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1. Overview

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Mirum Pharmaceuticals Inc. (Mirum) protocol LUM001-305, A Multicenter Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Patients with Alagille Syndrome, dated 13-May-2019 (Amendment 6.2).

The original LUM001-305 protocol, dated 14-Apr-2014, planned for a 48-week treatment period. This treatment period included 3 parts: a 4-week dose escalation period, at doses up to 280 µg/kg/day; a 7-week dose optimization period where dosing may be increased or decreased to 35, 70, 140 or 280 µg/kg/day; and a 35-week stable dosing period where participants continue to receive study drug according to the dose achieved in the dose-optimization period.

There have been 8 protocol amendments (PAs) to date. The summary list of changes to each of the protocol amendments are describe in the final amendment, Protocol Amendment 6.2. Several of the protocol amendments included optional long-term extensions.

Protocol Amendment 1, dated 29-Jan-2015, changed the number of participants from 24 to 36 to reflect the number of participants planned in the predecessor protocol, LUM001-301. Additionally, this amendment clarified that the age at LUM001-301 baseline will be used for determinations of the PedsQL among other minor changes to improve the clarity of the protocol and/or correct minor inconsistencies and typographical errors.

Protocol Amendment 2, dated 12-Feb-2015, changed the logo on the protocol cover page to reflect the Childhood Liver Disease Research Network's (ChiLDReN) current design.

Protocol Amendment 3, dated 27-Apr-2016, provided for an optional 48-week treatment period. At Week 48, all participants were to be assessed by the investigator to determine the participant's willingness and eligibility to roll over into the 48-week (through Week 96/Early Termination [ET]), safety monitoring period. Amendment 3 was not operationalized as Protocol Amendment 4 was finalized on the same day (27-Apr-2016) with additional edits to correct previously unidentified inconsistencies within the protocol.

Protocol Amendment 5, dated 13-Nov-2017, primarily changed the study design to allow participation in the long-term optional follow-up treatment period, beyond what was previously described in earlier amendments. After Week 96, participants are allowed to roll over into this additional 48-week treatment (through Week 144/ET) period.

Protocol Amendment 6, dated 25-Jun-2018, provided for an additional 72-week treatment period after Week 144/ET. After Week 144, participants are allowed to roll over into this 72-week treatment (through Week 216/End of Treatment [EOT]) period.

Protocol Amendment 6.1, dated 08-Feb-2019, was changed to reflect the new sponsorship from Lumena Pharmaceuticals to Mirum Pharmaceuticals, Inc. Several edits were made to clarify the different treatment periods for each amendment extending the study.

The final protocol amendment, Amendment 6.2, dated 13-May-2019, had the 6.1 version changed to 6.2, to coincide with the data safety monitoring board (DSMB) approval date of 13-May-2019. No changes were made to the text.

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 participant 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 adverse event [AE]), study drug compliance issues (e.g., missed consecutive doses), and dosing gaps due to being off study between protocol amendments. For example, a participant could complete study drug treatment through Week 48 under the original protocol before implementation of Protocol Amendment 4 that extended treatment through Week 96. The participant could subsequently provide informed consent under the amendment and be re-initiated on study drug.

Participants with a drug interruption of at least 7 days had their study drug dose re-escalated beginning at 35 µg/kg/day. Participants were escalated up to a maximum of 280 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 within this document.

2. Study Objectives and Endpoints

2.1. Study Objectives

The objectives of this study are:

- Evaluate the long-term safety and tolerability of MRX in pediatric participants with

Alagille Syndrome (ALGS).

- Evaluate the long-term effect of MRX on serum bile acid levels.
- Evaluate the long-term effect of LUM001 on pruritus associated with ALGS
- Explore the long-term effect of MRX on other biochemical markers of cholestasis and liver disease.
- Evaluate the long-term effect of MRX on xanthomas.
- Explore an expanded dosing range to identify the doses necessary to achieve the optimal benefit-to-risk ratio for this patient population.
- Evaluate the long-term effect of MRX on weight in pediatric participants with ALGS.

2.2. Study Endpoints

Safety and efficacy endpoints are examined overall and for each of the 6 treatment phases:

- Dose Escalation Period (Day 1 – Week 4),
- Dose Optimization Period (Week 5 – Week 12),
- Safety Dosing Period (Week 13 – Week 48),
- Safety Monitoring Period (Week 49 – Week 96),
- Long-term Optional Follow-up Treatment Period (Week 97 – Week 144 [148*]),
- Long-term Optional Follow-up Treatment Period-2 (Week 145 – Week 216; Week 220 assessments will occur 4 weeks after last dose).

* Week 148 is only completed for participants who do not wish to enter the long-term optional follow-up treatment period-2.

Unless otherwise specified, summaries will be provided by treatment sequence where applicable from the LUM001-301 core study (e.g., Placebo [PBO]-MRX), and overall.

2.2.1. Safety Endpoints

The safety endpoints for this study include the following:

- Incidence of 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 MRX baseline in clinical safety laboratory values at each clinic visit (if applicable).
- Change from MRX baseline in physical examination findings and vital signs at each clinic visit.
- Concomitant medication usage.

Physical examination findings include body weight and height, along with body mass index (BMI). Vital signs include heart rate, respiratory rate, body temperature, and blood pressure. Z-scores for height, weight, and BMI will be calculated. Note that the z-scores for body weight and height are considered as efficacy but are derived from safety variables.

Safety laboratory tests and units that will be used for reporting are listed in Appendix 2. Note that bilirubin (total and direct), alkaline phosphatase (ALP), GGT, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are considered as both safety and efficacy laboratory tests.

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the mean change from MRX baseline to Week 48 in fasting serum bile acid (sBA).

2.2.2.2. Secondary Endpoints

Secondary efficacy endpoints include mean change from MRX baseline through Week 216/EOT (as well as Week 220/EOS, which occurs 4 weeks after the last dose of study medication) in:

- Biochemical markers of cholestasis and liver disease (e.g., ALT, AST, ALP, GGT, and bilirubin [total and direct])
- Pruritus as measured by the ItchRO* instruments (ItchRO[Obs]^{TM} caregiver instrument/ItchRO[Pt]^{TM} patient instrument).
- Xanthomas as measured by clinician xanthoma scale.
- Clinician scratch scale.
- Fasting serum bile acid level.

* During the first 12 weeks of the study, the electronic diary (ItchRO) will be completed twice daily (AM & PM). During the stable dosing period (Weeks 13-48), twice daily completion of the electronic diary (ItchRO) for 4 consecutive weeks will be required following the Week 24 and Week 44 clinic visits. For participants who continue in the safety monitoring period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 60, 72, and 84 clinic visits. For participants who continue in the long-term, optional follow-up treatment period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 96, 108, 120, and 132 clinic visits, and for 4 weeks following the Week 144 visit. For participants who continue in the long-term optional follow-up treatment period-2, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 144, 156, 168, 180, 192, 204 clinic visits, and for 4 weeks following the Week 216 visit.

For the secondary ItchRO endpoint, only the weekly average morning severity score will be summarized.

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 MRX BL* Week	Through Week (LUM001-305)
ItchRO(Obs)	Weekly average morning severity score	0	220/EOS
sBA	Laboratory test level	0	220/EOS
Liver enzymes (ALP, AST, ALT, GGT, total bilirubin, direct bilirubin)	Laboratory test level	0	220/EOS
Clinician xanthoma scale	5-point scale	0	220/EOS
Clinician scratch scale	5-point scale	0	220/EOS

* The observation obtained at first dose of MRX (either in LUM001-301 or in LUM001-305)

2.2.2.3. Additional Efficacy Endpoints

The following additional efficacy evaluations will be assessed from Change from baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 through Week 220/EOS:

- Pediatric Quality of Life Inventory (PedsQL^{TM}), including 4 domains: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. In addition to these 4 domains, a total score will also be calculated. PedsQL is collected both for child and parent and will be summarized accordingly.
- Caregiver Impression of Change (CIC)

2.2.2.4. Sensitivity Endpoints

All efficacy endpoints for this study are described in

Table 2 and Table 3 for continuous and categorical endpoints, respectively. Note that data for participants who early terminated from the study prior to Week 216 or are otherwise missing Week 48, Week 96, Week 144, and/or Week 216 data will be imputed in a last-observation-carried-forward (LOCF) sensitivity analysis approach (see Section 6.1.5.2).

Table 2: Analysis of Continuous Efficacy Endpoints (including Sensitivity)

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From MRX BL** Week	Through Week (LUM001-305)
ItchRO(Obs)	Weekly average morning severity score	0	2, 4, 8, 12, 28, 46, 46/LOCF, 62, 74, 86, 98, 98/LOCF, 110, 122, 134, 146^, 146/LOCF, 158, 170, 182, 194, 206, 218, 218/LOCF^
sBA	Laboratory test level	0	2, 4, 8, 12, 16, 24, 36, 48^, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144^, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216^, 216/LOCF, and 220/EOS^
Liver enzymes (ALP, ALT, GGT, AST, total bilirubin, direct bilirubin)	Laboratory test level	0	2, 4, 8, 12, 16, 24, 36, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216^, 216/LOCF, and 220/EOS
Lipid panel and cholestasis biomarkers (cholesterol, LDL-C, C4)	Laboratory test level	0	2, 4, 8, 12, 16, 24, 36, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144^, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216^, 216/LOCF, and 220/EOS^
Clinician Scratch Score (CSS)	Score	0	2, 4, 8, 12, 24, 36, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216^, 216/LOCF, and 220/EOS
Clinician Xanthoma Scale	Score	0	24, 36, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216^, 216/LOCF, and 220/EOS

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	24, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 144, 144/LOCF, 148*, 156, 216, 216/LOCF, and 220/EOS
Caregiver Impression of Change - Xanthoma Severity (CIC-Xan)	Score	--	Summary statistics at Week: 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 144, 144/LOCF, 148* 156, 216, 216/LOCF, and 220/EOS
Height and Weight z-Score	Z-Score	0	2, 4, 8, 12, 16, 24, 36, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216^, 216/LOCF, and 220/EOS

* Applicable to only participants who elect not to participate in the long-term, optional follow-up treatment period-2.

^ Indicates endpoint defined as primary, secondary, or exploratory evaluation.

** The observation obtained at first dose of MRX (either in LUM001-301 or in LUM001-305)

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	Change from MRX BL** from LUM001-305 at Week: 2, 4, 8, 12, 24, 36, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216, 216/LOCF, and 220/EOS
Clinician Xanthoma Scale	Improved, Stable, or Worsened	Number and % of subjects at Week: 24, 36, 48, 48/LOCF, 60, 72, 84, 96, 96/LOCF, 108, 120, 132, 144/LOCF, 148*, 156, 168, 180, 192, 204, 216, 216/LOCF, and 220/EOS

* Applicable to only participants who elect not to participate in the long-term, optional follow-up treatment period-2.

^ Indicates endpoint defined as primary, secondary, or exploratory evaluation.

** The observation obtained at first dose of MRX (either in LUM001-301 or in LUM001-305)

2.2.2.5. Efficacy Parameter Descriptions

Itch Reported Outcome (ItchRO)

The primary assessment of pruritus will be the pruritus severity as assessed using the Itch caregiver reported outcome measure (ItchRO[Obs]™) administered as a twice daily electronic diary. Children ≥9 years of age will complete the patient instrument: ItchRO(Pt)™. Children between the ages of 5 and 8 years of age will complete the patient instrument with the assistance

of their caregiver: ItchRO(Pt). Participants and caregivers will be trained on the use of the electronic diary during their participation in LUM001-301 protocol. There is no ItchRO(Pt) report for participants under the age of 5 years.

Age at screening in the LUM001-301 study 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 not be analyzed.

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

- Screening through first 12 weeks during the dose escalation and dose optimization periods.
- 4 consecutive weeks that follow the Week 24 and Week 44 clinic visits during the stable dosing period.
- 2 consecutive weeks that follow the Week 60, Week 72, and Week 84 clinic visits during the safety monitoring period.
- 2 consecutive weeks that follow the Week 96, Week 108, Week 120, Week 132 clinic visits during the long-term optional follow-up treatment period.
- 2 consecutive weeks that follow each visit in the long-term optional follow-up treatment period-2; Week 144, Week 156, Week 168, Week 180, Week 192, and Week 204.
- 4 consecutive weeks that follow the Week 216 clinic visit.

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 weekly average morning severity score from ItchRO(Obs) is calculated and used in the analysis of pruritus.

The weekly average morning severity scores are calculated as the average of the morning scores over a defined study week consisting of the 7 days before the scheduled clinic visit (for Baseline [Day 0], Weeks 2, 4, 8, and 12) or a 7-day period starting the week after the scheduled clinic visit (for Weeks 24, 44, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216). 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.

In deriving weekly average morning severity post-baseline ItchRO score, each visit date will be

determined based on the varying eDiary collection periods (as applicable):

A. Weeks 2, 4, 8, and 12: The scheduled visit date is used.
B. Weeks 26, 46, 62, 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, 206, and 218: Each scheduled visit date will be determined based on the date of the associated scheduled clinic visit (i.e., Weeks 24, 44, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216) 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 participant 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 participant'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

The clinician's assessment of the participant's xanthomatosis is focused on the number of lesions present and the degree to which the participant's lesions interfere or limit his or her activities. The clinician xanthoma 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 – Xanthoma Severity (CIC-Xan)

The CIC-Xan is designed to assess the caregiver's perception of the participant'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.

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 participants 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 in the LUM001-301 study 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) participant 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 participant 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 participant 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 □.

2.2.3. Other Endpoints

Other endpoints of this study include the following:

- Plasma levels of maralixibat at baseline (pre-dose) and over time.

Pharmacokinetics

Due to poor absorption of maralixibat, 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 2, 8, 12, 24, 36, 48, 96, 144, 148, 216, and 220/EOS as selected by the site/investigator.

3. Overall Study Design and Plan

3.1. Overall Design

This is a multicenter, double-blind study of MRX in children >12 months of age diagnosed with ALGS who have completed participation in the LUM001-301 protocol. While all participants received maralixibat, the investigator, participants and sponsor were blinded to maralixibat dose. The study is divided into 6 parts:

- Dose Escalation Period (Day 1 – Week 4),
- Dose Optimization Period (Week 5 – Week 12),
- Safety Dosing Period (Week 13 – Week 48),
- Safety Monitoring Period (Week 49 – Week 96),
- Long-term Optional Follow-up Treatment Period (Week 97 – Week 144 [148*]),
- Long-term Optional Follow-up Treatment Period-2 (Week 145 – Week 220).

* Week 148 is only completed for participants who do not wish to enter the long-term optional follow-up treatment period-2.

For participants randomized to placebo in the LUM001-301 protocol, or those who complete the core study more than 7 days prior to enrollment into this study, the MRX dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day. For participants who were randomized to receive active drug in the LUM001-301 protocol, MRX doses will remain the same as the dose being taken at Week 13 in the core study. Following the dose escalation period, the MRX dose for each participant may be increased or decreased by the investigator. Dose optimization will occur in a blinded, titrated manner with four dose levels available as treatment options: 35, 70, 140, or 280 µg/kg/day.

At the end of the optimization period, participants will continue dosing to complete the stable dosing and safety monitoring periods at their current dose level. If at any time a participant experience intolerance due to gastrointestinal (GI) symptoms, the physician investigator may lower the dose to a previously tolerated dose.

Following the safety monitoring period, two sequential long-term optional follow-up periods will be available to participants willing and eligible to roll over. Participant's dose of MRX will

remain the same as administered at the end of the safety monitoring period. Any participant with dose interruptions >7 consecutive days due to a protocol amendment will be require dose escalation upon resumption of study drug.

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

Figure 1: Treatment Regimens

Treatment Regimen	MRX 70, 140, 280 µg/kg/day		MRX-MRX up to 280 µg/kg/day		MRX-MRX up to 280 µg/kg/day		MRX-MRX up to 280 µg/kg/day		MRX-MRX up to 280 µg/kg/day
	PBO		PBO-MRX up to 280 µg/kg/day		PBO-MRX up to 280 µg/kg/day		PBO-MRX up to 280 µg/kg/day		PBO-MRX up to 280 µg/kg/day
Protocol Version	**LUM001-301**		**Original LUM001-305 Protocol**		**Protocol Amendment 4**		**Protocol Amendment 5**		**Protocol Amendment 6**
Treatment Weeks *	0	13	0 (13)	48 (61)		96 (109)		144 (157)	216 (229)

* Participants who received MRX in LUM001-301 have their total planned treatment weeks of MRX in parenthesis.

3.2. Sample Size and Power

Approximately 36 participants meeting the study's inclusion and exclusion criteria will be enrolled in the study. The number of participants enrolled in this study will be determined by the number of participants who roll-over from the LUM001-301 protocol. Because this is an extension study for the LUM001-301 protocol, the sample size is not based on statistical considerations.

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 participants receive MRX, up to 280 µg/kg/day or a maximum daily dose of 20 mg/day, during the initial original protocol planned length of 48 weeks. After completion of 48 weeks of treatment participants enter the safety monitoring period for another 48 weeks.

Participants were then given the option to enroll in the optional long-term follow-up period of 48 additional treatment weeks, if eligible, receiving up to 280 µg/kg/day or a maximum daily dose of 20 mg/day of MRX.

A second optional long-term follow-up period was then offered for eligible participants for an additional 72 weeks of treatment of MRX receiving up to 280 µg/kg/day or a maximum daily dose of 20 mg/day of MRX.

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, all participants entering the extension study will participate in a 4-week double-blind dose escalation period during which:

- Participants randomized to receive placebo during the LUM001-301 protocol will receive weekly dose increases of MRX up to a target dose of 140 µg/kg/day.
- Participants randomized to active drug during the LUM001-301 protocol will continue to receive the dose of MRX that they were taking at Week 13 of the LUM001-301 study. The MRX doses for these participants will remain blinded and will not be altered during the dose-escalation period.

A minimum period of 7 days must elapse between increases in dose.

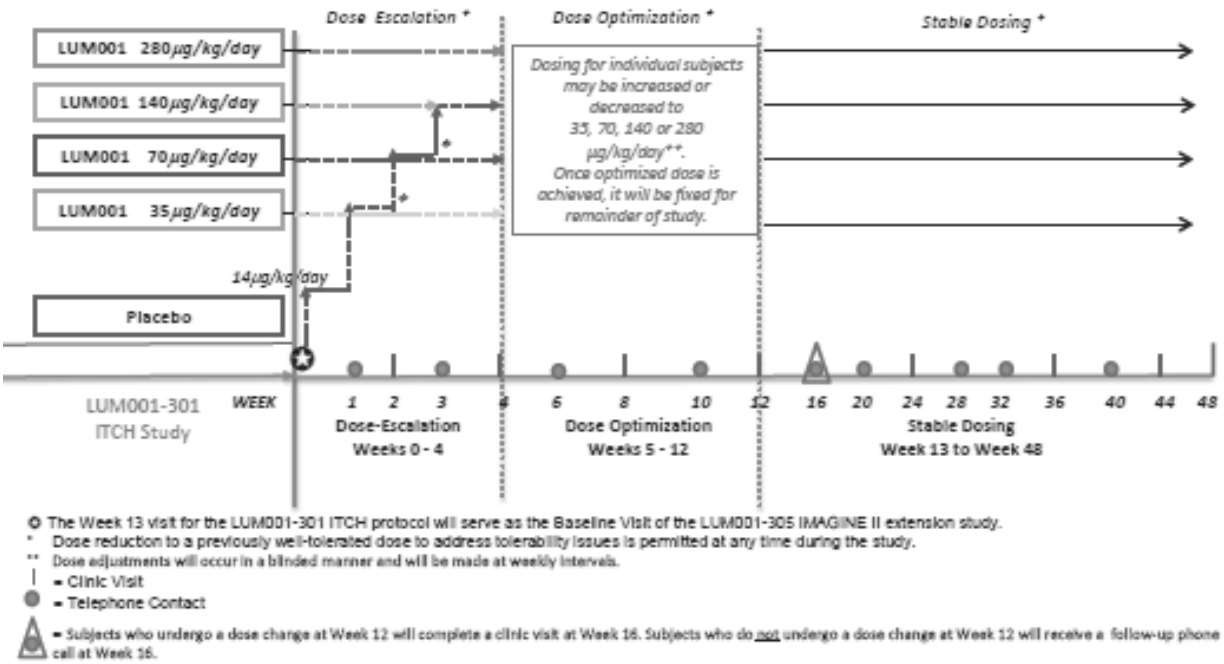
3.4.2. Dose Optimization Period

Following completion of the 4-week dose escalation period, participants will enter an 8 week dose-optimization period. During this period, the investigator will have the option to adjust MRX dosing with the objective of achieving optimal control of pruritus at a dose level that is tolerated by the participant and up to a maximum daily dose of 280 µg/kg MRX or 20 mg total dose. Study drug dose will be increased or decreased in a double-blind manner. Increases in dose will be based on effect on pruritus. Reductions in dose will be based on tolerability. At the investigator's discretion, the doses for participants who were previously reduced may be re challenged during the dose optimization period. Each participant will receive one of the following dose levels:

- MRX 35 µg/kg/day.
- MRX 70 µg/kg/day.
- MRX 140 µg/kg/day.
- MRX 280 µg/kg/day.

A minimum period of 7 days must elapse between increases in dose (see Figure 2).

Figure 2: Study Design for Day 0 – Week 48

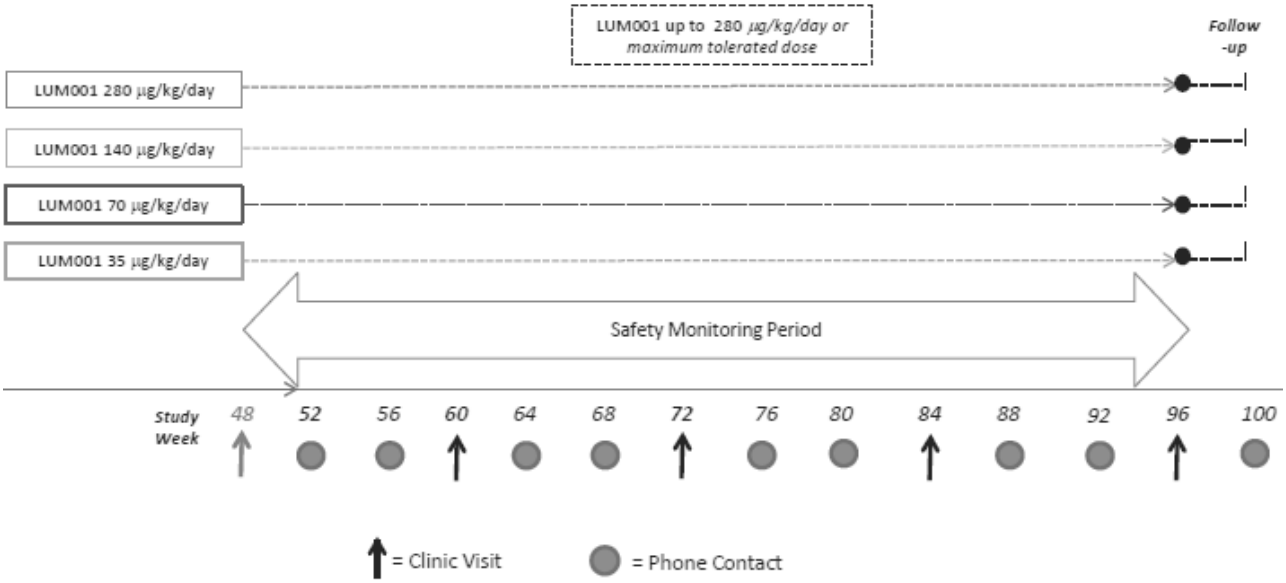


3.4.3. Stable Dosing and Safety Monitoring Period

Following completion of the 8-week dose optimization period, all participants will enter the stable dosing period lasting 36 weeks followed by a safety monitoring period lasting up to 48 weeks. During the stable dosing and safety monitoring periods, participants will be dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose. However, if a participant experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the ChiLDReN protocol chair and Medical Monitor, may lower the dose to a previously tolerated dose for the rest of the study (see Figure 2 and Figure 3).

Participants with dosing interruptions of greater than 7 consecutive days will require re-integration in the study to ensure that 1) their resumed visit schedule aligns with the protocol, and 2) their total MRX exposure during the study does not exceed 216 weeks (see Figure 6).

Figure 3: Study Design for Week 49 – Week 96

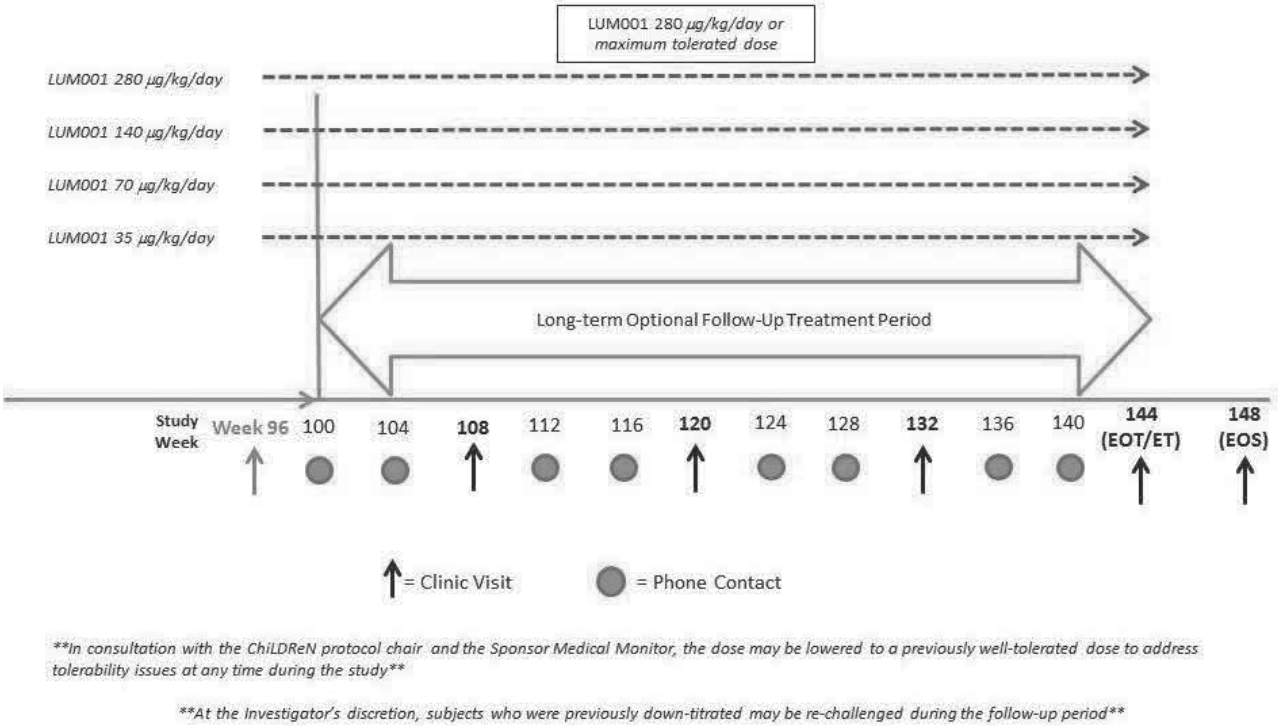


In consultation with the Protocol Chair and the Medical Monitor, the dose may be lowered to a previously well-tolerated dose to address tolerability issues at any time during the study
At the Investigator's discretion, subjects who were previously down-titrated may be re-challenged during the safety monitoring period

3.4.4. Long-Term Optional Follow-up Treatment Period

The long-term optional follow-up treatment period is for eligible participants who choose to remain on treatment with MRX following the initial 96 weeks of treatment. During this long-term optional follow-up treatment period, participants with MRX dosing interruptions ≤7 days will remain on the same dose they were taking at Week 96. Participants with MRX dosing interruptions >7 consecutive days will require dose escalation upon resumption of study drug. The dose of MRX will be increased at weekly intervals up to the participant's previously achieved highest tolerated dose. Study drug for each participant will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen (see Figure 4).

Figure 4: Study Design for Week 96 – Week 148



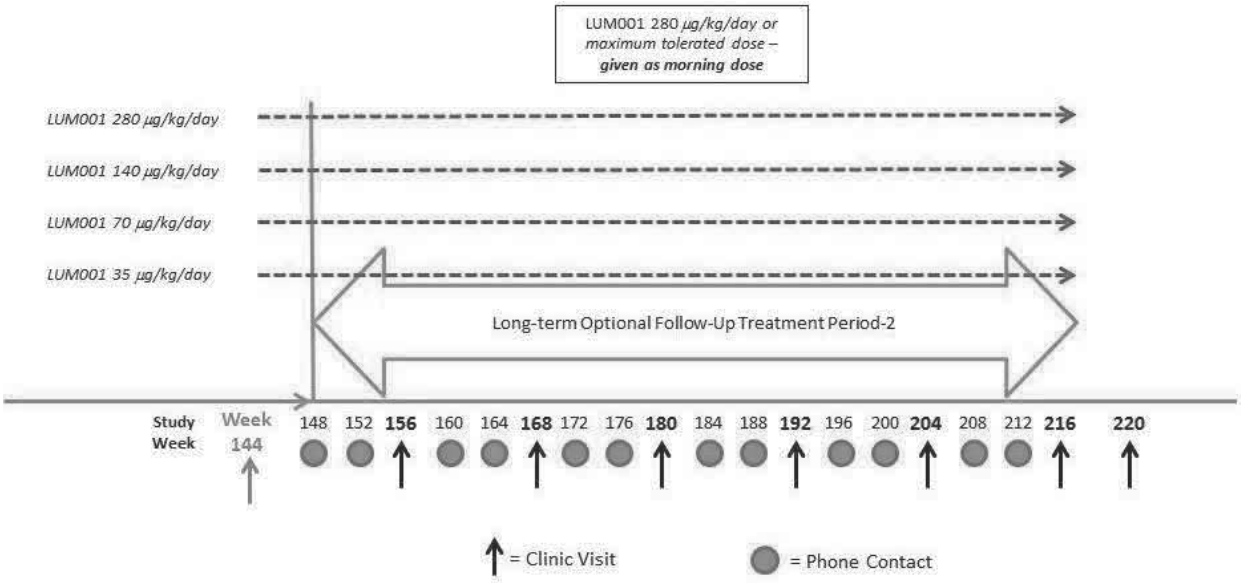
In consultation with the ChiLDReN protocol chair and the Sponsor Medical Monitor, the dose may be lowered to a previously well-tolerated dose to address tolerability issues at any time during the study

At the Investigator's discretion, subjects who were previously down-titrated may be re-challenged during the follow-up period

3.4.5. Long-Term Optional Follow-up Treatment Period-2

The long-term optional follow-up treatment period-2 is for eligible participants who choose to remain on treatment with MRX for an additional 72 weeks. During this long-term optional follow-up treatment period-2, participants will remain on the same dose they were taking at Week 144. Study drug for each participant will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen (see Figure 5).

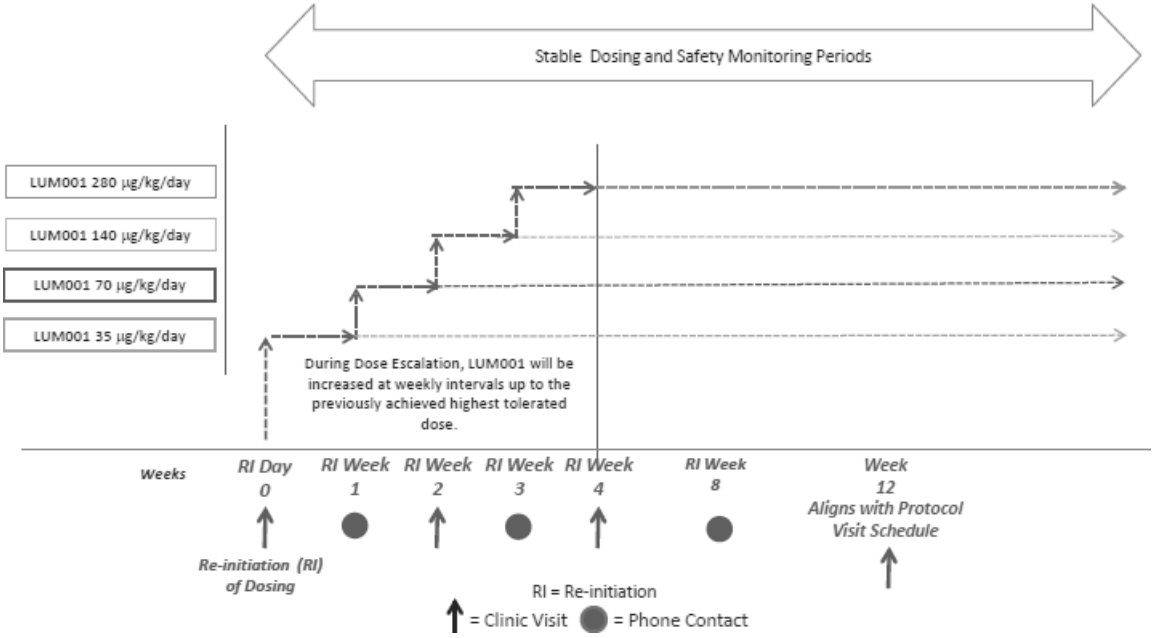
Figure 5: Study Design for Week 144 – Week 220



In consultation with Medical Monitor, the dose may be lowered to a previously well-tolerated dose to address tolerability issues at any time during the study

At the Investigator's discretion, subjects who were previously down-titrated may be re-challenged during the follow-up period

Figure 6: Study Design for Re-initiation of MRX when Dosing Interruption is Greater than 7 Consecutive Days



3.5. Method of Assigning Participants to Treatment Groups

This trial is an open-label extension of LUM001-301, and all participants will receive MRX at various dose regimens.

3.6. Blinding and Unblinding

Although all participants are treated with MRX, dose optimization will occur in a blinded, titrated manner. This regimen will represent a *real* dose escalation for participants previously randomized to placebo and a *mock* dose escalation for participants previously randomized to active study treatment in the LUM001-301 core study.

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 participant, the investigator will have the ability to unblind the treatment assignment for that participant. If a participant is unblinded by the investigator, the sponsor 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 the sponsor.

Breaking of the blind should not occur except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the participant, or when causality must be determined prior to submitting a regulatory safety report for a 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 participant assessment.

An administrative letter (dated 21-Nov-2019) has been accepted by all sites that allows for unblinding of subjects' doses from LUM001-301, as that database has now locked.

3.7. Schedule of Procedures

A detailed schedule of procedures for the study is provided in the below tables. Any references to "Section X.X" in the footnotes in this section are referring to the relevant section in the protocol.

3.7.1. Schedule of Procedures A – Baseline – Week 12

Study Period	Baseline	Treatment Period							
		Dose Escalation[c]				Dose Optimization			
Study Week		1	2	3	4	6	8	10	12
Study Day	Day 0[1]	7	14	21	28	42	56	70	84
Window (in days)		(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)
Informed Consent	X								
Eligibility Assessment / Medical History	X								
Physical Exam	X								
Body Weight & Height	X		X		X		X		X
Vital Signs[2]	X		X		X		X		X
CBC with Differential[3]	X		X		X		X		X
Coagulation[3]	X		X		X		X		X
Chemistry Panel[3]	X		X		X		X		X
Lipid Panel[3,4]	X		X		X		X		X
Cholestasis Biomarkers[3,4]	X		X		X		X		X
Fat Soluble Vitamins[3,4]	X						X		X
Plasma Sample for LUM001[d]	X		X		X		X		X
Urinalysis[3]	X[a]		X[a]		X[a]		X		X
Urine Pregnancy Test [5]	X		X		X		X		X
Participant eDiary / Caregiver eDiary (ItchRO)	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Clinician Scratch Scale	X		X		X		X		X
Clinician Xanthoma Scale	X								
PedsQL	X								
Enrollment	X								
Study Drug Supplied	X		X		X		X		X
Assess Study Drug Compliance			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

Adverse Events	X	X	X	X	X	X	X	X	X
Phone Contact[6]		X		X		X		X	

1 Evaluations and procedures completed for the Week 13 Visit of the LUM001-301 protocol will also serve as the evaluations for the Baseline Visit for this extension study.
2 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
3 See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
4 Subjects are required to fast at least 4 hrs. (only water permitted prior to collection).
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.

[a] At the indicated visits, oxalate will be part of the urinalysis.
[b] During the first 12 weeks of the study, the eDiary (ItchRO) will be completed twice daily (AM & PM). Compliance will be assessed at each visit/phone contact.
[c] Subjects should be dosed for at least 7 days at each dose level.
[d] At Weeks 2, 8, 12, 24, 36 and 48, blood will be drawn approximately 4 hours post dosing for drug level analysis. At Week 4, blood will be drawn approximately 2 hours post-dosing for drug level analysis.

3.7.2. Schedule of Procedures B – Stable Dosing: Week 16 – Week 48

Study Period	Treatment Period (cont'd) Stable Dosing								
Study Week	**16[6]**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**Week 48**
Study Day	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**
Window (in days)	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**
Physical Exam	X[6]		X			X			X
Body Weight & Height	X[6]		X			X			X
Vital Signs[1]	X[6]		X			X			X
CBC with Differential[2]	X[6]		X			X			X
Coagulation[2]	X[6]		X			X			X
Chemistry Panel[2]	X[6]		X			X			X
Lipid Panel[2,3]	X[6]		X			X			X
Cholestasis Biomarkers[2,3]	X[6]		X			X			X
Fat Soluble Vitamins[2,3]			X			X			X
Plasma Sample for LUM001[c]			X			X			X
Urinalysis[2]	X[6]		X			X			X[a]
Urine Pregnancy Test [4]	X[6]		X			X			X
Clinician Scratch Scale			X			X			X
Clinician Xanthoma Scale			X			X			X
Subject eDiary/Caregiver eDiary (ItchRO)			X[b]	X[b] to Week 28				X[b]	X[b] to Week 48
PedsQL			X						X
Caregiver Impression of Change (CIC)									X
Study Drug Supplied			X			X			X
Assess Study Drug Compliance			X			X		X	X
Review Study Diaries & Assess Compliance			X			X		X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Phone Contact[5]	X	X		X	X		X		

[1] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[2] See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[3] Subjects are required to fast at least 4 hrs. (only water permitted prior to collection).
[4] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[5] Subjects must be available to receive a phone call from study staff.
[6] A Week 16 Clinic Visit will be completed for all subjects who undergo a change in dose at Week 12; Subjects who do not undergo a dose change at Week 12 will be contacted by phone at Week 16.

[a] At the indicated visits, oxalate will be part of the urinalysis.
[b] During the stable dosing period, twice daily completion of the eDiary (ItchRO) for 4 consecutive weeks will be required following the Week 24 and Week 44 clinic visits.
[c] At Weeks 2, 8, 13, 24, 36 and 48, blood will be drawn approximately 4 hours post dosing for drug level analysis. At Week 4, blood will be drawn approximately 2 hours. post-dosing for drug level analysis

3.7.3. Schedule of Procedures C – Safety Monitoring Period: Week 52 – Week 96/Early Termination Schedule of Procedures

Study Period	Treatment Period (cont'd) Safety Monitoring Period											Study Termination	Follow-Up
Study Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**Week 96 (or Early Term[7])**	**30 days after final dose[8]**
Study Day	364	392	420	448	476	504	532	560	588	616	644	672	
Window (in days)	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±5)**
Informed Consent / Eligibility Assessment for PA5[1]												X	
Physical Exam			X			X			X			X	
Body Weight & Height			X			X			X			X	
Vital Signs[2]			X			X			X			X	
CBC with Differential[3]			X			X			X			X	
Coagulation[3]			X			X			X			X	
Chemistry Panel[3]			X			X			X			X	
Lipid Panel[3,4]			X			X			X			X	
Cholestasis Biomarkers[3,4]			X			X			X			X	
Fat Soluble Vitamins[3,4]			X			X			X			X	
Plasma Sample for LUM001												X	
Urinalysis[3]			X			X			X			X[a]	
Urine Pregnancy Test[5]			X			X			X			X	
Clinician Scratch Scale			X			X			X			X	
Clinician Xanthoma Scale			X			X			X			X	
Subject eDiary/Caregiver eDiary (ItchRO)			X[b]	X[b] to Week 62		X[b]	X[b] to Week 74		X[b]	X[b] to Week 86		X[b]	X[b] to Week 98
PedsQL			X			X			X			X	
Caregiver Impression of Change (CIC)			X			X			X			X	
Study Drug Supplied			X			X			X			X	
Assess Study Drug Compliance			X			X			X			X	
Review Study Diaries & Assess Compliance				X[c]			X[c]			X[c]			
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[6]	X	X		X	X		X	X		X	X		X

1 Subjects can consent to roll over into the long-term optional follow-up treatment period, per Schedule D.
2 Blood pressure (BP), heart rate (HR), temperature, respiration rate
3 See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
4 Subjects are required to fast at least 4 hrs. (only water permitted prior to collection).
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Subjects who withdraw early during the follow-up treatment period should complete all evaluations at this visit.
8 Visit not required for subjects with ≤7 days LUM001 dose interruption who roll over into the long-term optional follow-up treatment period (Schedule D) or for subjects with >7 days but less than 30 days LUM001 dose interruption who roll over into the long-term optional follow-up treatment period (Schedule E).

[a] At the indicated visits, oxalate will be part of the urinalysis.
[b] During the follow-up period, twice daily completion of the eDiary (ItchRO) for 2 consecutive weeks will be required following the Week 60, 72, 84, and 96 clinic visits.
[c] Study staff will review ItchRO diary data from the prior period and assess compliance.

	Clinic Visit
	Phone Contact

3.7.4. Schedule of Procedures D – Long-term Optional Treatment Period: Week 96 – Week 148

Study Period	Treatment Period (cont'd) Long-term, Optional Follow-up Treatment Period											EOT Visit/ET	EOS Visit[9]
Study Week	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**Week 144[8]**	**Week 148**
Study Day	700	728	756	784	812	840	868	896	924	952	980	1008	
Window (in days)	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±5)**
Informed Consent / Eligibility Assessment for PA6[1,10]												X	
Physical Exam			X			X			X			X	X
Body Weight[2] & Height			X			X			X			X	X
Vital Signs[3]			X			X			X			X	X
CBC with Differential[4]			X			X			X			X	X
Coagulation[4]			X			X			X			X	X
Chemistry Panel[4]			X			X			X			X	X
Lipid Panel[4,5]			X			X			X			X	X
Cholestasis Biomarkers[4,5]			X			X			X			X	X
Fat Soluble Vitamins[4,5]			X			X			X			X	X
Plasma Sample for LUM001												X	X
Urinalysis[4]			X			X			X			X[a]	X[a]
Urine Pregnancy Test[6]			X			X			X			X	X
Clinician Scratch Scale			X			X			X			X	X
Clinician Xanthoma Scale			X			X			X			X	X
Subject eDiary/Caregiver eDiary (ItchRO)	X[b] to Week 98		X[b]	X[b] to Week 110		X[b]	X[b] to Week 122		X[b]	X[b] to Week 134		X[b]	X[b] to Week 148
PedsQL			X									X	X
Caregiver Impression of Change (CIC)			X									X	X

Study Period	Treatment Period (cont'd) Long-term, Optional Follow-up Treatment Period											EOT Visit/ET	EOS Visit[9]
Study Week	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**Week 144[8]**	
Study Day	700	728	756	784	812	840	868	896	924	952	980	1008	**Week 148**
Window (in days)	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±5)**
Study Drug Supplied			X			X			X			X[11]	
Assess Study Drug Compliance			X			X			X			X	
Review Study Diaries & Assess Compliance	X[c]			X[c]			X[c]			X[c]		X[c]	X[c]
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[7]	X	X		X	X		X	X		X	X		

1 Subjects can consent to roll over into the long-term optional follow-up treatment period-2, per Schedule F.
2 Increases of 10% or more in a subject's weight from baseline will require a dose adjustment, per Section 10.1.
3 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
4 See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
5 Subjects are required to fast at least 4 hrs. (only water permitted prior to collection).
6 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
7 Subjects must be available to receive a phone call from study staff.
8 Subjects who withdraw early during the follow-up treatment period should complete all evaluations at this visit.
9 Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) should return to the study site 30 days after the last dose of study drug and complete all evaluations at this visit
10 Eligibility should only be assessed at Week 144 for subjects that complete PA5 (Week 144) and rollover directly to PA6. Subjects who did not consent to PA5 and who re-enter in PA6 from IPA5 or earlier will not be re-assessed for eligibility at Week 144
11. Subjects should continue dosing at Week 144 if entering PA6

[a] At the indicated visits, oxalate will be part of the urinalysis.
[b] During the follow-up period, twice daily completion of the eDiary (ItchRO) for 2 consecutive weeks will be required following the Week 108, 120, and 132 visits and for 4 consecutive weeks following the Week 144 clinic visit.
[c] Study staff will review ItchRO diary data from the prior period and assess compliance.

	Clinic Visit
	Phone Contact

3.7.5. Schedule of Procedures E – Re-entry into Long-term, Optional Treatment Period/Long-term, Optional Treatment Period-2

Study Period	Dose Escalation Treatment Period						
PA5 DE Study Week	PA5 RI -2[h]	PA5 RI Day 0	PA5 RI Week 1	PA5 RI Week 2	PA5 RI Week 3	PA5 RI Week 4	PA5 Schedule D - Week 104
Scheduling Considerations		0					
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)
Informed Consent/Assent	X						
Assess Eligibility for study re-entry	X	X					
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	
Cholestasis Biomarkers[b,c]		X		X		X	
Fat Soluble Vitamins[b,c,d]		X		X		X	
Urinalysis[b]		X		X		X	
Serum Pregnancy Test (if indicated)[e]	X	X		X		X	
Clinician Scratch Scale		X		X		X	
Clinician Xanthoma Scale		X		X		X	

Study Period	Dose Escalation Treatment Period						
PA5 DE Study Week	**PA5 RI -2[h]**	**PA5 RI Day 0**	**PA5 RI Week 1**	**PA5 RI Week 2**	**PA5 RI Week 3**	**PA5 RI Week 4**	**PA5 Schedule D - Week 104**
Scheduling Considerations		**0**					
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**
Caregiver ItchRO/ Patient ItchRO						X (collected for 2-week period following this visit)	
PedsQL		X					
Study Drug Supplied[f]		X		X		X	
Caregiver ItchRO/ Patient ItchRO Device Supplied						X	
Assess Study Drug Compliance				X		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

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 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] Subjects with dose interruptions prior to Week 96 or who early terminated may re-enter the study under Protocol Amendment 6. These subjects will initiate dose escalation at visit PA5 RI -2.

Clinic Visit
Phone Contact

3.7.6. Schedule of Procedures F – Long-term, Optional Treatment Period-2: Week 144 – Week 220 (Study Completion / Termination)

Study Period	Long-term, Optional Follow-up Treatment Period-2																	EOT/ET Visit	EOS Visit
Study Week	148	152	156	160	164	168	172	176	180	184	188	192	196	200	204	208	212	Week 216[7]	Week 220
Study Day																			
Window (in days)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±5)
Physical Exam			X			X			X			X			X			X	X
Body Weight[1] & Height			X			X			X			X			X			X	X
Vital Signs[2]			X			X			X			X			X			X	X
CBC with Differential[3]			X			X			X			X			X			X	X
Coagulation[3]			X			X			X			X			X			X	X
Chemistry Panel[3]			X			X			X			X			X			X	X
Lipid Panel[3,4]			X			X			X			X			X			X	X
Cholestasis Biomarkers[3,4]			X			X			X			X			X			X	X
Fat Soluble Vitamins[3,4]			X			X			X			X			X			X	X
Plasma Sample for LUM001																		X	X
Urinalysis[3]			X			X			X			X			X			X[a]	X[a]
Urine Pregnancy Test[5]			X			X			X			X			X			X	X
Clinician Scratch Scale			X			X			X			X			X			X	X
Clinician Xanthoma Scale			X			X			X			X			X			X	X

Study Period	Long-term, Optional Follow-up Treatment Period-2																	EOT/ET Visit	EOS Visit
Study Week	**148**	**152**	**156**	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208**	**212**	**Week 216[7]**	**Week 220**
Study Day																			
Window (in days)	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±5)**
Subject eDiary/ Caregiver eDiary (ItchRO)	X[b] to Week 146		X[b]	X[b] to Week 158		X[b]	X[b] to Week 170		X[b]	X[b] to Week 182		X[b]	X[b] to Week 194		X[b]	X[b] to Week206		X[b]	X[b] to Week 220
PedsQL			X															X	X
Caregiver Impression of Change (CIC)			X															X	X
Study Drug Supplied			X			X			X			X			X				
Assess Study Drug Compliance			X			X			X			X			X			X	
Review Study Diaries & Assess Compliance	X[c]			X[c]			X[c]			X[c]			X[c]			X[c]			
ItchRO/Patient ItchRO Device Returned																			X
Concomitant Medications	X	X	X	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	X	X	X
Phone Contact[6]	X	X		X	X		X	X		X	X		X	X		X	X		

[1] Increases of 10% or more in a subject's weight from baseline will require a dose adjustment, per Section 10.1.
[2] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[3] See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[4] Subjects are required to fast at least 4 hrs. (only water permitted prior to collection).
[5] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[6] Subjects must be available to receive a phone call from study staff.
[7] Subjects who withdraw early during the follow-up treatment period-2 should complete all evaluations at this visit.

[a] At the indicated visits, oxalate will be part of the urinalysis.
[b] During the follow-up period, twice daily completion of the eDiary (ItchRO) for 2 consecutive weeks will be required following the Week 144, 156, 168, 180, 192, and 204 visits and for 4 consecutive weeks following the Week 216 clinic visit. In cases where the the subject no longer lives with an ItchRO observer, the ItchRO(Obs) will not need to be completed; however, ItchRO(Pt) will need to be completed by subjects aged ≥9 years of age
[c] Study staff will review ItchRO diary data from the prior period and assess compliance.

	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 participants (n) with non-missing values, mean, standard deviation (SD) and/or standard error (SE) if appropriate, median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of participants in the analysis population for the treatment group and overall, unless otherwise specified.

For purposes of analysis of disposition of participants, there will be 4 treatment phases in addition to overall:

- Original Protocol Phase (Day 1 – Week 48),
- Protocol Amendment 4 Phase (Week 49 – Week 96)
- Protocol Amendment 5 Phase (Week 97 – Week 144)
- Protocol Amendment 6 Phase (Week >144)

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 and/or SE) will be reported to 2 degrees of precision more than the observed data.

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, weight and BMI 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 participants in a particular category is 0, a percentage (i.e., 0.0%) will not be displayed.

All statistical tests will be conducted using 2-tailed tests at the 0.05 significance level. No inference will be drawn from any p-values presented. Where appropriate, corresponding 95% confidence intervals (CIs) will be presented.

4.2. Interim Analysis

There is no planned interim analysis (IA) in this study. However, in preparation for briefing documents for the End-of-Phase 2 meeting with FDA on 21May2019 and the pre-New Drug Application (NDA) meeting with FDA on 19Nov2019, additional interim analyses were performed outside of what is noted in the protocol. In preparation for the NDA submission, currently planned in Aug2020, the analysis herein described will be performed using an interim data cut date of 01Dec2019.

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 serious adverse event (SAE) data and other key participant 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 population is planned for this study:

- **Safety Population (SAF):** The Safety Population is defined as all participants who were enrolled and received at least one dose of the study drug.

The Safety Population will be used for the analyses of all endpoints. Safety analyses will be conducted according to the treatment received and be displayed by treatment sequence from the core study in LUM001-301 (i.e., PBO-MRX, or MRX-MRX), as appropriate.

As of the 01Dec2019 datacut, a total of 34 patients were enrolled in this study from the LUM001-301 core study. Of those, 28 completed, 6 discontinued (1 re-entered after Week 96) by Week 48. At Week 96, 25 patients had completed, 1 had discontinued, and 2 did not consent to the amendment. At Week 144 there were 21 completers, and 4 discontinuations. The remaining 21 patients are still ongoing in the study. Visit-based safety 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), the following baseline will be used for change from baseline values:

- MRX Baseline: The observation obtained at first dose of MRX (either in LUM001-301 or in LUM001-305) will be used as the MRX baseline observation for all calculations of change from MRX baseline. This baseline is applicable only to visit-based analyses.

For ItchRO weekly average scores, baseline is defined as the average of daily scores in the week consisting of the 7 days immediately before the baseline visit in the respective study.

Safety Assessments After Drug Interruption

For visit-based analyses on safety data collected/assessed after an extended drug interruption period > 28 days (between protocol amendments), as described in Section 5, the following baseline definitions will be used for change from baseline values.

- MRX Baseline: 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 participants 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 participants with a drug interruption between protocol amendments 3 and 4, the PA Day 0 visit is described as "PA4 Dose Escalation Day 0". For participants with a drug interruption between protocol amendments 4 and 5, the PA Day 0 visit is described as "PA5 Dose Escalation Day 0".*

6.1.2. Study Day

Study Day 1 is defined as the date of first study drug administration in this study (LUM001-305). Study day is calculated relative to the date of Study Day 1.

MRX Day 1 is defined as the date of first MRX administration in either this study (LUM001-305) or the lead-in study (LUM001-301). MRX study day is calculated relative to the date of MRX Day 1. This study day definition will only be used for future ad hoc analyses, if needed,

and will not be used in any of the analyses outlined in this SAP.

6.1.3. Adjustments for Covariates

No adjustments will be made for covariates.

6.1.4. Multiple Comparisons

No adjustments will be made for multiple comparisons.

6.1.5. Handling of Dropouts or Missing Data

6.1.5.1. General

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

Any participant who withdraws from the study are 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, 96/ET, 144/ET, EOT/ET), visit-based assessments performed during that visit will not be used in analysis summaries.

For a participant who prematurely discontinues the study, their ET visit data will be assigned to a protocol-specified visit window 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 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. 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 48/LOCF, Week 96/LOCF, Week 144/LOCF, and Week 216/LOCF time points, where appropriate (i.e., if a participant entered a respective period; for example, if a participant did not enter the safety monitoring period, that participant would not have Week 96/LOCF, Week 144/LOCF, or Week 216/LOCF time points). Week 46/LOCF, Week 98/LOCF, Week 146/LOCF, and Week 218/LOCF imputed time points are only applicable for ItchRO(Obs) weekly morning average scores.

For participants 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).

6.1.5.3. Missing ItchRO Scores

In deriving the ItchRO weekly average morning score, 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 participant 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 participant/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. Compliance restrictions are not set for baseline ItchRO average scores.

If a participant/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. Additionally, the same ItchRO assessment day (morning/evening daily score) will not be used across different weekly time periods (i.e. no overlap).

6.1.5.4. 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 □).

6.1.5.5. Missing Last Dose

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

6.1.5.6. Missing Adverse Event Severity/Relationship

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

6.1.5.7. 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 participants 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 participant could be transferred to a principal investigator that did not enrol the participant. Unless otherwise specified, the investigative site of the enrolling investigator will be used for the unique participant identification (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 participants 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 participants that were dose-escalated after an extended 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 PA3, PA4, and PA5) 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 **Error! Reference source not found.**.

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 15 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 participants with an extended drug interruption, efficacy assessments after the interruption are essentially treated as if the participant was on study drug during the period of time that the participant 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 participants without such a drug interruption.

Table 4: Analysis Visit Windows – Primary Analysis

Analysis Visit	Analysis Visit Name	Target Day of Planned Visit	Assessment Window (Study Days[1])
2	Week 2	14	Post-dose – 21
4	Week 4	28	22 – 36
8	Week 8	56	37 – 70
12	Week 12	84	71 – 98
16	Week 16	112	99 – 133
24	Week 24	154	134 – 203
36	Week 36	252	204 – 301
48	Week 48	336	302 – 378
60	Week 60	420	379 – 462
72	Week 72	504	463 – 546
84	Week 84	588	547 – 630
96	Week 96	672	631 – 714
108	Week 108	756	715 – 798
120	Week 120	840	799 – 882
132	Week 132	924	883 – 966
144	Week 144	1008	967 – 1050
156	Week 156	1092	1051 – 1134
168	Week 168	1176	1135 – 1218
180	Week 180	1260	1219 – 1302
192	Week 192	1344	1303 – 1386
204	Week 204	1428	1387 – 1470
216	Week 216	1512	1471 – 1554

[1] Study day relative to the date of first dose of study medication on LUM001-305, unless otherwise specified.

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 participant 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 participant listings.

For visit-based analyses (and listings) on safety data collected or assessed after an extended 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 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 – 112
20	Week 20	140	113 – 168
28	Week 28	196	169 – 224
36	Week 36	252	225 – 280
44	Week 44	308	281 – 336
52	Week 52	364	337 – 392
60	Week 60	420	393 – 448
68	Week 68	476	449 – 504
76	Week 76	532	505 – 560
84	Week 84	588	561 – 616
92	Week 92	644	617 – 672
100	Week 100	700	673 – 728
108	Week 108	756	729 – 784
116	Week 116	812	785 – 840
124	Week 124	868	841 – 896
132	Week 140	924	953 – 1008
140	Week 148	980	1009 – 1064
148	Week 156	1036	1065 – 1120

[1] Study day relative to the date of first re-initiation of study drug after the drug interruption (i.e., PA Day 0).

6.1.8. Variable Definitions

- "Week 46/LOCF" / "Week 48/LOCF" (see Section 6.1.5.2)
- "Week 96/LOCF" / "Week 98/LOCF" (see Section 6.1.5.2)
- "Week 144/LOCF" / "Week 146/LOCF" (see Section 6.1.5.2)
- "Week 216/LOCF" / "Week 218/LOCF" (see Section 6.1.5.2)
- Treatment-emergent adverse events (TEAEs) are defined in Section **Error! Reference source not found.**.
- Concomitant medications are defined in Section **Error! Reference source not found.**.

6.1.9. Derived Variables

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

  For participants 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 to 4 years
  3 if age (full years) at baseline is 5 to 8 years
  4 if age (full years) at baseline is 9 to 12 years
  5 if age (full years) at baseline is 13 to 18 years

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

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

LASTDAY = date of the EOT visit OR the date of last dose for participants that withdrew from the study, FIRSTDAY = date of first dose, and GAP = total # of days participant was off study between protocol amendments.

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

- **% Compliance** = 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 participant being off study between protocol amendments]*

  Compliance is derived overall (Week 0-EOT) and for the following treatment phases: Week 0-48, Week >48-96, Week >96-144, and Week >144. Study drug compliance will not be calculated for those participants whose date of last dose is unknown.

- **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 $(\mu g/kg)_i$)]

  where,

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

  Total drug exposure is derived overall (Week 0-EOT) and for each treatment phase: Week 0-48, Week >48-96, Week >96-144, and Week >144. The time periods for which no study drug was administered due to dosing gaps while a participant is off study (between protocol amendments) are not included. For participants who are missing the date of last dose of study drug, the last known contact date will be used in the calculation of treatment duration and study drug exposure.

- **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 0-48, Week >48-96, Week >96-144, and Week >144. The time

periods for which no study drug was administered due to dosing gaps while a participant is off study (between protocol amendments) are not included.

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

  The above definition applies to both severity (Item 1) and frequency (Item 3, Observer only) weekly average score. The baseline weekly morning average score is derived using the 7 days immediately before the baseline visit date, according to the baseline definitions described in Section 6.1.1.

- **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

  Lipid 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.

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

  Height, weight, and BMI z-scores are based on a participant's gender and age at each scheduled visit. For participants 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 participants at least 24 months of age, the CDC growth charts[12] will be used to derive z-scores.

- **PedsQL Scoring Algorithm**

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

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.

Participant Age

Age at screening from the LUM001-301 study will be used as the age for the determination of the appropriate ItchRO instrument and 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. Prior and concomitant medications will be coded using WHO-Drug Dictionary (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 participants 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 participants 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 participants, 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 case report form (CRF) and an end date entered. A new event is recorded on the AE CRF with a start date that matches the end date, and the term recorded includes “Worsened” (e.g., “Worsened Headaches”). If an event becomes serious, the date that the event became serious is recorded on the AE CRF as the End Date of that AE and the Start Date of the corresponding SAE.

Adverse event severity grades are reported according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 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 ALGS 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 and bilirubin elevations. MRX is associated with gastrointestinal disturbances such as diarrhea.

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 participant'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 the below, first dose date is with respect to the first dose in LUM001-305.

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 (or the AE is ongoing), 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 or the AE is ongoing, 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 Quantitation

In general, for quantitative laboratory values reported as "<" or "≤" the lower limit of quantitation (LLOQ), one-half of the reported value (i.e., LLOQ/2) will be used for analysis. The exception to this data treatment is for plasma 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 quantitation (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, participants 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.

Treatment Duration and Exposure

For participants 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 participants whose date of last study drug application is unknown.

7. Study Participants and Demographics

7.1. Disposition of Participants and Withdrawals

Participant disposition will be presented overall and by treatment phase and treatment group.

Participant disposition will include tabulations of the number and percentage of participants 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, participants that did not consent to the optional long-term treatment extensions (PA4, PA5, or PA6) are not considered to have completed treatment. Reasons for withdrawal will include those collected on the CRF, along with not consenting to PA4, PA5, or PA6 (separately).

For the by study phase and treatment group summaries, the number and percentage of participants presented will be based on the number of participants in each treatment period.

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

Study drug accountability and compliance listings will be prepared for all participants, showing when the planned dosing schedule was not followed, along with the date and type of dosing deviation. Other disposition and study conduct information, including major protocol deviations will be listed. Additionally, a listing will be provided that identifies if a subject enters each phase, as discussed in Section 4.1.

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 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 the Sponsor and Premier to determine the final classification, however all deviation will be reviewed with the study team at regular intervals.

Major protocol deviations may include:

- Significant and/or persistent dosing error
- Participant 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 participant listing. Additionally, inclusion and exclusion criteria not met and reasons for screen failures will be listed.

7.3. Demographics and Other Baseline Characteristics

Participant demographics and other baseline characteristics will be presented by treatment group and overall.

Summary statistics for age (at baseline), age group, gender, country, weight z-score, height z-score, and BMI z-score 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. Prior Medications

Prior medications will be summarized descriptively by treatment group and overall, using the number and percent of participants by ATC class and preferred term. 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, 1 medication, 2 medications, and at least 3 medications.

Prior medications will be presented separately from concomitant medications.

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

7.5. Treatment Compliance

Treatment compliance will be calculated for each participant and summarized descriptively. This analysis will be completed using the Safety Population for each of the following study phases: Weeks 0-48, Weeks >48-96, Weeks >96-144, Weeks >144, and overall (Weeks 0-EOT). Participants that withdraw early before any given study phase are not included in the analysis of that study phase.

A participant is considered compliant with treatment (for a given day) if any amount of study drug was administered.

Study drug accountability will be presented in a participant listing.

8. Efficacy Analysis

The primary analysis population for efficacy analysis will be the Safety Population. Analyses for the primary and secondary efficacy outcome variables will also be done on the Safety Population. All sensitivity analysis will be done on the Safety Population. Efficacy data summaries will be provided by treatment group and overall, unless otherwise specified.

All efficacy data will be presented in participant listings

8.1. Primary Efficacy Analysis

The change from baseline in serum bile acid will be displayed for each treatment group and overall using summary statistics including a 95% confidence interval 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.

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 Student's t-test to determine if the mean change is statistically significant, where applicable. Categorical measures will be presented by level of response with frequencies and percentages.

Change from baseline in ItchRO(Obs) weekly average morning severity score, sBA, C4, bilirubin (total and direct), ALT, ALP, GGT, AST, 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.

Planned efficacy figures are described in Section **Error! Reference source not found.**. Additional figures may be added post-hoc to further examine study data.

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 an extended drug interruption > 28 days due to a participant 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, participants 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.

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

9.1. Treatment Exposure

Treatment exposure will be summarized descriptively overall and by each of the following treatment phases: Weeks 0-48, Weeks >48-96, Weeks >96-144, Weeks >144, and overall (Weeks 0-EOT). These summaries will include: average daily dose (µg/kg/day), total drug exposure (µg/kg), and treatment duration (days). Reference Section **Error! Reference source not found.** for the derivation of these variables.

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 (in LUM001-305) and a start date before the last dose of study drug plus 14 days. For participants 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 **Error! Reference source not found.**).

Analysis of TEAEs will be performed by treatment group and overall. TEAEs will be summarized overall and by MRX dose at the onset of the event.

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

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

All AEs will be coded using MedDRA version 22.1. All TEAEs summarized by SOC and PT will be sorted in alphabetical order of the SOC and by descending frequency order of the PT (overall participants) 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 **Error! Reference source not found.**.

In the AE data listings, events that are treatment-emergent will be flagged. AEs will be presented in by-participant 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 by dose at onset of the event. Participant 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. Participant 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 participant listing. The listing will include participant 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: diarrhea events, FSV deficiency events, elevated transaminases, and elevated bilirubin. The list of PTs used to identify FSV deficiency events are provided in Appendix 3.

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. Clinical Laboratory Evaluations

The primary analysis of safety laboratory data will exclude any laboratory samples that were collected from a participant after a drug interruption due to the participant 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 group and analysis visit as observed and change from baseline values.

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 participant 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 participant listings.

For select FSVs, including 25-hydroxyvitamin D, lipid 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 participants within each test level category will be presented. For these fat soluble vitamins, categories may include normal, sufficient, insufficient, possibly insufficient, indeterminate, and excess (see Section **Error! Reference source not found.** for specific definitions). Missing lab values will be reported in a "Missing" category.

In addition to participant 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 participant 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 an extended drug interruption due to a participant 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 **Error! Reference source not found.**. 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 participants within each test level category (see Section **Error! Reference source not found.** for category definitions) will be presented.

9.4. Physical Examination

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

Physical examination findings, including body height, body weight, and BMI (and their corresponding z-scores), will be included in participant listings.

9.5. Vital Signs

Vital signs (blood pressure, heart rate, body temperature, and respiration rate) will be summarized using descriptive statistics by scheduled study visit as both observed values 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 participants 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 group and overall, using the number and percent of participants by ATC class and preferred term. Pruritus medications that treat pruritus are listed in Section **Error! Reference source not found.**.

Concomitant medications will also be presented in participant listings. Medications that were started before the first dose of study drug in LUM001-305 and are ongoing at the time of first dose will be flagged.

9.7. Safety Data Graphical Presentations

Study drug exposure and TEAEs of special interest will be displayed graphically over time, as described in Section ***Error! Reference source not found.***. Additional figures may be added post-hoc to further examine study data.

10. Other Analysis

10.1. Pharmacokinetic Analysis

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

11. Changes from Planned Analysis

The protocol states all analyses will be descriptive in nature, however primary and secondary continuous measures include 95% CIs and a Student's t-test of mean change for consistency with other open-label trials.

The protocol defines Baseline (Day 0) and Baseline from LUM001-301, however in LUM001-305 at the sponsor's request, the first dose of MRX (either in LUM001-301 or LUM001-305) will be used as the baseline visit. As a result of this request, all endpoints have the terminology "change from MRX baseline" which is different from the nomenclature in the protocol.

In order to maintain consistency across other protocols in this program, efficacy analyses for AST and GGT were added.

12. References

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10. Little R., Rubin D. 1987. *Statistical Analysis with Missing Data*. New York: John Wiley.
11. World Health Organization (WHO) growth charts – A SAS Program for the WHO Growth Charts (ages 0 to <2 years) (www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm).
12. Centers for Disease Control (CDC) growth charts - A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years) (www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).
13. The PedsQL Measurement Model for the Pediatric Quality of Life Inventory – Scoring Instructions (www.pedsql.org).

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (listing number, where applicable).

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number LUM001-305. The table numbers are place holders only and will be determined when the tables are produced.

Table Number	Table Title
14.1 Disposition, Demographic, Disease History, Prior Medications, and Study Drug Compliance	
14.1.1.1	Participant Disposition: Overall – All Participants
14.1.1.2	Participant Disposition by Study Phase – Enrolled Participants
14.1.2	Demographics and Baseline Characteristics – Safety Population
14.1.3	Disease History and Baseline Disease Characteristics – 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
14.2 Efficacy Data	
14.2.1	Summary of ItchRO (Obs) Weekly Average Morning Severity Score and Change from Baseline by Analysis Visit – Safety Population
14.2.2	Summary of sBA (umol/L) and Change from Baseline by Analysis Visit – Safety Population
14.2.3	Summary of ALP (U/L) and Change from Baseline by Analysis Visit – Safety Population
14.2.4	Summary of ALT (U/L) and Change from Baseline by Analysis Visit – Safety Population
14.2.5	Summary of AST (U/L) and Change from Baseline by Analysis Visit – Safety Population
14.2.6	Summary of GGT (U/L) and Change from Baseline by Analysis Visit – Safety Population
14.2.7	Summary of Total Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Safety Population
14.2.8	Summary of Direct Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Safety Population

14.2.9	Summary of C4 (ng/mL) and Change from Baseline by Analysis Visit – Safety Population
14.2.10	Summary of Total Cholesterol (mg/dL) and Change from Baseline by Analysis Visit – Safety Population
14.2.11	Summary of LDL-C (mg/dL) and Change from Baseline by Analysis Visit – Safety Population
14.2.12.1	Summary of Clinician Scratch Score (CSS) and Change from Baseline by Analysis Visit – Safety Population
14.2.12.2	Summary of Clinician Scratch Score (CSS) Change from Baseline by Analysis Visit – Categorical Data Analysis – Safety Population
14.2.13.1	Summary of Clinician Xanthoma Severity Score and Change from Baseline by Analysis Visit – Safety Population
14.2.13.2	Summary of Clinician Xanthoma Severity Score and Change from Baseline by Analysis Visit – Categorical Data Analysis – Safety Population
14.2.14	Summary of Height Z-Score and Change from Baseline by Analysis Visit – Safety Population
14.2.15	Summary of Weight Z-Score and Change from Baseline by Analysis Visit – Safety Population
14.2.16	Summary of CIC (Itch-Related Symptoms) and Change from Baseline by Analysis Visit – Safety Population
14.2.17	Summary of CIC (Xanthoma Severity) and Change from Baseline by Analysis Visit – Safety Population
14.2.18	Summary of PedsQL Total Scale Score (Parent) and Change from Baseline by Analysis Visit – Safety Population
14.2.19	Summary of PedsQL Multidimensional Fatigue Scale Score (Parent) and Change from Baseline by Analysis Visit – Safety Population
14.2.20	Summary of PedsQL Family Impact Total Scale Score and Change from Baseline by Analysis Visit – Safety Population
14.2.21	Summary of PedsQL Psychosocial Health Summary Score (Parent) and Change from Baseline by Analysis Visit – Safety Population
14.2.22	Summary of PedsQL Total Scale Score (Child) and Change from Baseline by Analysis Visit – Safety Population
14.2.23	Summary of PedsQL Multidimensional Fatigue Scale Score (Child) and Change from Baseline by Analysis Visit – Safety Population

14.3 Safety Data

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 Summary of Treatment-Emergent Adverse Events by Dose at Onset of TEAE – Safety Population

14.3.2.2 Incidence of Treatment-Emergent Adverse Events by Dose at Onset of TEAE – Safety Population

14.3.2.3 Incidence of Treatment-Emergent Adverse Events by Maximum Severity and Dose at Onset of TEAE – Safety Population

14.3.2.4 Incidence of Treatment Related Adverse Events by Dose at Onset of TEAE – Safety Population

14.3.2.5 Incidence of Treatment Related Adverse Events by Maximum Severity and Dose at Onset of TEAE – Safety Population

14.3.3 Summary of Deaths, Other Serious and Significant Adverse Events

14.3.3.1 Incidence of Treatment-Emergent SAEs by Dose at Onset of TEAE – Safety Population

14.3.3.2 Incidence of Treatment Related SAEs by Dose at Onset of TEAE – Safety Population

14.3.3.3 Incidence of Adverse Events Leading to Permanent Treatment Discontinuation by Dose at Onset of TEAE – Safety Population

14.3.3.4 Incidence of Treatment-Emergent Adverse Events of Special Interest – Diarrhoea Events by Dose at Onset of TEAE – Safety Population

14.3.3.5 Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Transaminases Events by Dose at Onset of TEAE – Safety Population

14.3.3.6 Incidence of Treatment-Emergent Adverse Events of Special Interest – Fat Soluble Vitamin Deficiency Events by Dose at Onset of TEAE – Safety Population

14.3.3.7 Incidence of Treatment-Emergent Adverse Events of Special Interest – Elevated Bilirubin Events by Dose at Onset of TEAE – Safety Population

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 Z-Score 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 (°C) – Safety Population

14.3.6.6 Summary of Vital Signs by Analysis Visit: Respiratory Rate (rpm) – Safety Population

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

14.4 Other Data Summaries

14.4.1 Pharmacokinetic Data

14.4.1 Summary of Plasma Sample Maralixibat Concentrations (ng/mL) by Analysis Visit – Safety Population

13.2. Planned Listing Descriptions

For the planned interim analysis for protocol number LUM001-305, 3 participant data listings will be produced: SAEs, TEAEs leading to permanent treatment discontinuation, and deaths. These listings are imbedded within the safety tables and are included in Section 13.1.

All listings will be sorted by treatment phase, treatment received, site, and participant number.

All calculated variables (e.g., study day, TEAE flag) will be included in the listings.

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

In data listings, the information for one participant will be kept on one page if at all possible, rather than splitting a participant's information across pages.

Listing Number	Participant Listing Title
16.2	**Participant Disposition**
16.2.1	Analysis Populations and Treatment Assignments – Enrolled Participants
16.2.2	Participant Disposition – Enrolled Participants
16.2.3	Participant Disposition – Screen Failure
16.2.4	Participant Disposition – Entrance into Study Phases
16.3	**Protocol Deviations/Participants Excluded from Efficacy Analyses**
16.3.1	Inclusion and Exclusion Criteria – Enrolled Participants
16.3.2	Participant Excluded from Efficacy Analyses – Enrolled Participants
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	Prior Medications – Safety Population
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 – Safety Population
16.5.3	Maralixibat Chloride Dose Changes – Safety Population
16.6	**Individual Efficacy Response Data**

Listing Number	Participant Listing Title
16.6.1	ItchRO (Obs) Weekly Average Morning Severity Score and sBA Results – Safety Population
16.6.2	Clinician Scratch and Xanthoma Scores – Safety Population
16.6.3	Liver Biochemical Enzymes – Safety Population
16.6.5	ItchRO Reported Outcomes (Caregiver) Daily Morning Scores – Safety Population
16.6.6	CIC, and CIC-Xan – Safety Population
16.6.7	Efficacy Laboratory Tests – Safety Population
16.6.8	Total sBA – Safety Population
16.6.9	Height and Weight Z-Scores – Safety Population
16.2.10.1.1.1	Pediatric Quality of Life Inventory (Parent Report for Infants) - Physical Functioning – Safety Population
16.6.10.1.1.2	Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Physical Functioning – Safety Population
16.6.10.1.2	Pediatric Quality of Life Inventory (Parent Report for Infants) - Physical Symptoms – Safety Population
16.6.10.1.3.1	Pediatric Quality of Life Inventory (Parent Report for Infants) - Emotional Functioning – Safety Population
16.6.10.1.3.2	Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Emotional Functioning – Safety Population
16.6.10.1.4.1	Pediatric Quality of Life Inventory (Parent Report for Infants) - Social Functioning – Safety Population
16.6.10.1.4.2	Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Social Functioning – Safety Population
16.6.10.1.5	Pediatric Quality of Life Inventory (Parent Report for Infants) - Cognitive Functioning – Safety Population
16.6.10.1.6	Pediatric Quality of Life Inventory (Parent Report for Children 2 - 18 Years) - Nursery/Day Care/School Functioning – Safety Population
16.6.10.2.1	Pediatric Quality of Life Inventory (Participant Report) - Physical Functioning – Safety Population
16.6.10.2.2	Pediatric Quality of Life Inventory (Participant Report) - Emotional Functioning – Safety Population
16.6.10.2.3	Pediatric Quality of Life Inventory (Participant Report) - Social Functioning – Safety Population
16.6.10.2.4	Pediatric Quality of Life Inventory (Participant Report) - School Functioning – Safety Population

Listing Number	Participant Listing Title
16.6.10.3.1	Multidimensional Fatigue Scale (Parent Report) - General Fatigue – Safety Population
16.6.10.3.2	Multidimensional Fatigue Scale (Parent Report) - Sleep/Rest Fatigue – Safety Population
16.6.10.3.3	Multidimensional Fatigue Scale (Parent Report) - Mental Fatigue – Safety Population
16.6.10.4.1	Multidimensional Fatigue Scale (Participant Report) - General Fatigue – Safety Population
16.6.10.4.2	Multidimensional Fatigue Scale (Participant Report) - Sleep/Rest Fatigue – Safety Population
16.6.10.4.3	Multidimensional Fatigue Scale (Participant Report) - Cognitive Fatigue – Safety Population
16.6.10.5.1	Family Impact Module (Parent Report) - Physical Functioning – Safety Population
16.6.10.5.2	Family Impact Module (Parent Report) - Emotional Functioning – Safety Population
16.6.10.5.3	Family Impact Module (Parent Report) - Social Functioning – Safety Population
16.6.10.5.4	Family Impact Module (Parent Report) - Cognitive Functioning – Safety Population
16.6.10.5.5	Family Impact Module (Parent Report) – Communication – Safety Population
16.6.10.5.6	Family Impact Module (Parent Report) – Worry – Safety Population
16.6.10.5.7	Family Impact Module (Parent Report) - Daily Activities – Safety Population
16.6.10.5.8	Family Impact Module (Parent Report) - Family Relationships – Safety Population
16.6.10.6.1	Pediatric Quality of Life Inventory (Parent Report) - Total Scale and Summary Scores – Safety Population
16.6.10.6.2	Pediatric Quality of Life Inventory (Participant Report) - Total Scale and Summary Scores – Safety Population
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

Listing Number	Participant Listing Title
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
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 Participants
16.10 Concomitant Medications	
16.10.1	Concomitant Medications – Safety Population

Listing Number		Participant Listing Title
16.10.2		Concomitant Medications that Treat Pruritus – Safety Population
16.11	**Drug Concentration Data**	
16.11		Plasma Sample Maralixibat Concentrations

13.3. Planned Figure Descriptions

The following are planned summary figures for protocol number LUM001-305. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Mean (± SE) change from baseline for select efficacy variables will be displayed graphically by study week over time. 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.

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 participant 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 participant.

Figure Number		Figure Title
14.2 Efficacy Data		
14.2.1		Plot of Mean (± SE) Change from Baseline in ItchRO (Obs) Weekly Average Morning Severity Score by Treatment Group Over Time - Safety Population
14.2.2		Plot of Mean (± SE) Change from Baseline in sBA (umol/L) by Treatment Group Over Time - Safety Population
14.2.3		Plot of Mean (± SE) Change from Baseline in ALP (U/L) by Treatment Group Over Time - Safety Population
14.2.4		Plot of Mean (± SE) Change from Baseline in ALT (U/L) by Treatment Group Over Time - Safety Population
14.2.5		Plot of Mean (± SE) Change from Baseline in ALT (U/L) by Treatment Group Over Time - Safety Population
14.2.6		Plot of Mean (± SE) Change from Baseline in GGT (U/L) by Treatment Group Over Time - Safety Population
14.2.7		Plot of Mean (± SE) Change from Baseline in Total Bilirubin (mg/dL) by Treatment Group Over Time - Safety Population
14.2.8		Plot of Mean (± SE) Change from Baseline in Direct Bilirubin (mg/dL) by Treatment Group Over Time - Safety Population
14.2.9		Plot of Mean (± SE) Change from Baseline in C4 (ng/mL) by Treatment Group Over Time - Safety Population
14.2.10		Plot of Mean (± SE) Change from Baseline in Total Cholesterol (mg/dL) by Treatment Group Over Time - Safety Population

14.2.11 Plot of Mean (± SE) Change from Baseline in LDL-C (mg/dL) by Treatment Group Over Time - Safety Population

14.2.12 Plot of Mean (± SE) Change from Baseline in Height Z-Score by Treatment Group Over Time - Safety Population

14.2.13 Plot of Mean (± SE) Change from Baseline in Weight Z-Score by Treatment Group Over Time - Safety Population

14.2.14 Plot of Mean (± SE) Change from Baseline in PedsQL Total Score (Parent) by Treatment Group Over Time - Safety Population

14.2.15 Plot of Mean (± SE) Change from Baseline in PedsQL Multidimensional Fatigue Scale Score (Parent) by Treatment Group Over Time - Safety Population

14.3.1 Display of Study Drug Exposure

14.3.1 Study Drug Exposure Over Time by Participant – Safety Population

14.3.2 Displays of Adverse Events

14.3.2 Plot of Treatment-Emergent Adverse Events of Special Interest Over Time by Preferred Term and Individual Participant – 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
ALGS	alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASBTi	apical sodium dependent bile acid transporter inhibitor
ATC	anatomical therapeutic chemical
AST	aspartate aminotransferase
BMI	body mass index
C4	7-alpha-hydroxy-4-cholesten-3-one
CDC	Centers for Disease control
ChiLDReN	Childhood Liver Disease Research Network
CI	confidence interval
CIC	caregiver impression of change
CRF	case report form
CSR	clinical study report

Abbreviation	Definition
CSS	clinician scratch score
CTCAE	common terminology criteria for adverse events
DMC	data monitoring committee
DSMB	data safety monitoring board
eDiary	electronic diary
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	food and drug administration
FGF-19	fibroblast growth factor 19
FGF-21	fibroblast growth factor 21
FSV	fat soluble vitamin
GI	gastrointestinal
IA	interim analysis
ICH	International Council for Harmonisation
ID	identification
ItchRO	itch reported outcome
LLOQ	lower limit of quantitation

Abbreviation	Definition
LOCF	last-observation-carried-forward
MedDRA	medical dictionary for regulatory activities
MRX	maralixibat
NDA	new drug application
PA	protocol amendment
PBO	placebo
PedsQL	pediatric quality of life
PT	preferred term
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

Appendix 2: Listing of Safety and Efficacy Laboratory Analytes

SAFETY LABS

CBC with Differential

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

Coagulation

aPTT (sec)
PT (sec)

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
Lipid Ratio of Alpha Tocopherol to the sum of Cholesterol and Triglycerides, mg/g

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

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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