to Week 18, change from baseline to Week 48, and change from Week 18 to Week 22 values will also be performed on the following efficacy variables:

- ItchRO(Obs) weekly average morning severity score
- ItchRO(Obs) weekly average evening severity score
- ItchRO(Pt) weekly average morning severity score
- ItchRO(Pt) weekly average evening severity score
- CSS score

For each pairwise correlation, the number of non-missing pairs, the Pearson correlation coefficient, and associated 95% confidence limits and p-value will be presented. The confidence limits on the correlation coefficients will be based on Fisher's z transformation (without bias adjustment).

Correlation coefficient estimates for change from Week 18 to Week 22 will be presented by treatment sequence.

Correlation analyses will be performed on the ITT Population.

8.2.1.5. Efficacy Graphical Presentations

Change from baseline in ItchRO(Obs) and ItchRO(Pt) weekly average morning scores, sBA, C4, bilirubin (total and direct), ALT, ALP, total cholesterol, LDL-C, height and weight z-scores, and PedsQL total scale and multidimensional fatigue scale scores (parent) will be displayed graphically over the treatment period.

Change from Week 18 to Week 22 LS means and associated 95% CIs in sBA based on the ANCOVA will also be displayed using the MITT Population.

Planned efficacy figures are described in Section 13.3. Additional figures may be added post-hoc to further examine study data.

8.2.1.6. Efficacy Subject Listings

All efficacy data will be presented in subject listings, including the following efficacy variables that were not included in tabular summaries:

- ItchRO(Obs) and ItchRO(Pt) morning and evening daily scores, along with responses to all other questions on the ItchRO questionnaire.
- PedsQL total scale and summary scores, along with all individual responses to questions in the core generic PedsQL module, and the multidimensional fatigue and family impact questionnaires.
- Cholestasis biomarkers including autotaxin, FGF-19, FGF-21, % unconjugated bile acids, total conjugated bile acids, total unconjugated bile acids, and the 15 bile acid subspecies (i.e., chenodeoxycholic acid, cholic acid, deoxycholic acid, glycochenodeoxycholic acid, glycocholic acid, glycodeoxycholic acid, glycolithocholic acid, glycoursodeoxycholic acid, lithocholic acid, taurochenodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, taurolithocholic acid, tauroursodeoxycholic acid, and ursodeoxycholic acid).

8.2.2. Categorical Measures

CSS, PIC, CIC-Itch, CIC-Xan, and CGTB will be analyzed as both ordinal and binary (responder/non-responder) measures using CMH and chi-square (or Fisher's Exact) tests, respectively. These variables will be examined by analysis visit for each of the 3 treatment phases (i.e., OL, RW, and ARW).

ItchRO(Obs) and ItchRO(Pt) morning severity scores will be summarized by time period, overall and by treatment group, as the number and percent of days the daily morning score is ≤ 1 point. Time periods include Day 1 - Week 6, Weeks 7 - 12, Weeks 13 - 18, Weeks 19 - 22, Weeks 23 - 48, Weeks 49 - 98, and Week > 98. No inferential statistical tests will be performed.

Contingency cross-classification tables of ItchRO(Obs) and ItchRO(Pt) daily severity scores at Week 18 and Week 22 (i.e., for all 7 days in the week) will be presented individually for morning and evening scores. No inferential statistical tests will be performed.

For ALT and total bilirubin, the number and percent of subjects at varying threshold levels will be presented by analysis visit, overall and by treatment sequence. ALT thresholds include > 3 x upper limit normal (ULN), > 5 x ULN, > 10 x ULN, and > 20 x ULN, noting that these categories are not mutually exclusive. The threshold for total bilirubin is > 2.5 mg/dL. No inferential statistical tests will be performed.

Categorical analyses will be performed on the ITT Population.

8.2.2.1. CMH Analyses

For ordinal measures, the 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. Similar analysis will be performed on change from baseline in CSS scores by analysis visit.

8.2.2.2. Chi-Square or Fisher's Exact Tests

For binary measures, the chi-square or Fisher's Exact test will be used to test for no association between treatment group and response (responder/non-responder). For the OL and ARW treatment phases, the number and percentage of subjects categorized as a responder and non-responder will be presented overall and for each treatment group during the RW phase. For the RW phase, the number and percentage of subjects categorized as a responder and non-responder will be presented by the randomized treatment group. For PIC and CIC, a responder is defined as an impression of change score of ≤ 3 (i.e., a little better, better, or much better). For CGTB, a responder is defined as a score of ≤ 2 (i.e., somewhat, or definitely). For CSS, 2 responder definitions are analyzed separately. CSS responder criteria include (a) a decrease from baseline score of at least 1, and (b) a decrease from baseline score of at least 2.

9. SAFETY AND TOLERABILITY ANALYSIS

All safety analyses will be performed on the Safety Population.

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

For visit-based safety data (i.e., vital signs, BMI, and safety labs), the primary analysis will exclude any data collected or assessed after a drug interruption > 28 days due to a subject being off study (between protocol amendments). Visit-based data collected after the drug interruption, at the point of study drug re-initiation, will be analyzed separately as a sensitivity analysis.

For all safety analyses, subjects will be analyzed by the treatment received. In general, safety data summaries will be provided by treatment phase and treatment group. For AE summaries, MRX treatment groups are based on the dose received at the onset of the event. For all other safety summaries, treatment groups will be presented as either MRX (or PBO, where applicable).

All safety and tolerability data will be presented by treatment sequence in subject listings. All visit-based safety data collected or assessed after the drug interruption period (between protocol amendments) will be presented in separate subject listings.

9.1. Treatment Exposure

Treatment exposure will be summarized descriptively overall and by each of the following treatment periods: OL, RW, ARW Week > 22 - 48, and ARW Week > 48. These summaries will include: average daily dose (µg/kg/day), total drug exposure (µg/kg), and treatment duration (days). Reference Section 6.1.9 for the derivation of these variables.

For the RW treatment phase, treatment duration will be summarized for both treatment groups (MRX and PBO).

For the ARW Week > 48 treatment period, average daily dose, total drug exposure, and treatment duration will be summarized separately for the MRX QD and BID dosing regimens.

For the overall treatment period, the number of days on study drug for the entire study (date of last dose – date of first dose + 1 day – interval of drug interruption off study) will also be summarized categorically using the following mutually exclusive time intervals:

- ≤ 13 Weeks
- > 13 to 23 Weeks
- > 23 to 78 Weeks (0.5 - 1.5 yrs)
- > 78 to 104 Weeks (1.5 - 2 yrs)
- > 104 to 156 Weeks (2 - 3 yrs)
- > 156 to 208 Weeks (3 - 4 yrs)
- > 208 Weeks (> 4 years)

9.2. Adverse Events

In general, TEAEs are AEs with a start date on or after the first dose date of study drug and a start date before the last dose of study drug plus 14 days. For subjects with > 14 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 6.1.10).

Analysis of TEAEs will be performed overall and separately for each of the following treatment periods: OL, RW, ARW Week > 22 - 48, and ARW Week > 48. For the overall summary and the OL and ARW periods, TEAEs will be summarized overall and by MRX dose at the onset of the event. For the RW period, TEAEs will be summarized by treatment group, noting that during the RW period all subjects on MRX were dosed at a 400 µg/kg QD dosing regimen.

Subjects that withdrew early during the OL phase will not be included in the RW or ARW analyses. Similarly, subjects that withdrew early during the OL or RW phases will not be

included in the ARW analyses. In summarizing AEs for the 4 treatment periods, events will only be counted in the period in which the event started. For example, if an event starts during Week 16 and continues into Week 19, the event will only be counted in the OL phase.

A summary of TEAEs will be presented overall and by treatment period, and treatment group (including MRX overall and dose at onset). The summary will include the total number and percent of subjects reporting:

- Any TEAEs
- Any treatment-related TEAE
- Any serious TEAE
- Any serious treatment-related TEAE
- Any TEAE leading to study discontinuation
- TEAEs resulting in death

Similar TEAE summaries will also be presented by age group (< 2, 2 - 12, and > 12 years at baseline) and by MRX dose group (< 400, 400, and > 400 µg/kg/day). These summaries will not be presented by treatment period.

The number and percent of subjects reporting TEAEs, grouped by MedDRA system organ class (SOC) and preferred term (PT), will be tabulated overall and by maximum severity. These AE summaries will be repeated for treatment-related AEs. In the case of multiple occurrences of the same TEAE within the same subject (and the same treatment period), each subject will only be counted once for each preferred term.

In presenting TEAEs for the individual treatment periods, events will only be counted in the treatment period in which the event started. TEAEs that started on or after the date of the first dose and on or before the subject's Week 18 visit date are assigned to the OL period. TEAEs that started the day after the subject's Week 18 visit date and on or before the subject's Week 22 visit date are assigned to the RW period. TEAEs that started the day after the subject's Week 22 visit date and on or before the subject's Week 48 visit date are assigned to the ARW Week > 22 - 48 period. TEAEs that started the day after the subject's Week 48 visit date up to and including 14 days after the EOT visit date are assigned to the ARW Week > 48 period. TEAEs are assigned to the treatment and dose that the subject was receiving at the date of the start of the event.

All AEs will be coded using MedDRA version 22.1 thesaurus. All TEAEs 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.

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 6.1.10.

In the AE data listings, events that are treatment-emergent will be flagged. AEs will be presented in by-subject listings, detailing the treatment phase, 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.

9.2.1. Adverse Events Leading to Withdrawal

AEs that lead to permanent discontinuation of study drug will be tabulated by SOC and PT overall and separately for each of the 4 treatment periods by dose at onset of the event. Subject listings of AEs that lead to permanent discontinuation of study drug will also be presented.

9.2.2. Deaths and Serious Adverse Events

Treatment-emergent SAEs, and SAEs potentially related to study drug 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, including post-treatment follow-up periods, will be presented in a subject listing. The listing will include subject ID, treatment period, 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.

9.2.3. Adverse Events of Special Interest

Due to the nature of Alagille disease, as well as MRX, the following events have been defined as AESIs: diarrhoea events, FSV deficiency events, elevated transaminases, and elevated bilirubin. For each of the AESI events, the PTs are described in Section 6.1.10.

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

9.3. Safety Laboratory Evaluations

The primary analysis of safety laboratory data will exclude any laboratory samples that were collected from a subject after a drug interruption > 28 days due to the subject being off study (between protocol amendments).

Safety laboratory test results will be summarized using descriptive statistics by laboratory test panel (i.e., chemistry, hematology, FSVs, and lipids), treatment phase, and analysis visit as observed and change from baseline values. Summary statistics will be presented for each of the following 3 treatment phases:

OL Phase (Day 1 – Week 18): Observed and change from baseline (Day 0) values.

RW Phase (Weeks 19 - 22): Observed, change from baseline (Day 0), and change from Week 18 values.

ARW Phase (Weeks > 22): Observed and change from baseline (Day 0) values.

For the OL and ARW treatment phases, summary statistics will be presented for the MRX treatment group. For the RW phase, summary statistics will be presented by the randomized treatment group (MRX or PBO). For each post-baseline analysis visit, the null hypothesis that the mean change is equal to zero will be tested using the Student's t-test to determine if the mean change is statistically significant.

Specific laboratory tests, and associated units of measure, that will be used for safety reporting are listed in Appendix 2. As noted, summary statistics will not be presented for urinalysis results, but rather included in subject listings. Bilirubin (total and direct), ALP, and ALT are considered as both safety and efficacy laboratory tests, and will only be summarized as efficacy variables. All safety laboratory test parameters will be presented (by panel) in subject listings.

For select FSVs, including 25-hydroxyvitamin D, ratio of alpha tocopherol to estimated total lipids, corrected sodium, INR, retinol:RBP molar ratio, and vitamin A, a summary of abnormalities will be presented. The number and percent of subjects within each test level category will be presented for each of the following analysis visits: Baseline, Week 18, Week 22 (by treatment group), and Week 48. For these fat soluble vitamins, categories may include normal, sufficient, insufficient, possibly insufficient, indeterminate, and excess (see Section 6.1.9 for specific definitions). Missing lab values will be reported in a "Missing" category.

Observed values of AFP will also be summarized descriptively by time point, noting that AFP samples are only drawn during the optional follow-up treatment period at every other 12-week repeating period clinic visit and at the EOT/ET visit.

In addition to subject listings for each laboratory test, a listing that includes the timing of sample collection, date and time of last dose and last meal before sample collection. Pregnancy test results, for both serum and urine, along with screening-specific laboratory results will also be presented in subject listings.

Sensitivity Analyses on Laboratory Data Collected After Drug Interruption

A separate sensitivity analysis will be performed on chemistry panel test data from samples that are collected after a drug interruption > 28 days due to a subject being off study (between protocol amendments). Chemistry test results will be summarized using descriptive statistics by analysis visit as observed, change from baseline (Day 0), and change from baseline (PA Day 0) values. Baseline definitions for this analysis are described in Section 6.1.1. The analysis visit windows to be used (see Table 5) are defined by study day relative to the date of first re-initiation of study drug after the drug interruption (i.e., PA Day 0).

FSV level abnormalities (e.g., sufficient, insufficient, excess) will also be analyzed separately as a sensitivity analysis using laboratory samples collected after a drug interruption. The number and percent of subjects within each test level category (see Section 6.1.9 for category definitions) will be presented for each of the following analysis visits: Baseline (Day 0), Baseline (PA Day 0), Week 4, Week 12, Week 24, Week 36, and Week 48.

Because drug interruptions between protocol amendments occurred after the RW phase, all subjects were administered MRX following drug interruptions (between protocol amendments).

9.4. Physical Examination

BMI will be summarized using descriptive statistics by treatment phase and analysis visit as observed and change from baseline values as described above for safety laboratory evaluations.

Physical examination findings, body height, and body weight will be included in subject listings.

9.5. Vital Signs

Vital signs (body temperature, blood pressure, heart rate, and respiratory rate) will be summarized using descriptive statistics by analysis visit as observed and change from baseline values.

9.6. Concomitant Medication

A concomitant medication is any non-protocol specified drug or substance administered after the first dose of study drug. For subjects with study drug interruptions (for any reason), any concomitant medication that starts > 14 days after the last dose before the drug interruption and ended before the study drug was re-initiated will not be considered (for analysis purposes) as a concomitant medication.

Concomitant medications will be summarized descriptively by treatment phase (OL, RW, and ARW), and treatment group for the RW treatment phase, using the number and percent of subjects by ATC class and preferred term. A separate summary of concomitant medications that treat pruritus will also be presented. Pruritus medications that treat pruritus are listed in Section 6.1.10.

Concomitant medications will also be presented in subject listings. Medications that were started before the first dose of study drug and are ongoing at the time of first dose will be flagged. A separate listing of concomitant medications that treat pruritus will also be presented.

9.7. Safety Data Graphical Presentations

Study drug exposure and TEAEs of special interest will be displayed graphically over the treatment period, as described in Section 13.3. Additional figures may be added post-hoc to further examine study data.

10. OTHER ANALYSES

10.1. Palatability Analysis

Palatability data, which is collected at each clinic visit in the follow-up treatment period, will be listed for individual subjects and summarized by analysis visit. For each palatability question, the number and percent of subjects will be presented for each answer given.

10.2. Pharmacokinetic Analysis

MRX plasma concentrations will be summarized using descriptive statistics by analysis visit, overall and by the last dose of MRX received prior to the blood sample collection.

10.3. Genotyping Characteristics

Genotyping characteristics will be limited to the presentation of mutation type in a listing.

11. CHANGES FROM PLANNED ANALYSIS

The protocol states that the randomization will be conducted using a permuted block algorithm that is stratified by response criteria where response was defined as a ≥50% reduction in serum bile acids between Baseline and Week 12 or Week 18. The active protocol during randomization was Protocol Amendment 3 (dated 15Nov2015) which specified randomization based on sBA response at Week 12. Protocol Amendment 4 (dated 28Mar2017) was implemented after all eligible subjects were randomized. The description of the randomization criteria was changed in Protocol Amendment 4, despite randomization already being complete. Subjects were, in fact, randomized based on their sBA response at Week 12. Further, the method by which the randomization schedule was administered used a central by block randomization process (within IRT), with entire blocks assigned by study site. This randomization allocation method resulted in more subjects in the placebo group from those subjects with a ≥50% reduction in sBA at Week 12.

The protocol specifies that secondary efficacy evaluations of change from Week 18 to Week 22 will be performed in subjects who previously responded to MRX treatment, as defined by a reduction in ItchRO score > 1 point from baseline to Week 12 or Week 18. Validation of the ItchRO instrument, however, has indicated that a reduction of ≥1 point is considered clinically meaningful. Thus, the SAP defines an ItchRO responder as a subject with a reduction in ItchRO of ≥1 point from baseline to Week 12 or Week 18. The ItchRO(Obs) weekly average morning score is used in defining an ItchRO responder because it is considered as the primary pruritus endpoint, and the various ItchRO variables are consistent relative to determining a clinically meaningful response.

The protocol specifies that treatment group comparisons will be made using inferential statistics for demographic and baseline disease characteristics. In following Mirum Pharmaceutical's standards, only descriptive statistics will be presented for these baseline variables.

The protocol specifies that race and ethnicity will be summarized descriptively, however, these demographic variables are not collected in the countries where subjects are enrolled.

The protocol states that the subject disposition summary will include a tabulation of the duration of the follow-up period. This tabulation will not be included.

12. REFERENCES

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13. TABLES, LISTINGS, AND FIGURES

All listings, tables, and graphs will have a header that includes the Mirum Pharmaceuticals, Protocol LUM001-304, and the output version. The footer will include the file name and path, the date and time of program execution, and the data extraction date. Immediately below table- and figure-specific footnotes, the source of the data will be provided, where applicable (i.e., listing number(s) for tables, and table number(s) for figures).

13.1. Planned Table Descriptions

Table 6, Table 7, Table 8, and Table 9 list the planned summary tables for protocol number LUM001-304. The table numbers are place holders only and will be determined when the tables are produced.

13.1.1. Disposition, Demographic, Disease History, Prior Medications, and Study Drug Compliance Summary Tables

Table 6 Disposition, Demographic, Disease History, Prior Medications, and Study Drug Compliance Summary Tables

Table Number	Table Title
14.1	**Disposition, Demographic, Disease History, Prior Medications, and Study Drug Compliance**
14.1.1.1	Subject Disposition: Overall – All Subjects
14.1.1.2	Subject Disposition by Study Phase – Enrolled Subjects
14.1.2.1	Demographics and Baseline Characteristics – Safety Population
14.1.2.2	Demographics and Baseline Characteristics - (by sBA and ItchRO Responder/Non-Responder Groups) – Safety Population
14.1.3.1	Disease History and Baseline Disease Characteristics – Safety Population
14.1.3.2	Disease History and Baseline Disease Characteristics - (by sBA and ItchRO Responder/Non-Responder Groups) – Safety Population
14.1.4	Demographic and Baseline Disease Characteristics by Subject – Safety Population
14.1.5.1	Summary of Prior Anti-Pruritus Medications – Safety Population
14.1.5.2	Summary of Prior Medications (Excluding Anti-Pruritus Medications) – Safety Population
14.1.5.3	Summary of Therapies to Treat Pruritus in the Past – Safety Population
14.1.6	Study Drug Compliance – Safety Population

13.1.2. Efficacy Data Summary Tables

Table 7 Efficacy Data Summary Tables

Table Number	Table Title
14.2 Efficacy Data	
14.2.1.1	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.1.2	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.1.3	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.1.4	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.1.5	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.1.6	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in sBA Responders at Week 48
14.2.1.7	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit: Adjusting Subject 050007 Analysis Visits during Randomized Withdrawal Phase – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.1.8	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Age Group – ITT Population
14.2.1.9	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Baseline sBA Group – ITT Population
14.2.1.10	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Baseline Total Bilirubin Group – ITT Population
14.2.1.11	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Baseline ALT Group – ITT Population
14.2.1.12	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Baseline ItchRO (Obs) Weekly Average Morning Severity Score Group – ITT Population

Table Number	Table Title
14.2.1.13	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit: Using Minimum of 3 (rather than 4) Daily Scores to Determine a Compliant Weekly Average Score – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.1.14	Percent of Days ItchRO (Obs) Morning Severity Score is ≤ 1 Point by Time Period – ITT Population
14.2.1.15	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline Presence of Paucity - ITT Population
14.2.1.16	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline Clinician Scratch Scale Score - ITT Population
14.2.1.17	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline sBA Level - ITT Population
14.2.1.18	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline Total Bilirubin Level - ITT Population
14.2.1.19	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline C4 Level - ITT Population
14.2.1.20	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Age (months) at Baseline - ITT Population
14.2.1.21	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for BMI at Baseline - ITT Population
14.2.1.22	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline ALT Level - ITT Population
14.2.1.23	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Family History of ALGS - ITT Population
14.2.1.24	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline Cholesterol Level - ITT Population
14.2.1.25	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline GGT Level - ITT Population

Table Number	Table Title
14.2.1.26	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for Baseline Clinician Xanthoma Severity Score - ITT Population
14.2.1.27.1	Repeated Measures ANCOVA of Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score - Over the Randomized Withdrawal Period – ITT Population
14.2.1.27.2	Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score Over the Randomized Withdrawal Period – Tabulation of Fitted Summary Statistics from Repeated Measures ANCOVA – ITT Population
14.2.1.28.1	Repeated Measures ANCOVA of Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score - Over the Randomized Withdrawal Period (Controlling for sBA Responder Group) – ITT Population
14.2.1.28.2	Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score Over the Randomized Withdrawal Period – Tabulation of Fitted Summary Statistics from Repeated Measures ANCOVA Controlling for sBA Responder Group – ITT Population
14.2.1.29.1	Repeated Measures ANCOVA of Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score: Adjusting Subject 050007 Analysis Visits - Over the Randomized Withdrawal Period – ITT Population
14.2.1.29.2	Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score Over the Randomized Withdrawal Period – Tabulation of Fitted Summary Statistics from Repeated Measures ANCOVA (Adjusting Subject 050007 Analysis Visits) – ITT Population
14.2.1.30.1	Repeated Measures ANCOVA of Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score: - Using Minimum of 3 (rather than 4) Daily Scores to Determine a Compliant Weekly Average Score - Over the Randomized Withdrawal Period – ITT Population
14.2.1.30.2	Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score Over the Randomized Withdrawal Period – Using Minimum of 3 (rather than 4) Daily Scores to Determine a Compliant Weekly Average Score - Tabulation of Fitted Summary Statistics from Repeated Measures ANCOVA – ITT Population
14.2.1.31.1	Repeated Measures ANCOVA of Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score - Over the Randomized Withdrawal Period (Controlling for BMI at Baseline) – ITT Population
14.2.1.31.2	Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score Over the Randomized Withdrawal Period – Tabulation of Fitted Summary Statistics from Repeated Measures ANCOVA Controlling for BMI at Baseline – ITT Population
14.2.1.32.1	Repeated Measures ANCOVA of Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score - Over the Randomized Withdrawal Period (Controlling for Sex, and Age (months) and BMI at Baseline) – ITT Population

Table Number	Table Title
14.2.1.32.2	Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score Over the Randomized Withdrawal Period – Tabulation of Fitted Summary Statistics from Repeated Measures ANCOVA Controlling for Sex, and Age (months) and BMI at Baseline – ITT Population
14.2.2.1	Summary of ItchRO (Obs) Weekly Average Evening Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.2.2	Summary of ItchRO (Obs) Weekly Average Evening Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.3.1	Summary of ItchRO (Obs) 4-Week Average Morning Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.3.2	Summary of ItchRO (Obs) 4-Week Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.4.1	Summary of ItchRO (Obs) 4-Week Average Evening Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.4.2	Summary of ItchRO (Obs) 4-Week Average Evening Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.5.1	Summary of ItchRO (Obs) Weekly Average Morning Frequency Score and Change from Baseline by Analysis Visit - ITT Population
14.2.5.2	Summary of ItchRO (Obs) Weekly Average Morning Frequency Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.6.1	Summary of ItchRO (Obs) Weekly Average Evening Frequency Score and Change from Baseline by Analysis Visit - ITT Population
14.2.6.2	Summary of ItchRO (Obs) Weekly Average Evening Frequency Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.7.1	Summary of ItchRO (Obs) 4-Week Average Morning Frequency Score and Change from Baseline by Analysis Visit - ITT Population
14.2.7.2	Summary of ItchRO (Obs) 4-Week Average Morning Frequency Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population

Table Number	Table Title
14.2.8.1	Summary of ItchRO (Obs) 4-Week Average Evening Frequency Score and Change from Baseline by Analysis Visit - ITT Population
14.2.8.2	Summary of ItchRO (Obs) 4-Week Average Evening Frequency Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.9.1	Summary of ItchRO (Obs) Weekly Average Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit - ITT Population
14.2.9.2	Summary of ItchRO (Obs) Weekly Average Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.9.3	Summary of ItchRO (Obs) Weekly Average Morning Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.9.4	Summary of ItchRO (Obs) Weekly Average Morning Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.10.1	Summary of ItchRO (Obs) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit - ITT Population
14.2.10.2	Summary of ItchRO (Obs) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.10.3	Summary of ItchRO (Obs) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.10.4	Summary of ItchRO (Obs) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.11.1	Summary of ItchRO (Pt) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.11.2	Summary of ItchRO (Pt) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.11.3	Summary of ItchRO (Pt) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population

Table Number	Table Title
14.2.11.4.1	Repeated Measures ANCOVA of Change from Baseline in ItchRO (Pt) Weekly Average Morning Severity Score - Over the Randomized Withdrawal Period – ITT Population
14.2.11.4.2	Change from Baseline in ItchRO (Pt) Weekly Average Morning Severity Score Over the Randomized Withdrawal Period – Tabulation of Fitted Summary Statistics from Repeated Measures ANCOVA – ITT Population
14.2.11.5	Percent of Days ItchRO (Pt) Morning Severity Score is ≤ 1 Point by Time Period – ITT Population
14.2.12.1	Summary of ItchRO (Pt) Weekly Average Evening Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.12.2	Summary of ItchRO (Pt) Weekly Average Evening Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.13.1	Summary of ItchRO (Pt) 4-Week Average Morning Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.13.2	Summary of ItchRO (Pt) 4-Week Average Morning Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.14.1	Summary of ItchRO (Pt) 4-Week Average Evening Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.14.2	Summary of ItchRO (Pt) 4-Week Average Evening Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.15.1	Summary of ItchRO (Pt) Weekly Average Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit - ITT Population
14.2.15.2	Summary of ItchRO (Pt) Weekly Average Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.15.3	Summary of ItchRO (Pt) Weekly Average Morning Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.15.4	Summary of ItchRO (Pt) Weekly Average Morning Severity Score (Based on Daily Average of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders

Table Number	Table Title
14.2.16.1	Summary of ItchRO (Pt) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit - ITT Population
14.2.16.2	Summary of ItchRO (Pt) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.16.3	Summary of ItchRO (Pt) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.16.4	Summary of ItchRO (Pt) Weekly Average Severity Score (Based on Daily Maximum of Morning and Evening Scores) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.17.1	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit - ITT Population
14.2.17.2	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.17.3	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.17.4	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.17.5	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.17.6	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in sBA Responders at Week 48
14.2.17.7	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit: Adjusting Subject 050007 Analysis Visits during Randomized Withdrawal Phase – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.17.8	Summary of sBA (umol/L) and Change from Baseline by Age Group - ITT Population
14.2.17.9	Summary of sBA (umol/L) and Change from Baseline by Baseline sBA Group - ITT Population
14.2.17.10	Summary of sBA (umol/L) and Change from Baseline by Baseline Total Bilirubin Group - ITT Population
14.2.17.11	Summary of sBA (umol/L) and Change from Baseline by Baseline ALT Group - ITT Population
14.2.17.12	Summary of sBA (umol/L) and Change from Baseline by Baseline ItchRO (Obs) Weekly Average Morning Severity Score Group - ITT Population

Table Number	Table Title
14.2.18.1	Summary of ALP (U/L) and Change from Baseline by Analysis Visit - ITT Population
14.2.18.2	Summary of ALP (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.18.3	Summary of ALP (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.18.4	Summary of ALP (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.18.5	Summary of ALP (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.19.1	Summary of ALT (U/L) and Change from Baseline by Analysis Visit - ITT Population
14.2.19.2	Summary of ALT (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.19.3	Summary of ALT (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.19.4	Summary of ALT (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.19.5	Summary of ALT (U/L) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.19.6	ALT Threshold Summary by Analysis Visit – ITT Population
14.2.20.1	Summary of Total Bilirubin (mg/dL) and Change from Baseline by Analysis Visit - ITT Population
14.2.20.2	Summary of Total Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.20.3	Summary of Total Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.20.4	Summary of Total Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.20.5	Summary of Total Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.20.6	Total Bilirubin Threshold Summary by Analysis Visit – ITT Population

Table Number	Table Title
14.2.21.1	Summary of Direct Bilirubin (mg/dL) and Change from Baseline by Analysis Visit - ITT Population
14.2.21.2	Summary of Direct Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.21.3	Summary of Direct Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.21.4	Summary of Direct Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - MITT Population
14.2.21.5	Summary of Direct Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population in ItchRO Responders
14.2.22.1	Summary of C4 (ng/mL) and Change from Baseline by Analysis Visit - ITT Population
14.2.22.2	Summary of C4 (ng/mL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.22.3	Summary of C4 (ng/mL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.23.1	Summary of Total Cholesterol (mg/dL) and Change from Baseline by Analysis Visit - ITT Population
14.2.23.2	Summary of Total Cholesterol (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.23.3	Summary of Total Cholesterol (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.24.1	Summary of LDL-C (mg/dL) and Change from Baseline by Analysis Visit - ITT Population
14.2.24.2	Summary of LDL-C (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.24.3	Summary of LDL-C (mg/dL) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population

Table Number	Table Title
14.2.25.1	Summary of Clinician Scratch Score (CSS) and Change from Baseline by Analysis Visit - ITT Population
14.2.25.2	Summary of Clinician Scratch Score (CSS) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.25.3	Summary of Clinician Scratch Score (CSS) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.25.4	Summary of Clinician Scratch Score (CSS) Change from Baseline by Analysis Visit – Categorical Data Analysis – ITT Population
14.2.26.1	Summary of Clinician Xanthoma Severity Score and Change from Baseline by Analysis Visit - ITT Population
14.2.26.2	Summary of Clinician Xanthoma Severity Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.27.1	Summary of Height Z-Score and Change from Baseline by Analysis Visit - ITT Population
14.2.27.2	Summary of Height Z-Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.27.3	Summary of Height Z-Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.28.1	Summary of Weight Z-Score and Change from Baseline by Analysis Visit - ITT Population
14.2.28.2	Summary of Weight Z-Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.28.3	Summary of Weight Z-Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.29.1	Summary of PedsQL Total Scale Score (Parent) and Change from Baseline by Analysis Visit - ITT Population
14.2.29.2	Summary of PedsQL Total Scale Score (Parent) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.29.3	Summary of PedsQL Total Scale Score (Parent) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population

Table Number	Table Title
14.2.30.1	Summary of PedsQL Multidimensional Fatigue Scale Score (Parent) and Change from Baseline by Analysis Visit - ITT Population
14.2.30.2	Summary of PedsQL Multidimensional Fatigue Scale Score (Parent) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.30.3	Summary of PedsQL Multidimensional Fatigue Scale Score (Parent) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.31.1	Summary of PedsQL Family Impact Total Scale Score and Change from Baseline by Analysis Visit - ITT Population
14.2.31.2	Summary of PedsQL Family Impact Total Scale Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.31.3	Summary of PedsQL Family Impact Total Scale Score and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.32.1	Summary of PedsQL Psychosocial Health Summary Score (Parent) and Change from Baseline by Analysis Visit - ITT Population
14.2.32.2	Summary of PedsQL Psychosocial Health Summary Score (Parent) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.32.3	Summary of PedsQL Psychosocial Health Summary Score (Parent) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.33.1	Summary of PedsQL Total Scale Score (Child) and Change from Baseline by Analysis Visit - ITT Population
14.2.33.2	Summary of PedsQL Total Scale Score (Child) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.33.3	Summary of PedsQL Total Scale Score (Child) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population
14.2.34.1	Summary of PedsQL Multidimensional Fatigue Scale Score (Child) and Change from Baseline by Analysis Visit - ITT Population
14.2.34.2	Summary of PedsQL Multidimensional Fatigue Scale Score (Child) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA - ITT Population
14.2.34.3	Summary of PedsQL Multidimensional Fatigue Scale Score (Child) and Change from Baseline by Analysis Visit – Tabulation of Fitted Summary Statistics from ANCOVA Controlling for sBA Responder Group - ITT Population

Table Number	Table Title
14.2.35.1	Summary of PIC by Analysis Visit and Change from Week 18 to Week 22 - ITT Population
14.2.35.2	Summary of PIC by Analysis Visit – Categorical Data Analysis – ITT Population
14.2.36.1	Summary of CIC (Itch-Related Symptoms) by Analysis Visit and Change from Week 18 to Week 22 - ITT Population
14.2.36.2	Summary of CIC (Itch-Related Symptoms) by Analysis Visit – Categorical Data Analysis – ITT Population
14.2.37.1	Summary of CIC (Xanthoma Severity) by Analysis Visit and Change from Week 18 to Week 22 - ITT Population
14.2.37.2	Summary of CIC (Xanthoma Severity) by Analysis Visit – Categorical Data Analysis – ITT Population
14.2.38.1	Summary of CGTB by Analysis Visit and Change from Week 18 to Week 22 - ITT Population
14.2.38.2	Summary of CGTB by Analysis Visit – Categorical Data Analysis – ITT Population
14.2.39.1	Contingency Table of ItchRO (Pt) and ItchRO (Obs) Morning Scores – for the Weekly Average Morning Score at Week 18 - ITT Population
14.2.39.2	Contingency Table of ItchRO (Pt) and ItchRO (Obs) Evening Scores – for the Weekly Average Evening Score at Week 18 - ITT Population
14.2.39.3	Contingency Table of ItchRO (Pt) and ItchRO (Obs) Morning Scores – for the Weekly Average Morning Score at Week 22 - ITT Population
14.2.39.4	Contingency Table of ItchRO (Pt) and ItchRO (Obs) Evening Scores – for the Weekly Average Evening Score at Week 22 - ITT Population
14.2.40.1	Pairwise Correlation Estimates for Change from Baseline to Week 18 and Week 48 in ItchRO and CSS Variables – ITT Population
14.2.40.2	Pairwise Correlation Estimates for Change from Week 18 to Week 22 in ItchRO and CSS Variables – ITT Population

13.1.3. Safety Data Tables

Table 8 Safety Data Summary Tables

Table Number	Table Title
14.3.1 Study Drug Exposure	
14.3.1	Study Drug Exposure by Treatment Phase – Safety Population
14.3.2 Displays of Adverse Events	
14.3.2.1.1	Summary of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.2.1.2	Summary of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: Open-Label Phase (Day 1 – Week 18) – Safety Population
14.3.2.1.3	Summary of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.2.1.4	Summary of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.2.1.5	Summary of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.2.1.6	Summary of Treatment-Emergent Adverse Events by Age Group at Baseline – Safety Population – Subjects on Maralixibat Chloride
14.3.2.1.7	Summary of Treatment-Emergent Adverse Events by Maralixibat Chloride Dose Group (at Onset of TEAE) – Safety Population
14.3.2.2.1	Incidence of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.2.2.2	Incidence of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: Open-Label Phase (Day 1 – Week 18) – Safety Population
14.3.2.2.3	Incidence of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.2.2.4	Incidence of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.2.2.5	Incidence of Treatment-Emergent Adverse Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.2.3.1	Incidence of Treatment-Emergent Adverse Events by Maximum Severity and Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.2.3.2	Incidence of Treatment-Emergent Adverse Events by Maximum Severity and Dose at Onset of TEAE: Open-Label Phase (Day 1 – Week 18) – Safety Population
14.3.2.3.3	Incidence of Treatment-Emergent Adverse Events by Maximum Severity and Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population

Table Number	Table Title
14.3.2.3.4	Incidence of Treatment-Emergent Adverse Events by Maximum Severity and Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.2.3.5	Incidence of Treatment-Emergent Adverse Events by Maximum Severity and Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.2.4.1	Incidence of Treatment Related Adverse Events by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.2.4.2	Incidence of Treatment Related Adverse Events by Dose at Onset of TEAE: Open-Label Phase (Day 1 – Week 18) – Safety Population
14.3.2.4.3	Incidence of Treatment Related Adverse Events by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.2.4.4	Incidence of Treatment Related Adverse Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.2.4.5	Incidence of Treatment Related Adverse Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.2.5.1	Incidence of Treatment Related Adverse Events by Maximum Severity and Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.2.5.2	Incidence of Treatment Related Adverse Events by Maximum Severity and Dose at Onset of TEAE: Open-Label Phase (Day 1 – Week 18) – Safety Population
14.3.2.5.3	Incidence of Treatment Related Adverse Events by Maximum Severity and Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.2.5.4	Incidence of Treatment Related Adverse Events by Maximum Severity and Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.2.5.5	Incidence of Treatment Related Adverse Events by Maximum Severity and Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.3 Summary of Deaths, Other Serious and Significant Adverse Events	
14.3.3.1.1	Incidence of Treatment-Emergent SAEs by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.3.1.2	Incidence of Treatment-Emergent SAEs by Dose at Onset of TEAE: Open-Label Phase (Day 1 – Week 18) – Safety Population
14.3.3.1.3	Incidence of Treatment-Emergent SAEs by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.3.1.4	Incidence of Treatment-Emergent SAEs by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.3.1.5	Incidence of Treatment-Emergent SAEs by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population

Table Number	Table Title
14.3.3.2.1	Incidence of Treatment Related SAEs by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.3.2.2	Incidence of Treatment Related SAEs by Dose at Onset of TEAE: Open-Label Phase (Day 1 - Week 18) – Safety Population
14.3.3.2.3	Incidence of Treatment Related SAEs by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.3.2.4	Incidence of Treatment Related SAEs by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.3.2.5	Incidence of Treatment Related SAEs by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.3.3.1	Incidence of Adverse Events Leading to Permanent Treatment Discontinuation by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.3.3.2	Incidence of Adverse Events Leading to Permanent Treatment Discontinuation by Dose at Onset of TEAE: Open-Label Phase (Day 1 – Week 18) – Safety Population
14.3.3.3.3	Incidence of Adverse Events Leading to Permanent Treatment Discontinuation by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.3.3.4	Incidence of Adverse Events Leading to Permanent Treatment Discontinuation by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.3.3.5	Incidence of Adverse Events Leading to Permanent Treatment Discontinuation by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.3.4.1	Incidence of Treatment-Emergent Adverse Events of Special Interest – Diarrhoea Events by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.3.4.2	Incidence of Treatment-Emergent Adverse Events of Special Interest – Diarrhoea Events by Dose at Onset of TEAE: Open-Label Phase (Day 1 - Week 18) – Safety Population
14.3.3.4.3	Incidence of Treatment-Emergent Adverse Events of Special Interest – Diarrhoea Events by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.3.4.4	Incidence of Treatment-Emergent Adverse Events of Special Interest – Diarrhoea Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.3.4.5	Incidence of Treatment-Emergent Adverse Events of Special Interest – Diarrhoea Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.3.5.1	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Transaminases Events by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.3.5.2	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Transaminases Events by Dose at Onset of TEAE: Open-Label Phase (Day 1 - Week 18) – Safety Population

Table Number	Table Title
14.3.3.5.3	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Transaminases Events by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.3.5.4	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Transaminases Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.3.5.5	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Transaminases Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.3.6.1	Incidence of Treatment-Emergent Adverse Events of Special Interest – Fat Soluble Vitamin Deficiency Events by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.3.6.2	Incidence of Treatment-Emergent Adverse Events of Special Interest – Fat Soluble Vitamin Deficiency Events by Dose at Onset of TEAE: Open-Label Phase (Day 1 - Week 18) – Safety Population
14.3.3.6.3	Incidence of Treatment-Emergent Adverse Events of Special Interest – Fat Soluble Vitamin Deficiency Events by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.3.6.4	Incidence of Treatment-Emergent Adverse Events of Special Interest – Fat Soluble Vitamin Deficiency Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.3.6.5	Incidence of Treatment-Emergent Adverse Events of Special Interest – Fat Soluble Vitamin Deficiency Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population
14.3.3.7.1	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Bilirubin Events by Dose at Onset of TEAE: Overall MRX – Safety Population
14.3.3.7.2	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Bilirubin Events by Dose at Onset of TEAE: Open-Label Phase (Day 1 - Week 18) – Safety Population
14.3.3.7.3	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Bilirubin Events by Dose at Onset of TEAE: Randomized Withdrawal Phase – Safety Population
14.3.3.7.4	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Bilirubin Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 22 - 48) – Safety Population
14.3.3.7.5	Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Bilirubin Events by Dose at Onset of TEAE: After Randomized Withdrawal Phase (Week > 48) – Safety Population

Table Number	Table Title
14.3.4 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	
14.3.4.1	Listing of Serious Adverse Events – Safety Population
14.3.4.2	Listing of Adverse Events Leading to Permanent Treatment Discontinuation – Safety Population
14.3.4.3	Listing of Deaths
14.3.5 Laboratory Data Summary Tables	
14.3.5.1.1	Summary of Safety Laboratory Data by Analysis Visit: Chemistry – Safety Population
14.3.5.1.2	Summary of Safety Chemistry Data by Analysis Visit – on Laboratory Samples Collected After Extended Drug Interruption – Safety Population
14.3.5.2	Summary of Safety Laboratory Data by Analysis Visit: Hematology – Safety Population
14.3.5.3.1	Summary of Safety Laboratory Data by Analysis Visit: Fat Soluble Vitamins – Safety Population
14.3.5.3.2	Summary of Fat Soluble Vitamin Level Abnormalities – Safety Population
14.3.5.3.3	Summary of Fat Soluble Vitamin Level Abnormalities – on Laboratory Samples Collected After Extended Drug Interruption – Safety Population
14.3.5.4	Summary of Safety Laboratory Data by Analysis Visit: Lipid Panel – Safety Population
14.3.5.5	Summary of Safety Laboratory Data by Analysis Visit: Alpha-Fetoprotein (AFP) – Safety Population
14.3.6 Other Safety Data Summary Tables	
14.3.6.1	Summary of BMI (kg/m^2) by Analysis Visit – Safety Population
14.3.6.2	Summary of Vital Signs by Analysis Visit: Systolic Blood Pressure (mmHg) – Safety Population
14.3.6.3	Summary of Vital Signs by Analysis Visit: Diastolic Blood Pressure (mmHg) – Safety Population
14.3.6.4	Summary of Vital Signs by Analysis Visit: Heart Rate (bpm) – Safety Population
14.3.6.5	Summary of Vital Signs by Analysis Visit: Body Temperature (^oC) – Safety Population
14.3.6.6	Summary of Vital Signs by Analysis Visit: Respiratory Rate (rpm) – Safety Population

Table Number	Table Title
14.3.7 Concomitant Medications	
14.3.7.1	Summary of Concomitant Medications – Safety Population
14.3.7.2	Summary of Concomitant Medications that Treat Pruritus – Safety Population

13.1.4. Other Data Summary Tables

Table 9 Other Data Summary Tables

Table Number	Table Title
14.4 Other Data Summaries	
14.4.1 Palatability Data	
14.4.1	Summary of Palatability Data by Analysis Visit – Safety Population
14.4.2 Pharmacokinetic Data	
14.4.2	Summary of Plasma Sample Maralixibat Concentrations (ng/mL) by Analysis Visit – Safety Population

13.2. Planned Listing Descriptions

Table 10 provides the planned listings for protocol number LUM001-304. The listing numbers are place holders only and will be determined when the listings are produced. Three subject data listings will be imbedded within the safety tables: SAEs, AEs leading to permanent treatment discontinuation, and deaths (see Table 8).

Subject listings will be presented by treatment sequence, and sorted by site, subject ID, and assessment date (where applicable). All pertinent calculated variables (e.g., study day, TEAE flag) will be included in the listings, along with the treatment received (MRX dose or Placebo) on the date of assessment/sample collection.

In all listings, a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed. The information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 10 Planned Subject Listings

Listing Number	Subject Listing Title
16.1	**Subject Profile Listings**
16.1.1	Subject Profile: Select Efficacy Labs and Pruritus Scores – ITT Population
16.1.2	Subject Profile: PedsQL Total Scale and Summary Scores – ITT Population
16.1.3	Subject Profile: Serum Bile Acid, Lipids, and Fat Soluble Vitamins – ITT Population
16.2	**Subject Disposition**
16.2.1	Analysis Populations and Treatment Assignments – Enrolled Subjects
16.2.2	Subject Disposition – Enrolled Subjects
16.2.3	Subject Disposition – Screen Failure
16.3	**Protocol Deviations/Subjects Excluded from Efficacy Analyses**
16.3.1	Inclusion and Exclusion Criteria – Enrolled Subjects
16.3.2	Subject Excluded from Efficacy Analyses – Enrolled Subjects
16.3.3	Major Protocol Deviations – Safety Population
16.4	**Demographic Data and Other Baseline Characteristics**
16.4.1	Demographics and Informed Consent – Safety Population
16.4.2	Medical History – Safety Population
16.4.3	ALGS Disease History – Safety Population
16.4.4	Prior Medications – Safety Population

Listing Number		Subject Listing Title
16.5		**Study Drug Exposure, Compliance and Changes to MRX Dose**
16.5.1		Study Drug Exposure – Safety Population
16.5.2		Study Drug Accountability and Compliance
16.5.3		Maralixibat Chloride Dose Changes – Safety Population
16.6		**Individual Efficacy Response Data**
16.6.1		ItchRO (Obs) Weekly Average Morning Score and sBA Results – (Baseline, Week 48, and Change from Baseline to Week 48) – ITT Population
16.6.2		Clinician Scratch and Xanthoma Scores – ITT Population
16.6.3		Liver Biochemical Enzymes – (Baseline and Change from Baseline to Week 48 – ITT Population
16.6.4		ItchRO Reported Outcomes (Subject and Caregiver) Weekly Morning and Average Evening Scores – ITT Population
16.6.5		ItchRO Reported Outcomes (Subject and Caregiver) Daily Morning and Evening Scores – ITT Population
16.6.6		PIC, CIC, and CGTB – ITT Population
16.6.7		Efficacy Laboratory Tests – ITT Population
16.6.8		Total sBA – ITT Population
16.6.9		Height and Weight Z-Scores – ITT Population
16.2.10.1.1.1		Pediatric Quality of Life Inventory (Parent Report for Infants) - Physical Functioning - ITT Population
16.6.10.1.1.2		Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Physical Functioning - ITT Population
16.6.10.1.2		Pediatric Quality of Life Inventory (Parent Report for Infants) - Physical Symptoms - ITT Population
16.6.10.1.3.1		Pediatric Quality of Life Inventory (Parent Report for Infants) - Emotional Functioning - ITT Population
16.6.10.1.3.2		Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Emotional Functioning - ITT Population
16.6.10.1.4.1		Pediatric Quality of Life Inventory (Parent Report for Infants) - Social Functioning - ITT Population
16.6.10.1.4.2		Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Social Functioning - ITT Population

Listing Number	Subject Listing Title
16.6.10.1.5	Pediatric Quality of Life Inventory (Parent Report for Infants) - Cognitive Functioning - ITT Population
16.6.10.1.6	Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Nursery/Day Care/School Functioning - ITT Population
16.6.10.2.1	Pediatric Quality of Life Inventory (Subject Report) - Physical Functioning - ITT Population
16.6.10.2.2	Pediatric Quality of Life Inventory (Subject Report) - Emotional Functioning - ITT Population
16.6.10.2.3	Pediatric Quality of Life Inventory (Subject Report) - Social Functioning - ITT Population
16.6.10.2.4	Pediatric Quality of Life Inventory (Subject Report) - School Functioning - ITT Population
16.6.10.3.1	Multidimensional Fatigue Scale (Parent Report) - General Fatigue - ITT Population
16.6.10.3.2	Multidimensional Fatigue Scale (Parent Report) - Sleep/Rest Fatigue - ITT Population
16.6.10.3.3	Multidimensional Fatigue Scale (Parent Report) - Mental Fatigue - ITT Population
16.6.10.4.1	Multidimensional Fatigue Scale (Subject Report) - General Fatigue - ITT Population
16.6.10.4.2	Multidimensional Fatigue Scale (Subject Report) - Sleep/Rest Fatigue - ITT Population
16.6.10.4.3	Multidimensional Fatigue Scale (Subject Report) - Cognitive Fatigue - ITT Population
16.6.10.5.1	Family Impact Module (Parent Report) - Physical Functioning - ITT Population
16.6.10.5.2	Family Impact Module (Parent Report) - Emotional Functioning - ITT Population
16.6.10.5.3	Family Impact Module (Parent Report) - Social Functioning - ITT Population
16.6.10.5.4	Family Impact Module (Parent Report) - Cognitive Functioning - ITT Population
16.6.10.5.5	Family Impact Module (Parent Report) – Communication - ITT Population
16.6.10.5.6	Family Impact Module (Parent Report) – Worry - ITT Population
16.6.10.5.7	Family Impact Module (Parent Report) - Daily Activities - ITT Population
16.6.10.5.8	Family Impact Module (Parent Report) - Family Relationships - ITT Population
16.6.10.6.1	Pediatric Quality of Life Inventory (Parent Report) - Total Scale and Summary Scores - ITT Population
16.6.10.6.2	Pediatric Quality of Life Inventory (Subject Report) - Total Scale and Summary Scores - ITT Population

Listing Number		Subject Listing Title
16.7	**Adverse Events**	
16.7.1		Adverse Events – Safety Population
16.7.2.1		Adverse Events of Special Interest: Diarrhoea Events – Safety Population
16.7.2.2		Adverse Events of Special Interest: Fat Soluble Vitamin Deficiency Events – Safety Population
16.7.2.3		Adverse Events of Special Interest: Elevated Transaminases Events – Safety Population
16.7.2.4		Adverse Events of Special Interest: Elevated Bilirubin Events – Safety Population
16.7.3.1		Serious Adverse Events – Safety Population
16.7.3.2		Serious Related Adverse Events – Safety Population
16.7.4.1		Adverse Events Leading to Study Drug Discontinuation – Safety Population
16.7.4.2		Adverse Events Leading to Dose Reduction – Safety Population
16.7.5.1		Severe or Life Threatening Adverse Events – Safety Population
16.7.5.2		Life Threatening Adverse Events – Safety Population
16.7.6		Adverse Events Causing Death – Safety Population
16.8	**Laboratory Values**	
16.8.1.1		Safety Laboratory Tests: Chemistry – Safety Population
16.8.1.2		Safety Laboratory Tests: Chemistry – on Samples Collected After Extended Drug Interruption - Safety Population
16.8.2.1		Safety Laboratory Tests: Hematology – Safety Population
16.8.2.2		Safety Laboratory Tests: Hematology – on Samples Collected After Extended Drug Interruption - Safety Population
16.8.3.1		Safety Laboratory Tests: Urinalysis – Safety Population
16.8.3.2		Safety Laboratory Tests: Urinalysis – on Samples Collected After Extended Drug Interruption - Safety Population
16.8.4.1		Safety Laboratory Tests: Fat Soluble Vitamins – Safety Population
16.8.4.2		Safety Laboratory Tests: Fat Soluble Vitamins – on Samples Collected After Extended Drug Interruption - Safety Population
16.8.5.1		Safety Laboratory Tests: Lipid Panel – Safety Population
16.8.5.2		Safety Laboratory Tests: Lipid Panel – on Samples Collected After Extended Drug Interruption - Safety Population

Listing Number		Subject Listing Title
16.8.6		Safety Laboratory Tests: Hepatocellular Carcinoma Marker – Alpha-Fetoprotein (AFP) – Safety Population
16.8.7		Clinical Laboratory Tests : Timing of Sample Collection, Last Dose and Last Meal – Safety Population
16.8.8		Pregnancy Test Results – Safety Population
16.9	**Vital Signs/Physical Examination/Telephone Contact Log**	
16.9.1.1		Vital Signs – Safety Population
16.9.1.2		Vital Signs – on Measures After Extended Drug Interruption - Safety Population
16.9.2		Physical Examination – Safety Population
16.9.3		Telephone Contact Log – Enrolled Subjects
16.10	**Concomitant Medications**	
16.10.1		Concomitant Medications – Safety Population
16.10.2		Concomitant Medications that Treat Pruritus – Safety Population
16.11	**Palatability Data**	
16.11		Palatability Questionnaire – Safety Population
16.12	**Drug Concentration Data**	
16.12		Plasma Sample Maralixibat Concentrations

13.3. Planned Figure Descriptions

Table 11 provides the planned figures for protocol number LUM001-304. The figure numbers are place holders only and will be determined when the figures are produced. Additional figures may be added post-hoc to further examine study data.

13.3.1. Efficacy Figures

ANCOVA LS means and associated 95% CIs will be graphically displayed for sBA change from Week 18 to Week 22 in the MITT Population. This plot will display the LS means and CIs for each treatment group and the difference (MRX minus Placebo), along with the associated p-value for testing statistically significance between treatment groups. Each of the LS means will be displayed side-by-side, with vertical lines emanating from each mean to represent the 95% CI for the mean.

Mean (± SE) change from baseline (Day 0) for select efficacy variables will be displayed graphically by study week over the treatment period. For these line plots over time, study week will be based on the analysis visit mapping described in Table 4. Separate methods of displaying this data will be used as described below.

For ItchRO(Obs) and ItchRO(Pt) weekly average morning scores and sBA, 2 figures will be presented. One plot will display the data by treatment sequence up through Week 48, with vertical references lines included at the Week 18 and Week 22 time points to represent the RW phase. The other plot will present consolidated data (i.e., treatment sequences combined) through the entire treatment period, with the exclusion of the Week 22 time point.

For ALP, ALT, bilirubin (total and direct), C4, total cholesterol, and LDL-C, the first 48 weeks of data will be broken out by treatment sequence, with a consolidated single line (labeled as "MRX Extension") for post-Week 48 data. Vertical reference lines will be displayed at the Week 18 and Week 22 time points to represent the RW phase.

For height and weight z-scores, and PedsQL total scale and multidimensional fatigue scale scores (parent), data will be presented as a single line graph through the entire treatment period. Vertical reference lines will be displayed at the Week 18 and Week 22 time points to represent the RW phase.

13.3.2. Study Drug Exposure Figure

Study drug exposure will be displayed as a swimmer plot that includes a horizontal bar showing treatment duration for each subject in the study. Each bar will be color coded in a manner that displays the time periods in which each subject was on the varying daily doses (i.e., 14 µg/kg/day, 35 µg/kg/day, 70 µg/kg/day, 140 µg/kg/day, 280 µg/kg/day, 400 µg/kg/day, 540 µg/kg/day, 800 µg/kg/day, and placebo). Gaps in line segments will indicate a drug interruption or missed dose for any reason.

13.3.3. Adverse Event Figures

TEAEs of special interest will be displayed in swimmer-type plots. A plot will be displayed for each individual AESI (as the preferred term) and present the start and stop study day of each event over time. The vertical axis will represent each unique subject that reported the respective AESI. The horizontal axis will represent time, as study day. The severity of each event will be depicted as color-coded lines and symbols. Treatment sequence will be identified for each subject.

Table 11 Planned Figures

Figure Number	Figure Title
14.2 Efficacy Data	
14.2.1.1.1	Plot of Mean (± SE) Change from Baseline in ItchRO (Obs) Weekly Average Morning Score by Randomized Treatment Group Over Time (through Week 48) - ITT Population
14.2.1.1.2	Plot of Mean (± SE) Change from Baseline in ItchRO (Obs) Weekly Average Morning Score by Randomized Treatment Group Over Time (through Treatment Duration) - ITT Population
14.2.1.11.1	Plot of Mean (± SE) Change from Baseline in ItchRO (Pt) Weekly Average Morning Score by Randomized Treatment Group Over Time (through Week 48) - ITT Population
14.2.1.11.2	Plot of Mean (± SE) Change from Baseline in ItchRO (Pt) Weekly Average Morning Score by Randomized Treatment Group Over Time (through Treatment Duration) - ITT Population
14.2.17.1.1	Plot of Mean (± SE) Change from Baseline in sBA (umol/L) by Randomized Treatment Group Over Time (through Week 48) - ITT Population
14.2.17.1.2	Plot of Mean (± SE) Change from Baseline in sBA (umol/L) by Randomized Treatment Group Over Time (through Treatment Duration) - ITT Population
14.2.17.4	Plot of sBA (umol/L) Change from Week 18 to Week 22 LS Means and 95% Confidence Intervals from ANCOVA – MITT Population
14.2.18.1	Plot of Mean (± SE) Change from Baseline in ALP (U/L) by Randomized Treatment Group Over Time - ITT Population
14.2.19.1	Plot of Mean (± SE) Change from Baseline in ALT (U/L) by Randomized Treatment Group Over Time - ITT Population
14.2.20.1	Plot of Mean (± SE) Change from Baseline in Total Bilirubin (mg/dL) by Randomized Treatment Group Over Time - ITT Population
14.2.21.1	Plot of Mean (± SE) Change from Baseline in Direct Bilirubin (mg/dL) by Randomized Treatment Group Over Time - ITT Population
14.2.22.1	Plot of Mean (± SE) Change from Baseline in C4 (ng/mL) by Randomized Treatment Group Over Time - ITT Population
14.2.23.1	Plot of Mean (± SE) Change from Baseline in Total Cholesterol (mg/dL) by Randomized Treatment Group Over Time - ITT Population
14.2.24.1	Plot of Mean (± SE) Change from Baseline in LDL-C (mg/dL) by Randomized Treatment Group Over Time - ITT Population
14.2.27.1	Plot of Mean (± SE) Change from Baseline in Height Z-Score Over Time - ITT Population
14.2.28.1	Plot of Mean (± SE) Change from Baseline in Weight Z-Score Over Time - ITT Population
14.2.29.1	Plot of Mean (SE) Change from Baseline in PedsQL Total Score (Parent) Over Time - ITT Population

14.2.30.1 Plot of Mean (± SE) Change from Baseline in PedsQL Multidimensional Fatigue Scale Score (Parent) Over Time - ITT Population

14.3.1 Display of Study Drug Exposure

14.3.1 Study Drug Exposure Over Time by Subject – Safety Population

14.3.2 Displays of Adverse Events

14.3.3 Plot of Treatment-Emergent Adverse Events of Special Interest Over Time by Preferred Term and Individual Subject – Safety Population

14. TABLES, LISTINGS, AND LISTING SHELLS

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

Table and listing shells are provided in a separate document. Programming notes may be added if appropriate after each TLF shell.

Appendix 1 Premier Research Library of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
AFP	alpha-fetoprotein
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARW	after randomized withdrawal
ASA	American statistical association
ASBTi	apical sodium dependent bile acid transporter inhibitor
AST	aspartate aminotransferase
BID	twice-a-day dosing regimen
BP	blood pressure
C4	7-alpha-hydroxy-4-cholesten-3-one
CDC	centers for disease control
CGTB	caregiver global therapeutic benefit
CI	confidence interval
CIC-Itch	caregiver impression of change (itch-related symptoms)

Abbreviation	Definition
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSS	clinician scratch score
CTCAE	common terminology criteria for adverse events
DMC	data monitoring committee
eDiary	electronic diary
EMA	European medicines agency
ET	early termination
FDA	food and drug administration
FGF-19	fibroblast growth factor 19
FGF-21	fibroblast growth factor 21
FSV	fat soluble vitamin
GGT	gamma glutamyl transferase
GI	gastrointestinal
HR	heart rate
HRQoL	health-related quality of life
IA	interim analysis
ICH	international council for harmonization
IRT	interactive response technology

Abbreviation	Definition
ItchRO	itch reported outcome
ITT	intent-to-treat
LLOQ	lower limit of quantification
LOCF	last-observation-carried-forward
LS	least squares
MedDRA	medical dictionary for regulatory activities
MMRM	mixed-effects model for repeated measurements
MRX	MRX
OL	open-label
PBO	placebo
PedsQL	pediatric quality of life
PIC	patient impression of change
PT	preferred term
RBP	retinol binding protein
REML	restricted maximum likelihood
RSS	royal statistical society
RW	randomized withdrawal
SAE	serious adverse event
SAS®	a software system used for data analysis

Abbreviation	Definition
sBA	serum bile acid
SD	standard deviation
SE	standard error
SIAP	statistical interim analysis plan
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit normal
ULOQ	upper limit of quantification
WHO	world health organization

Appendix 2 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
Total Protein, g/dL
Albumin, g/dL
Calcium, mg/dL
Phosphate, mg/dL
Glucose, mg/dL
BUN, mg/dL
Creatinine, mg/dL
Urate, mg/dL
Corrected Sodium, mmol/L
AST (SGOT), U/L
GGT, U/L

Lipid Panel

Triglycerides, mg/dL

Fat Soluble Vitamins

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

Marker of hepatocellular carcinoma

Alpha-Fetoprotein (AFP), ng/mL

Urinalysis [1]

pH
Specific Gravity
Oxalate, µmol/L
Epithelial Cells, HPF
Granular Casts, LPF
Hyaline Casts, LPF
RBC Casts, LPF
Urine Erythrocytes, HPF
Urine Leukocytes, HPF
WBC Casts, LPF
Waxy Casts, LPF
Urine Protein *
Urine Glucose *
Ketones *
Urine Bilirubin *
Nitrite *
Urobilinogen *
Leukocyte Esterase *
Crystals *
Mucous Threads *
Urine Bacteria *
Urine Hemoglobin *
Yeast Cells *

EFFICACY LABS

Clinical Chemistry [2]

Total Bilirubin, mg/dL
Direct Bilirubin, mg/dL
Alkaline Phosphatase (ALP), U/L
ALT (SGPT), U/L

Lipid Panel

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

Cholestasis Biomarkers

Serum Bile Acids, µmol/L
7 alpha hydroxy-4-cholesten-3-one (C4), ng/mL
Autotaxin, ng/mL [1]
FGF-19, pg/mL [1]
FGF-21, pg/mL [1]
Bile Acid Subspecies, µmol/L (15 subspecies) [1]
% Unconjugated Bile Acids, % [1]
Total Conjugated Bile Acids, µmol/L [1]
Total Unconjugated Bile Acids, µmol/L [1]

[1] Listing only; [2] Safety and efficacy laboratory tests; * Qualitative urinalysis

AD-ST-33.04 Effective date: 30 Jun 2017

Appendix 3 Listing Fat Soluble Vitamin Deficiency Events

The following MedDRA Preferred Terms associated with fat soluble vitamin deficiency events are included as an AESI:

- vitamin A deficiency
- vitamin A abnormal
- vitamin A decreased
- vitamin A deficiency related corneal disorders
- night blindness
- ketokomalacia
- haemorrhagic disorders of the new born
- xerophthalmia
- growth retardation
- nail disorder
- dry skin
- eye disorder
- eye irritation
- eye pruritus
- vitamin D deficiency
- vitamin D abnormal
- vitamin D decreased
- rickets
- osteomalacia
- osteoporosis
- osteopenia
- heartrate abnormal
- heartrate increased
- heartrate irregular
- tachycardia
- arrhythmia
- hypocalcemia
- tetany
- tremor
- irritability
- hunger
- seizure
- confusional state
- anxiety
- fatigue
- calcium deficiency
- pallor

- palpitation
- hyperhidrosis
- paraesthesia oral
- tooth demineralization
- bone deformity
- bone density abnormal
- bone density decreased
- fractures
- vitamin E deficiency
- vitamin E decreased
- hyporeflexia
- ataxia
- nystagmus
- areflexia
- ophthalmoplegia
- visual acuity reduced
- visual impairment
- abnormal behavior
- personality disorder
- personality change
- muscular wasting
- muscle disorder
- muscle spasms
- hair disorder
- alopecia
- alopecia areata
- vitamin K deficiency
- vitamin K decreased
- mean platelet volume abnormal
- mean platelet volume decreased
- platelet count abnormal
- platelet count decreased
- cold feet
- cold hand
- cold hands & feet
- coldness of limbs
- coldness of lower extremities
- blood glucose increased
- bleeding time abnormal
- bleeding time prolonged
- coagulation time abnormal
- coagulation time prolonged

- international normalised ratio increased
- international normalised ratio abnormal
- haemorrhage
- melaena
- epistaxis
- haematochezia
- haemoptysis