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1. Overview

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Mirum Pharmaceuticals Inc. (Mirum) protocol LUM001-303, 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 08-Feb-2019 (Amendment 5.1).

The original LUM001-303 protocol, dated 13-Sep-2013, planned for a 48-week treatment period. This treatment period included 3 parts: a 4-week double-blind dose escalation period, at doses up to a target dose of 140 µg/kg/day; a 8-week dose optimization period where dosing may be increased or decreased to 35, 70, 140 or 280 µg/kg/day; and a 36-week stable dosing period where participants continue to receive the Week 12 dose, or the highest tolerated dose below the Week 12 dose from dose optimization period.

There have been 6 protocol amendments to date. The summary list of changes to each of the protocol amendments are describe in the final amendment, Protocol Amendment 5.1. Several of the protocol amendments included optional long-term extensions.

Protocol Amendment 1, dated 05-Nov-2013, changed the exclusion criteria 3 by adding history or presence of gallstones or kidney stones, clarification added regarding dose escalation, and included other minor changes to improve the clarity of the protocol and/or correct minor inconsistencies and typographical errors.

Protocol Amendment 2, dated 28-Feb-2014, lowered eligibility age from 2 years of age to 12 months to 18 years, changed the number of participants from 60 to 42, revised text regarding volume administrated (i.e. participants who weigh 10 kg or more will receive 1.0 mL solution, and participants who weigh less than 10 kg will receive 0.5 mL solution). Additionally, clarification was included that dosing errors will be captured in eCRF and in paper dosing diaries, PedQL for infants was added, and other corrections of minor inconsistencies and typographical errors were applied.

Protocol Amendment 3, dated 17-Sep-2014, changed treatment duration to collect additional long-term safety data from 48 weeks to 76 weeks including 4 weeks follow-up. The treatment period was changed from 48 weeks to 72 weeks. The stable dosing period was changed from 36 to 60 weeks, study visits at Weeks 60 and 72 were added, study termination changed from week 48 to 72, and PedsQL evaluation at week 72 and Caregiver Impression of Change evaluation were added. Assessments were added at Weeks 60 and 72. The number of participants was changed from 42 to 18, the number of centers changed from 14 to 3 and other corrections of minor inconsistencies and typographical errors were applied.

Protocol Amendment 4, dated 04-Nov-2015, added an Optional Follow-up treatment period (after week 72) that offers opportunity to eligible participants treated in the study to continue on treatment after week 72 until the first of (i) up to 52 weeks of additional treatment (Week 124) or (ii) in the event that a new study opens to enrollment.

Protocol Amendment 5, dated 16-May-2017, allowed continued participation in the long-term optional follow-up treatment period, beyond what was previously added in Protocol Amendment 4. Study treatment in the long-term optional follow-up treatment period will continue until the first of the following occurs: (i) the participants are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication. This amendment also describes the way in which eligible participants who had previously discontinued from the study may re-enter and receive study treatment in the long-term optional follow-up treatment period (after Week 124). Additional objectives for the long-term optional follow-up treatment period were added, as follows:

- Exploration of a twice daily (BID) dosing regimen and higher daily dosing of LUM001;
- Assessment of alpha-fetoprotein (AFP) levels, a marker of hepatocellular carcinoma;
- Assessment of the palatability of the LUM001 formulation in all participants, by-proxy in participants <4 years old and by patient questionnaire in children ≥4 years old;
- Obtain safety and efficacy data in participants treated long term in LUM001.

A list of detailed changes to the protocol is included in the final amendment, Protocol Amendment 5.1.

The final protocol amendment, Amendment 5.1, dated 08-Feb-2019, reflects the change of sponsorship from Lumena Pharmaceuticals LLC to Mirum Pharmaceuticals, Inc.

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 (MRX) and that label will be used hereinafter within this document.

2. Study Objectives and Endpoints

2.1. Study Objectives

The primary objective of the study (up to and including Week 72) is to:

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

Secondary objectives of the study (up to and including Week 72) are to:

- Evaluate the long-term effect of MRX on serum bile acid levels.
- Evaluate the long-term effect of MRX 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.

Objectives of the long-term optional follow-up treatment period for participants who are eligible for Protocol Amendment 5:

- To offer eligible participants in the LUM001-303 study continued study treatment until the first of the following occur: (i) the participants are eligible to enter another LUM001 study, or (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
- To explore twice a day (BID) dosing regimen and higher daily dosing of MRX.
- To obtain safety and efficacy data in participants treated long-term on MRX.
- To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma.
- To assess palatability of the MRX formulation.

2.2. Study Endpoints

Safety and efficacy endpoints are examined overall and for each of the 5 treatment phases:

- Dose Escalation Period (Day 1 – Week 4),
- Dose Optimization Period (Week 5 – Week 12),
- Stable Dosing Period (Week 13 – Week 72),
- Optional Follow-up Treatment Period (Week 73 – Week 124)
- Long-term Optional Follow-up Treatment Period (Week 125 – EOT/ET).

Unless otherwise specified, summaries will be provided by treatment sequence where applicable from the LUM001-302 core study (e.g., PBO-MRX), and overall.

2.2.1. Safety Endpoints

The following assessments will be used to monitor safety:

- Adverse events (AEs) and serious adverse events (SAEs).
- Clinical laboratory results.
- Vital signs.
- Physical exam findings, including body weight and height.
- Concomitant medication usage.
- Serum alpha-fetoprotein (AFP).

Physical examination findings include body weight and height, along with BMI. Vital signs include heart rate, respiratory rate, body temperature, and blood pressure. Note that the z-scores for body weight, height and BMI are considered as efficacy but are derived from safety variables. Z-scores are derived as described in Section 6.1.9.

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

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary evaluation will be the mean change from Baseline (Day 0) to Week 48 in:

- Fasting serum bile acid level (sBA).

2.2.2.2. Secondary Endpoints

Secondary evaluations will be the mean change from Baseline (Day 0) to Week 48 in:

- Biochemical markers of cholestasis and liver disease [ALT, AST, ALP, GGT and total and direct bilirubin].
- Pruritus as measured by the ItchRO instruments (ItchRO(Obs)™, caregiver instrument/ItchRO(Pt) ™ patient instrument).

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 follow-up treatment period, twice daily completion of the electronic diary (ItchRO) for 2 consecutive weeks will be required following the Week 84, 96, 108, and 120 clinic visits. For participants who continue to long-term optional follow-up, twice daily completion of electronic diary (ItchRO) for 2 consecutive weeks will be required following Protocol Amendment 5 screening visit, Week 4 visit and for repeating Week 12 visits.

- Xanthomas as measured by clinician xanthoma scale.

Efficacy variables will be presented for each time point at which they are measured (see Section 3.7).

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
ItchRO(Obs),	Weekly average morning severity score	0	48
Liver enzymes (ALP, ALT, AST, GGT, total bilirubin, direct bilirubin)	Laboratory test level	0	48
Clinician xanthoma scale	5-point scale	0	48
sBA	Laboratory test level	0	48

* The observation obtained at first dose of MRX (either in LUM001-302 or in LUM001-303)

2.2.2.3. 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 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	To Week
ItchRO(Obs)	Weekly morning average severity score	0	1) Baseline to Week 12: 2, 4, 8, 12 2) Stable Dosing: 24, 44, 48 3) 52-week optional follow-up: 84, 96, 108, 120, 122/LOCF 4) Long-term optional follow-up: Protocol Amendment 5 screening visit, Week 4 visit, Week 12 visit (for repeating visits)
sBA	Laboratory test level	0	1) Baseline to Week 12:

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From MRX BL* Week	To Week
			2, 4, 8, 12, 2) Stable Dosing: 24, 36, 48, 60, 72/LOCF 3) 52-week optional follow-up: 84, 96, 108, 120, 124/LOCF, including Dose Escalation visit (DE) -2, DE 0, DE74, DE 76 for participants with ≥7 days from last dose 4) Long-term optional follow-up: Protocol amendment 5 screening visit, Day 0 (Baseline), Week 4 visit, Week 12 visit (for repeating visits), including Afternoon Dose Escalation (ADE) ADE 0, ADE Week 4, ADE Week 8 for participants eligible for afternoon dose escalation, EOT/ET
Liver enzymes (ALP, ALT, AST GGT, total bilirubin, direct bilirubin)	Laboratory test level	0	1) Baseline to Week 12: 2, 4, 8, 12, 2) Stable Dosing: 24, 36, 48, 60, 72/LOCF 3) 52-week optional follow-up: 84, 96, 108, 120, 124/LOCF, including Dose Escalation visit (DE) -2, DE 0, DE74, DE 76 for participants with ≥7 days from last dose 4) Long-term optional follow-up: Protocol amendment 5 screening visit, Day 0 (Baseline), Week 4 visit, Week 12 visit (for repeating visits), including Afternoon Dose Escalation (ADE) ADE 0, ADE Week 4, ADE Week 8 for participants eligible for afternoon dose escalation, EOT/ET
Clinician Scratch Score (CSS)	Score	0	1) Baseline to Week 12: 2, 4, 8, 12, 2) Stable Dosing: 24, 36, 48, 60, 72/LOCF 3) 52-week optional follow-up: 84, 96, 108, 120, 124/LOCF, including Dose Escalation visit (DE) -2, DE 0, DE74, DE 76 for participants with ≥7 days from last dose 4) Long-term optional follow-up: Protocol amendment 5 screening visit, Day 0 (Baseline), Week 4 visit, Week 12 visit (for

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From MRX BL* Week	To Week
			repeating visits), including Afternoon Dose Escalation (ADE) Week 4, ADE Week 8 for participants eligible for afternoon dose escalation, EOT/ET
Clinician Xanthoma Scale	Score	0	1) Stable Dosing: 16 (for participants who undergo a dose change at Week 12), 24, 36, 48, 60, 72/LOCF 2) 52-week optional follow-up: 84, 96, 108, 120, 124/LOCF, including Dose Escalation visit (DE) 76 for participants with ≥7 days from last dose 3) Long-term optional follow-up: Protocol amendment 5 screening visit, Day 0 (Baseline), Week 4 visit, Week 12 visit (for repeating visits), including Afternoon Dose Escalation (ADE) Week 4, ADE Week 8 for participants eligible for afternoon dose escalation
PedsQL	Total Scale Score (Parent); Total Scale Score (Child); Multidimensional Fatigue Scale Score (Parent); Multidimensional Fatigue Scale Score (Child) Family Impact Total Scale Score; Psychosocial Health Summary Score (Parent);	0	1) Stable Dosing: 24, 48, 72/LOCF 2) 52-week optional follow-up: 84, 96, 108, 120, 124/LOCF, including Dose Escalation visit (DE) 0 for participants with ≥7 days from last dose 3) Long-term optional follow-up: Protocol amendment 5 Day 0 (Baseline), Week 12 visit (for repeating visits), including Afternoon Dose Escalation (ADE) 0, ADE Week 4, ADE Week 8 for participants eligible for afternoon dose escalation, EOT/ET
Caregiver Impression of Change	Score	--	Summary statistics at Week: 48, 72/LOCF, 108, 120, 124/LOCF
Height and Weight z-Score	Z-Score	0	2, 4, 8, 12, 16 (only for participants who undergo a change in dose at Week 12), 24, 36, 48, 60, 72/LOCF, 84, 96, 108, 120, 124/LOCF, Protocol amendment 5 screening visit, Day 0 (Baseline), Week 4 visit, Week 12 visit (for repeating visits), including

Efficacy Parameter(s)	Variable(s)	Mean Change	
		From MRX BL* Week	To Week
			Afternoon Dose Escalation (ADE) 0, ADE Week 4, ADE Week 8 for participants eligible for afternoon dose escalation, EOT/ET

* The observation obtained at first dose of MRX (either in LUM001-302 or in LUM001-303)

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	Descriptive summaries at Week: 1) Baseline to Week 12: 2, 4, 8, 12, 2) Stable Dosing: 24, 36, 48, 60, 72/LOCF 3) 52-week optional follow-up: 84, 96, 108, 120, 124/LOCF, including Dose Escalation visit (DE) -2, DE 0, DE74, DE 76 for participants with ≥7 days from last dose 4) Long-term optional follow-up: Protocol amendment 5 screening visit, Day 0 (Baseline), Week 4 visit, Week 12 visit (for repeating visits), including Afternoon Dose Escalation (ADE) Week 4, ADE Week 8 for participants eligible for afternoon dose escalation, EOT/ET

Efficacy Parameter(s)	Scale and Responder Criteria or Variables	Endpoint
Clinician Xanthoma Scale	improved, stable or worsened.	Number and % of participants at Week: 1) Stable Dosing: 16 (for participants who undergo a dose change at Week 12), 24, 36, 48, 60, 72/LOCF 2) 52-week optional follow-up: 84, 96, 108, 120, 124/LOCF, including Dose Escalation visit (DE) 76 for participants with ≥7 days from last dose 3) Long-term optional follow-up: Protocol amendment 5 screening visit, Day 0 (Baseline), Week 4 visit, Week 12 visit (for repeating visits), including Afternoon Dose Escalation (ADE) Week 4, ADE Week 8 for participants eligible for afternoon dose escalation,

2.2.2.4. 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 LUM001-302 protocol. There is no ItchRO(Pt) report for participants under the age of 5 years.

Age at screening (from lead-in study 302) 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 subject 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 74, Week 84, Week 96, Week 108, Week 120 clinic visits during the 52-week optional follow-up treatment period.
- 2 consecutive weeks that following Protocol Amendment 5 screening visit, Week 4 visit and Week 12 visit (repeating visits) for the long-term optional follow-up treatment period

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

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) or more frequent (Item 3) itching. The 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 (i.e., Baseline [Day 0], Weeks 2, 4, 8, 12, 24, 44, 48, 84, 88, 96, 108, 120, and Protocol Amendment 5 screening visit, Week 4 visit and Week 12 visit). 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) Week 2, 4, 8, and 12, (B) Week 24 and 44 (C) Week 86, 98, 110, 122 and (D) Week 6 and 14.

A. Week 2, 4, 8, and 12: The scheduled visit date is used.
B. Week 28 and 48: Each scheduled visit date will be determined based on the date of the associated scheduled clinic visit (i.e., Week 24 and 44) plus 28 days.
C. Week 86, 98, 110, 122: Each scheduled visit date will be determined based on the date of the associated scheduled clinic visit (i.e., Week 84, 96, 108 and 120) plus 14 days.
D. Long term optional follow-up: Week 6 and 14: Each scheduled visit date will be determined based on the date of the associated scheduled clinic visit (i.e., Week 4 and 12) plus 14 days. Week 12 visits will be repeated until EOT/ET.

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

Clinician Scratch Score

The CSS provides an assessment of itch severity. The clinician's assessment of the subject's pruritus is focused on scratching and visible damage to the skin as a result of scratching as observed by the physician. This assessment will be completed at Baseline (Day 0) and at all clinic visits thereafter (Weeks 2, 4, 8, 12, 24, 36, 48, 60 and 72). For participants who enter into the 52-week optional and long-term optional follow-up treatment periods, the clinician scratch scale will be administered as outlined in the Schedule of Procedures in Section 3.7.

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 subject's xanthomatosis is focused on the number of lesions present and the degree to which the subject's lesions interfere or limit his or her activities. The clinician xanthoma 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).

A clinician's assessment of xanthomatosis will be made by the principle investigator or appropriate designee using the clinician xanthoma scale. This assessment will be completed at Baseline (Day 0) and at Weeks 24, 36, 48, 60 and 72. For participants who enter into the 52-week optional and long-term optional follow-up treatment periods, the clinician's assessment of xanthomatosis will be administered as outlined in the Schedule of Procedures in Section 3.7.

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

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

The CIC will be completed by all caregivers at the Week 48 and Week 72 visit. For participants who enter into the 52-week optional follow-up treatment periods, the CIC will be administered as outlined in the Schedule of Procedures in Section 3.7.

Pediatric Quality of Life (PedsQL)

The PedsQL[13] is a questionnaire that will be administered to participants and or caregivers at the Baseline (Day 0) and Weeks 24, 48 and 72 clinical visits using the age-appropriate PedsQL module. For participants who enter the 52-week optional follow-up treatment period, the PedsQL

will also be administered at Weeks 84, 96, 108, 120, and 124. For participants with interruptions in MRX dosing of ≥7 days, the PedsQL will also be administered at DE Day 0.

In addition to the core generic PedsQL module, the multidimensional fatigue and family impact questionnaires will also be administered at the Baseline (Day 0) and Weeks 24, 48 and 72 clinical visits using the age appropriate module, see Section 16.6. For participants who enter into the 52-week optional and long-term optional follow-up treatment periods, the multidimensional fatigue and family impact questionnaires will be administered as outlined in the Schedule of Procedures in Section 3.7.

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 Study LUM001-302 baseline will be used as the age for the determination of the appropriate module to be used for the study, and this same module will be used for the duration of the study (regardless of subsequent birthdays after the baseline visit).

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

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

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

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

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

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

Palatability

A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age) at clinic visits at time points as outlined in the Schedule of Procedures in Section 3.7.

2.2.3. Other Endpoints

Other endpoints of this study include the following:

- Analysis of MRX plasma concentrations.

Pharmacokinetics

Pharmacokinetic blood samples are collected at baseline and then approximately 4 hours post-dosing at one additional time point – at Week 12, 24, 36, 48, 72, and 4 hours post-dose during afternoon dose escalation in the long term follow-up at Day 0, Week, Week 8 and 3 clinic visits following completion of the afternoon dose escalation 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 LUM001-302 protocol. While all participants will receive active drug (MRX) in this study, the investigator, participants and study personnel were blinded to individual subject dose. The study is divided into 5 parts: a dose escalation period, a dose optimization period, a stable dosing period, an optional 52- week follow-up period, and a long-term optional follow-up treatment period for eligible participants who choose to stay on treatment with MRX.

Dose Escalation Period (Day 1 – Week 4):

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

- Participants who were randomized to receive placebo during the LUM001-302 study will

receive weekly dose increases of MRX up to a target dose of 140 µg/kg/day.
- Participants who were randomized to receive active drug during the LUM001-302 study will continue to receive the dose of MRX that they were taking at Week 13 of the LUM001-302 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.

Dose Optimization Period (Week 5 – Week 12):

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 subject and up to a maximum daily dose of 280 µg/kg MRX or 20 mg total dose. Study drug dose level will be increased or decreased in a double-blind manner. Increases in dose will be based on effect on efficacy (sBA and ItchRO[Obs] score) and safety assessments. Reductions in dose will be based on tolerability. At the investigator's discretion, the doses for participants who were previously down-titrated may be re-challenged during the dose optimization period. Each subject 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.

Stable Dosing Period (Week 13 – 72):

Following completion of the 8-week dose optimization period, all participants will enter the stable dosing period lasting 60 weeks. During the remainder of the study, participants will be dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose. However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose.

Optional Follow-up Treatment Period (Week 73 – 124):

At Week 72, all participants will be assessed by the investigator to determine their willingness and eligibility to roll-over into the optional 52-week, follow-up treatment period to receive study drug at the dose they were receiving at Week 72.

- For participants who are eligible to roll over into the follow-up treatment period, those with <7 days since the last dose of MRX, will be maintained at the same dose level.
- For participants who are eligible to roll over into the follow-up treatment period having ≥7 days since the last dose of MRX, will be dose escalated up to 280 µg/kg/day or the highest tolerated dose following a 4 week dose escalation beginning at 35 µg/kg/day.
- For participants who do not wish to enter the follow-up treatment period, or are not eligible to enter the follow-up treatment period, a safety follow-up phone call will be made by the study site 30 days after the last dose of study drug.

Long-term optional Follow Up Treatment Period (Week 125 – EOT/ET):

The long-term optional follow up treatment period is for eligible participants who choose to stay on treatment with MRX. During this long-term optional follow-up treatment period, participants may have their dose of MRX increased to a maximum of 560 µg/kg/day (280 µg/kg BID), based on efficacy (sBA and ItchRO score) and safety assessments. Participants' participation in the long-term optional follow-up treatment period will continue until the first of the following occur: i) the participants are eligible to enter another LUM001 study, (ii) MRX is available commercially, or (iii) the sponsor stops the program or development in this indication.

3.2. Sample Size and Power

Approximately 18 participants meeting the study's inclusion and exclusion criteria may be enrolled in the study. Because this is an extension study for participants who participated in the LUM001- 302 study, the sample size is not based on statistical considerations.

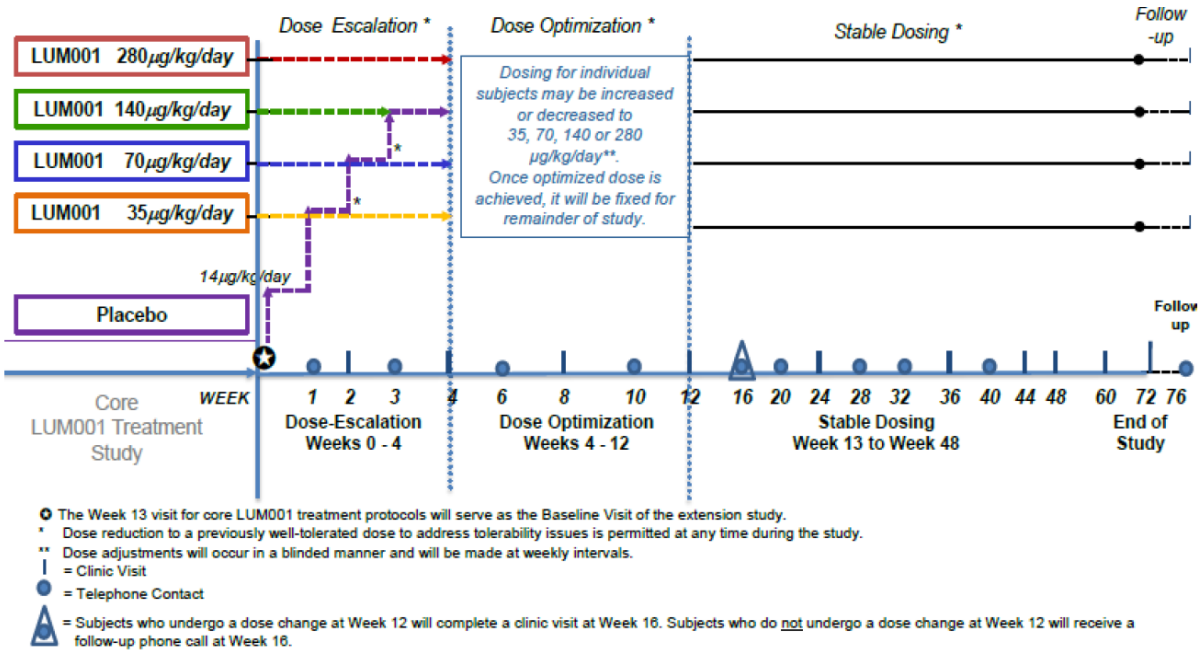
3.3. Study Population

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

3.4. Treatments

For an individual subject, the study participation period will consist of a 4-week dose escalation period, an 8-week dose optimization period, a 60-week stable dosing period, an optional 52-week follow-up treatment period, and a long-term optional follow-up treatment period. A safety follow-up phone call will be made by the study site 30 days after the last dose of study drug. The Week 13 visit from the LUM001-302 study will also serve as the Baseline Visit for the LUM001-303 extension protocol. Eligible participants will be enrolled in the extension study at the Baseline Visit (Day 0). Dosing with study drug will begin on Day 1, following the Baseline Visit on (Day 0). 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.

Figure 1 Study Design for LUM001-303 (Up to and including Week 72)



3.4.1. Dose Escalation Period

For participants randomized to placebo in the LUM001-302 study, or those who complete the LUM001-302 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, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose). For participants who were randomized to receive active drug in the LUM001-302 study MRX doses will remain the same as the dose taken at Week 13 of the LUM001-302 study. Study treatment for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to a specified dose-escalation regimen. 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.

Table 1 Dose Escalation regimens

LUM001-302 Study	Extension Study LUM001-303 Dose Escalation Period			
Week 13 (µg/kg/day)	Week 1 Days 1 - 7 (µg/kg/day)	Week 2 Days 8 - 14 (µg/kg/day)	Week 3 Days 15 - 21 (µg/kg/day)	Week 4 Days 22 - 28 (µg/kg/day)
Placebo [1]	14	35	70	140
35 [2]	35	35	35	35
70 [3]	70	70	70	70
140 [4]	140	140	140	140
280 [5]	280	280	280	280

[1] For subjects randomized to placebo in theLUM001-302 study, or those who complete the core study more than 7 days prior to enrollment into this study, the LUM001 dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose).

[2] LUM001 doses for subjects whose stable dose upon completion of LUM001-302 study was 35 µg/kg/day will remain stable at 35 µg/kg/day, or to a maximum daily dose of 2.5 mg/day.

[3] LUM001 doses for subjects whose stable dose upon completion of LUM001-302 study was 70 µg/kg/day will remain stable at 70 µg/kg/day, or to a maximum daily dose of 5 mg/day.

[4] LUM001 doses for subjects whose stable dose upon completion of LUM001-302 study was 140 µg/kg/day will remain stable at 140 µg/kg/day, or to a maximum daily dose of 10 mg/day.

[5] LUM001 doses for subjects whose stable dose upon completion of LUM001-302 study was 280 µg/kg/day will remain stable at 280 µg/kg/day, or to a maximum daily dose of 20 mg/day.

If a subject experiences intolerance due to gastrointestinal symptoms (e.g., diarrhea, abdominal pain, cramping) at any time during the study, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted. In these circumstances, an unscheduled visit will occur and the appropriate replacement study medication will be provided to the subject/caregiver.

3.4.2. Dose Optimization Period

Following the dose escalation period, the MRX dose for each subject may be increased or decreased by the investigator as clinically indicated with the objective of achieving control of pruritus at a dose level that is tolerated by the subject. 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. Adjustments may occur at weekly intervals. Once an optimal MRX dose is achieved, the dose will be fixed for the duration of the period. However, if at any time during the study, a subject experiences intolerance due to gastrointestinal symptoms, the physician investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose.

The maximum daily dose of MRX in this period is 280 µg/kg/day, up to a maximum daily dose of 20 mg. Blinded investigators may request dose adjustment for any subject based on an assessment of tolerability and effect on pruritus. Caregivers and age-appropriate participants will be asked whether they wish to take a higher dose of the study medication to achieve greater relief

of itching. If so, the dose may be adjusted upward, within the permitted dose range. However, the subject, caregiver, physician investigator, or the medical monitor may recommend against further escalation if there are safety or tolerability concerns. Doses of MRX will not be increased above 280 µg/kg/day or 20 mg per day during this period.

3.4.3. Stable Dosing Period

At the end of the Dose Optimization Period, participants will continue dosing to complete 72 weeks of cumulative MRX exposure in this study. If, at any time during the study, a subject experiences intolerance due to gastrointestinal symptoms, the physician investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose. To ensure the safety of participants participating in this study, a DMC will review serious adverse event data, other key subject safety and study data at specified intervals for the duration of the study.

3.4.4. Optional Follow-up Treatment Period

Participants who are eligible to roll over on to the optional follow-up treatment period with no MRX dosing interruption or an interruption of <7 days will continue to receive study drug at the dose they were receiving at Week 72 for up to 52 weeks of additional treatment or in the event that a new study opens to enrollment, whichever occurs first.

Participants who are eligible to roll over into the follow-up treatment period with no MRX dosing interruption or an interruption of <7 days will be maintained at the same dose level. Participants with ≥7 days since last dose of MRX will be dose escalated up to 280 µg/kg/day or to the highest tolerated dose starting at 35 µg/kg/day. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of MRX and allows for participants to reach 280 µg/kg/day or a highest tolerated dose within a 4-week period.

3.4.5. Follow-up

Study drug will be discontinued at Week 72 if the subject chooses not to participate in the optional follow-up treatment period. A safety follow-up phone call will be made by the study site at 30 days after the last dose of study drug. Follow-up phone calls will be made for all participants who complete the study, as well as any subject who terminates from the study early. Concomitant medications and any adverse events noted during this phone call will be recorded.

3.4.6. Long-term Optional Follow-up Treatment Period

Upon completion (or early termination) of the 52-week optional follow-up treatment period and/or implementation of this amendment, participants will be assessed by the investigator to determine their willingness and eligibility for entry into the long-term optional follow-up treatment period. All participants will be re-initiated at the same MRX dose they last received during LUM001-303. Eligibility assessment for afternoon dose escalation will then occur in all participants based on efficacy (ItchRO[Obs] and sBA) and safety assessments following approximately 12 weeks of dose re-initiation as follows:

- Participants with normal sBA level AND ItchRO(Obs) score <1.5 will be maintained at the same dose level and will continue morning dosing only.
- Participants with sBA level above normal AND/OR ItchRO(Obs) score ≥1.5 will start BID dosing (afternoon dose escalation) as follows:
    - The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated in order to limit the amount of propylene glycol in the diluent administered.
    - The afternoon dose will be initiated at half the dose level of the morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be doubled to match the morning dose.
- Participants with abnormal sBA level AND ItchRO(Obs) score ≥1.5 who had normal sBA level and ItchRO(Obs) score <1.5 prior to dose interruption will remain on the maximum tolerated morning dose (the dose they received last during LUM001-303) for an additional 2 weeks until their efficacy and safety assessments are repeated for eligibility assessment for afternoon dose escalation.
- The sBA value used for determination of afternoon dose escalation eligibility will be the most recent available value collected within the prior 16 weeks. The ItchRO(Obs) score used for afternoon dose escalation eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 16 weeks.
- The maximum daily dose will be 280 µg/kg BID, i.e.., 560 µg/kg/day (up to a maximum possible daily dose of 50 mg/day).
- Participants who do not wish to enter the long-term optional follow-up treatment period, will be contacted via telephone by the study site approximately 30 days after the last dose of study drug.

3.5. Method of Assigning Participants to Treatment Groups

This trial is an open-label extension of LUM001-302, and all participants will receive MRX at various dose regimens.

3.6. Blinding and Unblinding

Although all participants are treated are on 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 LUM001-302 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 subject, the investigator will have the ability to unblind the treatment assignment for that subject. If a subject 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 subject, or when causality must be determined prior to submitting a regulatory safety report for a SAE as defined in the protocol.

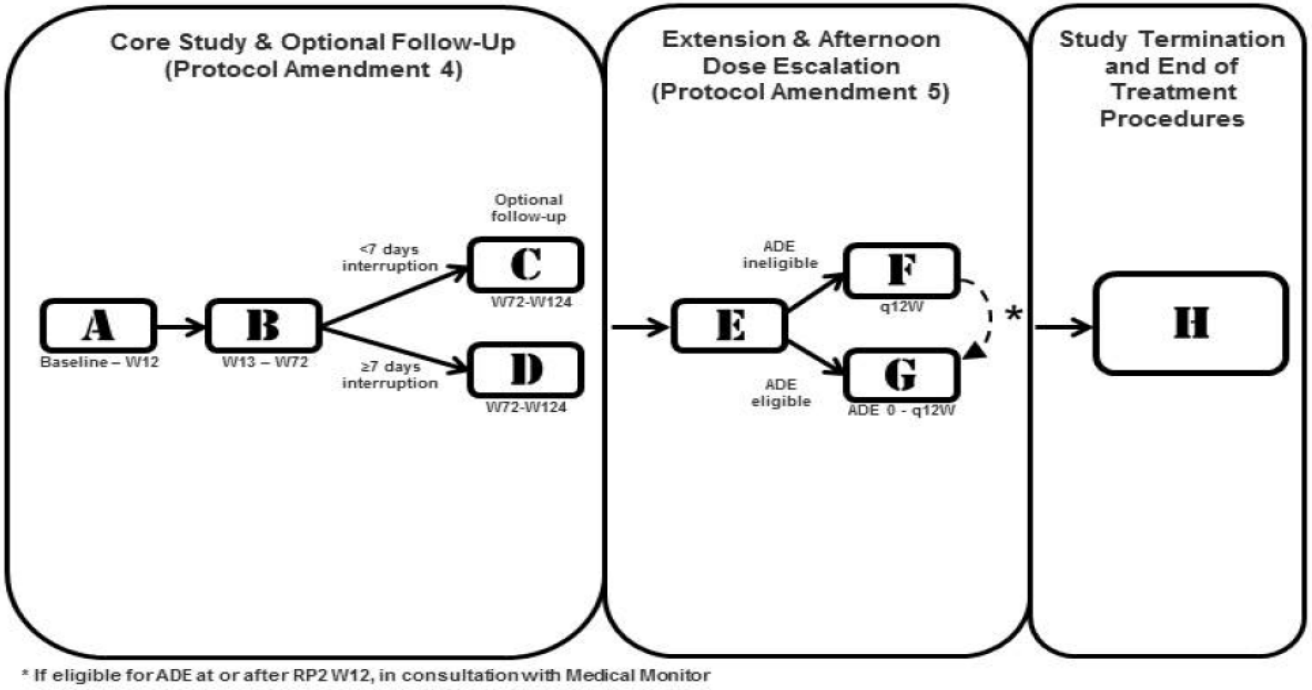
Any unblinding event carried out in connection with submission of a regulatory safety report will be conducted by the sponsor as described in the protocol.

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 subject 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

Overall Scheme and Corresponding Schedule of Procedures. The following schematic shows the study flow and corresponding Schedule of Procedures (A –G). Study Termination and End of Treatment Procedures are outlined in Schedule H.



3.7.1. Schedule of Procedures A: Baseline – Week 12

Study Period	Baseline	Treatment Period							
		Dose Escalation[i]				Dose Optimization			
Study Week		1	2	3	4	6	8	10	12
Study Day	Day 0[a]	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[b]	X		X		X		X		X
CBC with Differential[c]	X		X		X		X		X
Coagulation[c]	X		X		X		X		X
Chemistry Panel[c]	X		X		X		X		X
Lipid Panel[c,d]	X		X		X		X		X
Cholestasis Biomarkers[c,d]	X		X		X		X		X
Fat Soluble Vitamins[c,d]	X						X		X
Plasma Sample for LUM001	X								X
Urinalysis[c]	X[g]		X[g]		X[g]		X[g]		X[g]
Urine Pregnancy Test[e]	X		X		X		X		X
Subject eDiary / Caregiver eDiary (ItchRO)	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Clinician Scratch Scale	X		X		X		X		X
Clinician Xanthoma Scale	X								
PedsQL	X								
Enrolment	X								
Study Drug Supplied	X		X		X		X		X
Review Study Diaries & Assess Compliance	X		X		X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Phone Contact[f]		X		X		X		X	

[a] Evaluations and procedures completed for the Week 13 Visit of LUM001-302 study will also serve as the evaluations for the Baseline Visit for this extension study.
[b] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[c] See Section 16.2 in the protocol for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[d] Participants are required to fast at least 4 hr (only water permitted prior to collection).
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Participants must be available to receive a phone call from study staff.
[g] At the indicated visits during the treatment period, oxalate will be part of the urinalysis.
[h] During 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.
[i] Participants should be dosed for at least 7 days at each dose level.

	Clinic Visit
	Phone Contact

3.7.2. Schedule of Procedures B – Stable Dosing: Week 16 – Week 72 / Study Termination

Study Period	Treatment Period (continued) Stable Dosing										Study Termination[h]	Follow-Up[i]
Study Week	16[f]	20	24	28	32	36	40	44	48	60	Week 72 (or Early Term[g])	30 days after final dose[h]
Study Day	112	140	168	196	224	252	280	308	336	420	504	
Window (in days)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±5)
Physical Exam	X[f]		X			X			X	X	X	
Body Weight & Height	X[f]		X			X			X	X	X	
Vital Signs[a]	X[f]		X			X			X	X	X	
CBC with Differential[b]	X[f]		X			X			X	X	X	
Coagulation[c]	X[f]		X			X			X	X	X	
Chemistry Panel[c]	X[f]		X			X			X	X	X	
Lipid Panel[c,d]	X[f]		X			X			X	X	X	
Cholestasis Biomarkers[c,d]	X[f]		X			X			X	X	X	
Fat Soluble Vitamins[c,d]			X			X			X	X	X	
Plasma Sample for LUM001			X			X			X		X	
Urinalysis[b]	X[f,j]		X[j]			X[j]			X[j]	X[j]	X[j]	
Urine Pregnancy Test[e]	X[f]		X			X			X	X	X	
Clinician Scratch Scale			X			X			X	X	X	
Clinician Xanthoma Scale	X		X			X			X	X	X	
Subject eDiary/Caregiver eDiary			X[k]	X[k] to Week 28				X[k]	X[k] to Week 48			
PedsQL			X						X		X	
Caregiver Impression of Change									X		X	
Study Drug Supplied			X			X			X	X		
Review Study Diaries & Assess Compliance			X			X		X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[f]	X	X		X	X		X					X

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 in the protocol for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[c] Participants are required to fast at least 4 hr (only water permitted prior to collection).
[d] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[e] Participants must be available to receive a phone call from study staff.
[f] A Week 16 Clinic Visit will be completed for all participants who undergo a change in dose at Week 12; Participants who do not undergo a dose change at Week 12 will be contacted by phone at Week 16.
[g] Participants who withdraw early should complete all evaluations at this visit.
[h] Participants who roll directly into the Week 76 visit will not have a follow-up visit until after Week 124.
[i] Follow-up visit is only for participants who exit the study at the Study Termination Visit.
[j] At the indicated visits during the treatment period, oxalate will be part of the urinalysis
[k] 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.

	Clinic Visit
	Phone Contact

3.7.3. Schedule of Procedures C – 52-Week Optional Follow-Up Treatment Period for those participants < 7 days from last dose of MRX (Protocol Amendment 4)

Study Period	52-week FU Treatment Period												Study Termination[j]	Follow-Up[k]
Study Week	76	80	84	88	92	96	100	104	108	112	116	120	124[i]	30 days after final dose
Study Day	553	560	588	616	644	672	700	728	756	336	812	840	868	
Window (in days)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±14)	(±5)
Informed Consent/Assent for Protocol Amendment 5[a]			X			X			X			X		
Afternoon dose escalation eligibility assessment followed by shift in visit schedule[b]	Xb	Xb	Xb	Xb	Xb	Xb	Xb	Xb	Xb	Xb	Xb	Xb	Xb	Xb
Physical Exam			X			X			X			X	X	
Body Weight & Height			X			X			X			X	X	
Vital Signs[c]			X			X			X			X	X	
CBC with Differential[d]			X			X			X			X	X	
Coagulation[d]			X			X			X			X	X	
Chemistry Panel[d]			X			X			X			X	X	
Lipid Panel[d,e]			X			X			X			X	X	
Cholestasis Biomarkers[d,e]			X			X			X			X	X	
Fat Soluble Vitamins[d,e]			X			X			X			X	X	
Optional Genotyping[f]			X											
Urinalysis[d]			X			X			X			X	Xl	
Urine Pregnancy Test[g]			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			Xm	Xm to Week 86		Xb	Xm to Week 98		Xb	Xm to Week 110		Xm	Xm to Week 122	
PedsQL			X			X			X			X	X	
Caregiver Impression of Change									X			X	X	
Study Drug Supplied			X			X			X					
Review Study Diaries & Assess Compliance			X			X			X			X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[h]	X	X		X	X		X	X		X	X			X

[a] Once necessary approvals are received for Protocol Amendment 5 and associated consent/assent documents are available, site will consent/assent subject for Protocol Amendment 5 at the next clinic visit.
[b] Once necessary approvals are received for Protocol Amendment 5 and associated consent/assent has been signed, site will assess subject eligibility for Protocol Amendment 5. Depending on the outcome of afternoon dose escalation eligibility assessment, the subject will move into either Schedule of Procedures F or G. Note: It is possible that subject will not necessarily complete up through Week 124 before they move to Schedule of Procedures F or G.
[c] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[d] See Section 16.2 in the protocol for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[e] Participants are required to fast at least 4 hr (only water permitted prior to collection).
[f] Genotyping sample will be drawn at Week 84 or at the time of re-consent for the optional follow-up treatment period; sample will be used to provide a full characterization and documentation of the mutation type in support of the diagnosis of ALGS.
[g] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[h] Participants must be available to receive a phone call from study staff.
[i] Participants who withdraw early should complete all evaluations at this visit.
[j] Study termination only for participants who discontinue early and/or decide not to continue into optional follow-up period(s). Participants who choose to stay in the study go straight from this visit to the Optional Follow-up Treatment Period (Weeks 72-124).
[k] Follow-up visit is only for participants who exit the study at the Study Termination Visit.
[l] At the indicated visits during the treatment period, oxalate will be part of the urinalysis.
[m] During the stable dosing period, twice daily completion of the eDiary (ItchRO) for 2 consecutive weeks will be required following the Weeks 84, 96, 108, 120 clinic visits.

	Clinic Visit
	Phone Contact

3.7.4. Schedule of Procedures D – 52-Week Optional Follow-up Treatment Period: DE-2 –Week 176 for participants with ≥7days

Study Period	Treatment Period (continued)																	Study Termination[k]	Follow-Up[l]
	Follow-up Treatment Period Dose Escalation (DE)						Follow-up Treatment												
FTP Study Week	DE -2	DE Day 0	DE 73	DE 74	DE 75	DE 76	80	84	88	92	96	100	104	108	112	116	120	Week 124 (or ET[k])	30 days after final dose
Study Day	-14	0	511[a]	518[a]	525[a]	532[a]	560[a]	588[a]	616[a]	644[a]	672[a]	700[a]	728[a]	756[a]	784[a]	812[a]	840[a]	868[a]	
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±14)	(±5)
Informed Consent/Assent for Protocol Amendment 5[b]	X																		
Assess eligibility	X	X		X		X													
Afternoon Dose Escalation (ADE) eligibility assessment followed by shift in visit schedule[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Physical Exam	X	X		X		X		X			X			X			X	X	
Body Weight & Height	X	X		X		X		X			X			X			X	X	
Vital Signs[d]	X	X		X		X		X			X			X			X	X	
CBC with Differential[e]	X	X		X		X		X			X			X			X	X	
Coagulation[e]	X	X		X		X		X			X			X			X	X	
Chemistry Panel[e]	X	X		X		X		X			X			X			X	X	
Lipid Panel[e,f]	X	X		X		X		X			X			X			X	X	
Cholestasis Biomarkers[e,f]	X	X		X		X		X			X			X			X	X	
Fat Soluble Vitamins[e,f,g]	X	X		X		X		X			X			X			X	X	
Optional Genotyping[h]	X																		
Urinalysis[e]	X	X		X		X		X			X			X			X	X[m]	

Study Period	Treatment Period (continued)																	Study Termination[k]	Follow-Up[l]
	Follow-up Treatment Period Dose Escalation (DE)						Follow-up Treatment												
FTP Study Week	DE -2	DE Day 0	DE 73	DE 74	DE 75	DE 76	80	84	88	92	96	100	104	108	112	116	120	Week 124 (or ET[k])	30 days after final dose
Study Day	-14	0	511[a]	518[a]	525[a]	532[a]	560[a]	588[a]	616[a]	644[a]	672[a]	700[a]	728[a]	756[a]	784[a]	812[a]	840[a]	868[a]	
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±14)	(±5)
Urine Pregnancy Test (if indicated)[i]	X	X		X		X		X			X			X			X	X	
Clinician Scratch Scale	X	X		X		X		X			X			X			X	X	
Clinician Xanthoma Scale						X		X			X			X			X	X	
Subject eDiary/Caregiver eDiary								X^n	X^n to Week 86		X^n	X^n to Week 98		X^n	X^n to Week 110		X^n	X^n to Week 122	
PedsQL		X						X			X			X			X	X	
Caregiver Impression of Change														X			X	X	
Study Drug Supplied		X		X		X		X			X			X					
Review Study Diaries and Assess Compliance				X		X		X			X			X			X	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
Follow-up Phone Contact[j]			X		X		X		X	X		X	X		X	X			

[a] Calculation of Study Day includes subject's participation through the first 72 weeks.

[b] Once necessary approvals are received for Protocol Amendment 5 and associated consent/assent are available, site will consent/assent subject for Protocol Amendment 5 at the next clinic visit.
[c] Depending on the outcome of afternoon dose escalation eligibility assessment, the subject will move into either Schedule of Procedures For G. Note: It is possible that subject will not necessarily complete up through Week 124 before they move to Schedule of Procedures F or G.
[d] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[e] See Section 16.2 in the protocol for detailed list of laboratory analytes.
[f] Participants are required to fast at least 4 hr (only water permitted) prior to collection.
[g] Blood samples must be drawn before administration of vitamin supplementation.
[h] Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation type in support of the diagnosis of ALGS.
[i] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[j] Participants must be available to receive a phone call from study staff.
[k] Participants who withdraw early should complete all evaluations at this visit.
[l] Follow-up visit is only for participants who exit the study at the Study Termination Visit.
[m] At indicated visits during treatment period, oxalate will be part of the UA.
[n] During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 74, Week 84, Week 96, Week 108, and Week 120 visits .

	Clinic Visit
	Phone Contact

3.7.5. Schedule of Procedures E – Long-term Optional Follow-up Treatment Period: Protocol Amendment 5 Screening (Week -2) and on MRX. Includes Evaluation of Eligibility for Afternoon Dose Escalation Dosing Regimen at Protocol Amendment 5, Week 12

Any subject who re-enters the study under Protocol Amendment 5. The subject returns to their last previously administered dose for 12 weeks and then moves to either Schedule F or G, depending on afternoon dose eligibility. Proceed to Schedule H for Early Termination or End of Treatment Procedures.

Study Period	Treatment Period (continued)					
	Long-Term Optional Follow-up Treatment Period					
FTP Study Week	Screening PA5 (Week -2)	PA 5 Day 0/Baseline	PA 5 Week 2	PA 5 Week 4	PA 5 Week 8	PA 5 Week 12
Study Day	-14	0	518[a]	532[a]	546[a]	560[a]
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)
Informed Consent/Assent for Protocol Amendment 5[b]	X					
Assess eligibility	X	X				
Afternoon Dose Escalation (ADE) eligibility assessment followed by shift in visit schedule						X
Physical Exam	X	X		X		X
Body Weight & Height	X	X		X		X
Vital Signs[c]	X	X		X		X
CBC with Differential[d]	X	X		X		X
Coagulation[d]	X	X		X		X
Chemistry Panel[d]	X	X		X		X
Lipid Panel[d,e]		X		X		X
Cholestasis Biomarkers[d,e]		X		X		X
Fat Soluble Vitamins[d,e,f]		X		X		X
Urinalysis[d]	X[i]	X[i]		X[i]		X[i]

Study Period	Treatment Period (continued)					
	Long-Term Optional Follow-up Treatment Period					
FTP Study Week	Screening PA5 (Week -2)	PA 5 Day 0/Baseline	PA 5 Week 2	PA 5 Week 4	PA 5 Week 8	PA 5 Week 12
Study Day	-14	0	518[a]	532[a]	546[a]	560[a]
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)
Urine Pregnancy Test (if indicated)[g]	X	X		X		X
Clinician Scratch Scale		X		X		X
Clinician Xanthoma Scale		X		X		X
Subject eDiary/Caregiver eDiary	X[j]			X[j]		
PedsQL		X				
Palatability Questionnaire				X		X
Study Drug Supplied		X		X		X
Assess Study Drug Compliance				X		
Review Study Diaries and Assess Compliance		X				X
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Follow-up Phone Contact[h]			X		X	

[a] Calculation of Study Day includes subject's participation through the first 72 weeks.
[b] Once necessary approvals are received for Protocol Amendment 5 and associated consent/assent are available, site will consent/assent subject for Protocol Amendment 5 at the Protocol Amendment 5 screening visit.
[c] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[d] See Section 16.2 in the protocol for detailed list of laboratory analytes.
[e] Participants are required to fast at least 4 hr (only water permitted) prior to collection.
[f] Blood samples must be drawn before administration of vitamin supplementation.
[g] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[h] Participants must be available to receive a phone call from study staff.
[i] Oxalate will be part of the UA.
[j] During the Re-entry for Protocol Amendment 5, daily completion of the study diary for 2 consecutive weeks following the Protocol Amendment 5 screening visit and the Protocol Amendment 5 Week 4 visit. .

	Clinic Visit
	Phone Contact

3.7.6. Schedule of Procedures F – Extension of Long-term Optional Follow-up Treatment Period, for participants ineligible for afternoon dose escalation

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

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 in the protocol for detailed list of laboratory analytes.
[c] Participants are required to fast at least 4 hr (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] Participants must be available to receive a phone call from study staff.
[h] Study visits will continue in the same pattern until the first of the following occur: (i) participants are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
[i] At indicated visits during treatment period, oxalate will be part of the UA.
[j] Sample will be drawn at every other clinic visit starting with RP1 Week 12.
[k] Starting at Week 12 RP2 participants should be re-assessed for ADE eligibility

	Clinic Visit
	Phone Contact

3.7.7. Schedule of Procedures G – Extension of Long-term Optional Follow-up Treatment Period, for participants eligible for afternoon

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeat in repeating 12-week periods after completion of the ADE period[i]		
Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±7)	(±7)	(±14)
Physical Exam	X			X			X			X
Body Weight & Height	X			X			X			X
Vital Signs[a]	X			X			X			X
CBC with Differential[b]	X			X			X			X
Coagulation[b]	X			X			X			X
Chemistry Panel[b]	X			X			X			X
Lipid Panel[b,c]	X			X			X			X
Cholestasis Biomarkers[b,c]	X			X			X			X
Fat Soluble Vitamins[b,c,d]	X			X			X			X
Urinalysis[b]	X[j]			X[j]			X[j]			X[j]
AFP Sample										X[k]
Plasma Sample for LUM001[e]	X			X			X			X[e]
Serum or Urine Pregnancy Test (if indicated)[f]	X			X			X			X

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

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 in the protocol for detailed list of laboratory analytes.
[c] Participants are required to fast at least 4 hr (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Pharmacokinetic sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose escalation period.
[f] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[g] Study drug may be dispensed at unscheduled clinic visits.
[h] Participants must be available to receive a phone call from study staff.
[i] Study visits will continue in the same pattern until the first of the following occur: (i) participants are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
[j] At indicated visits during treatment period, oxalate will be part of the UA.
[k] Sample will be drawn at every other clinic visit starting with RP1 Week 12.

	Clinic Visit
	Phone Contact

3.7.8. Schedule of Procedures H – End of Treatment (EOT) / Early Termination (ET) Visit and Post-Treatment Safety Follow Up

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

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 in the protocol for detailed list of laboratory analytes.
[c] Participants are required to fast at least 4 hr (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential.
[f] Participants must be available to receive a phone call from study staff.
[g] Will take place when the first of the following occur: (i) participants are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) or the sponsor stops the program or development in this indication.
[h] At indicated visits during treatment period, oxalate will be part of the UA.

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 3 treatment phases in addition to overall:

- Original Protocol Phase (Day 1 – Week 72),
- 52-Week Optional Follow-up Phase (Week 72 – Week 124)
- Long-term Optional Follow-up Phase (Week >124)

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

5. Analysis Populations

The following analysis 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.

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 LUM001-302 or in LUM001-303) will be used as the baseline MRX observation for all calculations of change from baseline MRX. 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.

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), 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).

6.1.2. Study Day

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

6.1.3. Adjustments for Covariates

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 subject 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 72/ET, 124/ET, EOT/ET), visit-based assessments performed during that visit will not be used in analysis summaries.

For a subject who prematurely discontinues the study, their ET visit data will be assigned to a protocol-specified visit window 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 72/LOCF, Week 124/LOCF time points, where appropriate. 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 participants 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 participants/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 participants/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 6.1.9).

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

6.1.7. Analysis Visit Windows

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

For those 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 (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 6.1.9.

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 subject was on study drug during the period of time that the subject was off study drug.

The analysis visit windows in Table 4 will also be used for all visit-based safety assessments that occurred before a drug interruption (due to a protocol amendment), including those 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
44	Week 44	308	302 ─ 324
48	Week 48	336	325 – 378
60	Week 60	420	379 – 462
72	Week 72	504	463 – 546/511*
74*	Week 73	518	512 - 525
76*	Week 76	532	526 - 546
84	Week 84	588	547 – 630
96	Week 96	672	631 – 714
108	Week 108	756	715 – 798
120	Week 120	840	799 – 852
124	Week 124	868	853 - 882
128[2]	PA5 Week 4	896	883 - 910
136[2]	PA5 Week 12	952	911 - 994[3]/966[4]
148[3]	RP Week 12	1036	995 - 1078[6]
140[4]	ADE Week 4	980	967 - 1008
148[4]	ADE Week 8	1036	1009 - 1078
160[5]	ADE RP Week 12	1120	1079 - 1162[6]

[1]Study day relative to the date of first dose of study medication, unless otherwise specified.
[2]Related to Long – term optional follow-up all participants
[3]Related to Long – term optional follow-up for participants ineligible for afternoon dose escalation
[4]Related to Long – term optional follow-up for participants eligible for afternoon dose escalation
[5]Related to Long – term optional follow-up for participants after completion of afternoon dose escalation
[6]This will include repeated visits until EOT/ET. Assessment windowing will be adjusted as relevant.
*Dose Escalation period for participants with ≥ 7 days from last dose of MRX

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

For visit-based analyses (and listings) on safety data collected or assessed after a drug interruption period (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 ─ 35
12	Week 12	84	70 ─ 98
16	Week 16	112	99 – 126
20	Week 20	140	127 – 209
34	Week 34	238	210 – 266
46	Week 46	322	288 – 364
58	Week 58	406	365 – 448
70	Week 70	490	449 – 532
82	Week 82	574	533 – 616
94	Week 94	658	617 – 700
106	Week 106	742	701 – 784
118	Week 118	826	785 – 868

[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 48/LOCF" (see Section 6.1.5.2)
- "Week 72/LOCF" (see Section 6.1.5.2)
- "Week 124/LOCF" (see Section 6.1.5.2)

- Treatment-emergent adverse events (TEAEs) are defined in Section 9.2.
- Concomitant medications are defined in Section 9.6.

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 subject 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 subject being off study between protocol amendments]*

Compliance is derived overall (Week 0-EOT) and for the following treatment phases: Week 0-72, Week >72-124, and Week >124. 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 (µg/kg)$_i$)]

  where,

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

  Total drug exposure is derived overall (Week 0-EOT) and for each treatment phase: Week 0-72, Week >72-124, and Week >124. The time periods for which no study drug was administered due to dosing gaps while a subject is off study (between protocol amendments) are not included. For 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 0-72, Week >72-124, and Week >124. The time periods for which no study drug was administered due to dosing gaps while a subject is off study (between protocol amendments) are not included.
- **ItchRO Weekly Morning Average Score** = Sum of ItchRO daily morning scores (over a 7-day period) divided by the number of days ItchRO completed

  The above definitions apply to both severity (Item 1) and frequency (Item 3, Observer only) weekly average scores. The baseline weekly morning/evening 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, 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 (mg/dL)]

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

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

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

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

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

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

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

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

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

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

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

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

  Refer to Section 6.1.1 for various baseline definitions.

  For ItchRO average scores, "Value" is the average score over the specified time period, as defined above.

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

Height and weight z-scores are based on a subject'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 subject), a 5-point response scale is used (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always). Items are reverse-scored and linearly transformed to a 0-100 scale (0 → 100, 1 → 75, 2 → 50, 3 → 25, 4 → 0), so that higher scores indicate better HRQoL (less negative impact). Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed. See Reference 13 in Section 12 for scoring instructions on the PedsQL.

  PedsQL scale scores are computed for the following:

  - Total Scale Score – computed as the sum of the items over the number of items answered on the PedsQL Generic Core Scales (up to 45 items)
  - Physical Health Summary Score – computed as the sum of the items over the number of items answered in the Physical Functioning Scale (and Physical Symptoms Scale for infants) from the PedsQL Generic Core Scales (up to 19 items)
  - Psychosocial Health Summary Score – computed as the sum of the items over the number of items answered in the Emotional, Social, and Nursery/Day Care/School Functioning Scales for children age 2 to 18 years or Emotional, Social, and Cognitive Functioning Scales for infants (<2 years) from the PedsQL Generic Core Scales (up to 26 items)
  - Multidimensional Fatigue Scale Score – computed as the sum of the items over the number of items answered in the PedsQL Multidimensional Fatigue Scales (18 items)
  - Family Impact Total Scale Score – computed as the sum of the items over the number of items answered in the PedsQL Family Impact module (36 items)
  - Parent Functioning Summary Score – computed as the sum of the items over the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning Scales from the PedsQL Family Impact module (20 items)
  - Family Impact Summary Score – computed as the sum of the items over the number of items answered in the Daily Activities and Family Relationships Scales from the PedsQL Family Impact module (8 items)

Total scale, physical health summary, psychosocial health summary, and multidimensional fatigue scale scores are computed individually for the parent and subject reports.

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 LUM001-302 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-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 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 disease as well as of MRX:

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

All of these events occur during the natural history of ALGS. 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 'loose stool', "increased stool frequency". Elevated transaminases events include PTs of 'Alanine aminotransferase increased' and 'Aspartate aminotransferase increased'. Elevated bilirubin events include the PT of 'Blood bilirubin increased'.

Partial Date Imputation

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

Partial ALGS Diagnosis Dates

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

Partial Dates of Birth

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

Partial AE or Medication Dates

Adverse events or medications with entirely missing start dates will be classified as treatment-emergent or concomitant, as appropriate. For the below, first dose date is with respect to the first dose in LUM001-303.

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 event 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 event 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

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

Subject disposition will include tabulations of the number and percentage of participants in each of the analysis populations, down-titrated during the study, completed treatment, and discontinued treatment early (along with reasons for withdrawal). For the overall summary and the Week >72 treatment period, participants that did not consent to the optional long-term treatment extensions (PA4 and PA5) are not considered to have completed treatment. Reasons for withdrawal will include those collected on the CRF, along with not consenting to PA4 and PA5 (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 subject 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.

7.2. Protocol Violations and Deviations

Protocol deviations will be tracked, recorded, and reviewed prior to database lock, following the Protocol Deviation Guidance Plan for the Maralixibat program, including:

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

Other protocol deviations may be identified during the study.

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

Major protocol deviations may include:

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

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

7.3. Demographics and Other Baseline Characteristics

Subject demographics and other baseline characteristics will be presented 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 subject 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 subject and summarized descriptively. This analysis will be completed using the Safety Population for each of the following study phases: Weeks 0-72, Weeks >72-124, Weeks >124, 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 listing of all participants and their participation in each study phase will be provided.

A subject 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 subject 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 ad overall, unless otherwise specified.

All efficacy data will be presented in subject listings.

8.1. Primary Efficacy Analysis

The change from baseline to Week 48 in the serum bile acid will be displayed for each treatment group and overall by study visit, using summary statistics including the number of observations, the mean, median, standard deviation, minimum and maximum. Differences from baseline will be calculated and summarized as above, with a 95% confidence interval for the mean.

8.2. Secondary, Exploratory and Other Efficacy Analyses

Secondary efficacy variables that are continuous measures will be analyzed similarly to the primary efficacy analyses, using summary statistics and ANCOVA model to determine if the mean change is statistically significant, where applicable. 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.

Categorical measures will be presented by level of response with frequencies and percentages.

Change from baseline in Xanthoma scale will be categorized as improved, stable or worsened and will be compared between treatment groups using the chi-square test.

Change from baseline in ItchRO(Obs) weekly average morning severity score, sBA, C4, bilirubin (total and direct), ALT, AST, ALP, GGT, total cholesterol, LDL-C, height, weight and BMI 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 13.3. 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 a drug interruption > 28 days due to a subject being off study (between protocol amendments). Visit-based data collected after the drug interruption, at the point of study drug re-initiation, will be analyzed separately as a sensitivity analysis.

For all safety analyses, 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 subject listings. All visit-based safety data collected or assessed after the drug interruption period (between protocol amendments) will be presented in separate subject listings.

9.1. Treatment Exposure

Treatment exposure will be summarized descriptively overall and by each of the following treatment phases: Weeks 0-72, Weeks >72-124, Weeks >124, 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 6.1.9 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 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 6.1.9).

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 overall and 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 subject, each subject 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 total frequency order of the PT within each SOC.

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

In the AE data listings, events that are treatment-emergent will be flagged. AEs will be presented in by-subject listings, detailing the treatment phase, treatment received at the start of the event including dose for active study drug, SOC, PT, verbatim term given by the investigator, onset date and study day, end date and study day, event duration, severity, relationship to study drug, outcome, action taken with study drug, seriousness, and treatment required.

9.2.1. Adverse Events Leading to Withdrawal

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

9.2.2. Deaths and Serious Adverse Events

Treatment-emergent SAEs, and SAEs potentially related to study drug will be summarized in the same manner as AEs that lead to permanent discontinuation of study drug. Subject listings of all SAEs will also be presented.

Any deaths that occur during the study, including post-treatment follow-up periods, will be presented in a subject listing. The listing will include subject ID, treatment period, study drug and dose received at the time of death (or the last study drug/dose received prior to death), date of death, number of days from the 1st and last dose, MedDRA PT, and relationship to study drug.

9.2.3. Adverse Events of Special Interest

Due to the nature of Alagille disease, as well as MRX, the following events have been defined as AESIs: 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 subject after a drug interruption due to the subject being off study (between protocol amendments).

Safety laboratory test results will be summarized using descriptive statistics by laboratory test panel (i.e., chemistry, hematology, FSVs, and lipids), by 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 subject listings. Bilirubin (total and direct), ALT, AST, ALP, GGT and ALT are considered as both safety and efficacy laboratory tests, and will only be summarized as efficacy variables. All safety laboratory test parameters will be presented (by panel) in subject listings.

For select FSVs, including 25-hydroxyvitamin D, 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 6.1.9 for specific definitions). Missing lab values will be reported in a 'Missing' category.

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

Sensitivity Analyses on Laboratory Data Collected After Drug Interruption

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

FSV level abnormalities (e.g., sufficient, insufficient, excess) will also be analyzed separately as a sensitivity analysis using laboratory samples collected after a drug interruption. The number and percent of participants within each test level category (see Section 6.1.9 for category definitions) will be presented.

9.4. Physical Examination

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

Physical examination findings, body height, and body weight, along with z-scores for height, weight and BMI will be included in subject 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 13.1.

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

9.7. Safety Data Graphical Presentations

Study drug exposure and TEAEs of special interest will be displayed graphically over time, as described in Section 13.3. 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.

10.2. Palatability

Palatability data will be summarized using descriptive statistics by treatment group and analysis visit as observed.

10.3. Serum Alpha-fetoprotein

Assessments of serum AFP will be listed for individual participants and summarized using descriptive statistics by study visit.

11. Changes from Planned Analysis

The protocol defines Baseline (Day 0) and Baseline from LUM001-302, however in LUM001-303, the first dose of MRX (either in LUM001-302 or LUM001-303) will be used as the baseline visit to harmonize across the ALGS program.

Other changes from the protocol include:

- Change from Week 12 to Week 48 removed from the secondary endpoints, this change analysis will be no longer meaningful with the use of MRX baseline.
- AST, ALP and direct bilirubin added to the secondary endpoints to harmonize across the ALGS program.
- The protocol states the ANCOVA analysis will be performed for the primary endpoint, however Student t-test will be used.

12. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
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3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
4. Molenberghs G., Kenward M. G. 2007. *Missing Data in Clinical Studies.* New York: Wiley.
5. Molenberghs G., Thijs H., Jansen I., et al. 2004. Analyzing incomplete longitudinal clinical trial data. *Biostatistics*, 5, 445-464.
6. Mallinckrodt C. H., Clark W. S., David S. R. 2001. Accounting for dropout bias using mixed-effects models. *Journal of Biopharmaceuticals Statistics,* 11, 9-21.
7. European Medicines Agency. 2010. Guideline on Missing Data in Confirmatory Clinical Trials.
8. Siddiqui O., Hung H. M., O'Neill R. 2009. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. *Journal of Biopharmaceuticals Statistics*, 19(2), 227-246.
9. Mallinckrodt C. H., Roger J., Chuang-Stein C., Molenberghs G., O'Kelly M., Ratitch B., Janssens M., Bunouf P. 2013. Recent Developments in the Prevention and Treatment of Missing Data. *Drug Information Journal*, 48, 68-80.
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 LUM001-303. 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		Subject Disposition: Overall – All Participants
14.1.1.2		Subject 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 (µmol/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

14.2.6 Summary of Total Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Safety Population

14.2.7 Summary of Direct Bilirubin (mg/dL) and Change from Baseline by Analysis Visit – Safety Population

14.2.8 Summary of C4 (ng/mL) and Change from Baseline by Analysis Visit – Safety Population

14.2.9 Summary of Total Cholesterol (mg/dL) and Change from Baseline by Analysis Visit – Safety Population

14.2.10 Summary of LDL-C (mg/dL) and Change from Baseline by Analysis Visit – Safety Population

14.2.11.1 Summary of Clinician Scratch Score (CSS) and Change from Baseline by Analysis Visit – Safety Population

14.2.11.2 Summary of Clinician Scratch Score (CSS) Change from Baseline by Analysis Visit – Categorical Data Analysis – Safety Population

14.2.12 Summary of Clinician Xanthoma Severity Score and Change from Baseline by Analysis Visit – Safety Population

14.2.12.1 Secondary analysis: Change from Baseline in Clinician Xanthoma Severity Score, Chi-square test – Safety Population

14.2.13 Summary of Height z-Score and Change from Baseline by Analysis Visit – Safety Population

14.2.14 Summary of Weight z-Score and Change from Baseline by Analysis Visit – Safety Population

14.2.15 Summary of CIC (Itch-Related Symptoms) and Change from Baseline by Analysis Visit – Safety Population

14.2.16 Summary of CIC (Xanthoma Severity) and Change from Baseline by Analysis Visit – Safety Population

14.2.17 Summary of PedsQL Total Scale Score (Parent) and Change from Baseline by Analysis Visit – Safety

	Population
14.2.18	Summary of PedsQL Multidimensional Fatigue Scale Score (Parent) and Change from Baseline by Analysis Visit – Safety Population
14.2.19	Summary of PedsQL Family Impact Total Scale Score and Change from Baseline by Analysis Visit – Safety Population
14.2.20	Summary of PedsQL Psychosocial Health Summary Score (Parent) and Change from Baseline by Analysis Visit – Safety Population
14.2.21	Summary of PedsQL Total Scale Score (Child) and Change from Baseline by Analysis Visit – Safety Population
14.2.22	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 (kg/m2) 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

14.4.2 Palatability Data

14.4.2 Summary of Palatability data by Analysis Visit – Safety Population

13.2. Planned Listing Descriptions

For the planned interim analysis for protocol number LUM001-303, 3 subject data listings will be produced: SAEs, TEAEs leading to permanent treatment discontinuation, and deaths. These listings are imbedded within the safety tables.

All listings will be sorted by treatment phase, treatment received, site, and subject 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 subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

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

Listing Number		Subject Listing Title
16.2	**Subject Disposition**	
16.2.1		Analysis Populations and Treatment Assignments – Enrolled Participants
16.2.2		Subject Disposition – Enrolled Participants
16.2.3		Subject Disposition – Screen Failure
16.3	**Protocol Deviations/ Participants Excluded from Efficacy Analyses**	
16.3.1		Inclusion and Exclusion Criteria – Enrolled Participants
16.3.2		Subject 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

Listing Number		Subject Listing Title
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**	
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

Listing Number	Subject Listing Title
16.6.10.2.1	Pediatric Quality of Life Inventory (Subject Report) - Physical Functioning – Safety Population
16.6.10.2.2	Pediatric Quality of Life Inventory (Subject Report) - Emotional Functioning – Safety Population
16.6.10.2.3	Pediatric Quality of Life Inventory (Subject Report) - Social Functioning – Safety Population
16.6.10.2.4	Pediatric Quality of Life Inventory (Subject Report) - School Functioning – Safety Population
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 (Subject Report) - General Fatigue – Safety Population
16.6.10.4.2	Multidimensional Fatigue Scale (Subject Report) - Sleep/Rest Fatigue – Safety Population
16.6.10.4.3	Multidimensional Fatigue Scale (Subject 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 (Subject 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

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

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

13.3. Planned Figure Descriptions

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 subject that reported the respective AESI. The horizontal axis will represent time, as study day. The severity of each event will be depicted as color-coded lines and symbols. Treatment sequence will be identified for each subject.

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
14.2.4.1	Plot of Mean (± SE) Change from Baseline in AST (U/L) by Treatment Group Over Time - Safety Population
14.2.5	Plot of Mean (± SE) Change from Baseline in GGT (U/L) by Treatment Group Over Time - Safety Population
14.2.6	Plot of Mean (± SE) Change from Baseline in Total Bilirubin (mg/dL) by Treatment Group Over Time - Safety Population
14.2.7	Plot of Mean (± SE) Change from Baseline in Direct Bilirubin (mg/dL) by Treatment Group Over Time - Safety Population (footnote about the cap at 10 mg/dL of direct Bilirubin)
14.2.8	Plot of Mean (± SE) Change from Baseline in C4 (ng/mL) by Treatment Group Over Time - Safety Population
14.2.9	Plot of Mean (± SE) Change from Baseline in Total Cholesterol (mg/dL) by Treatment Group Over Time - Safety Population
14.2.10	Plot of Mean (± SE) Change from Baseline in LDL-C (mg/dL) by Treatment Group Over Time - Safety Population
14.2.11	Plot of Mean (± SE) Change from Baseline in Height z-Score by Treatment Group Over Time - Safety Population
14.2.12	Plot of Mean (± SE) Change from Baseline in Weight z-Score by Treatment Group Over Time - Safety Population
14.2.13	Plot of Mean (± SE) Change from Baseline in PedsQL Total Score (Parent) by Treatment Group Over Time - Safety Population
14.2.14	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 Subject – 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 Subject – Safety Population

14. Tables, Listings, and Listing Shells

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

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

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
ALGS	alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	Aspartate aminotransferase
ASA	American statistical association
ASBTi	apical sodium dependent bile acid transporter inhibitor
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BID	twice-a-day dosing regimen
BMI	body mass index
BP	blood pressure
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

Abbreviation	Definition
CRF	case report form
CSR	clinical study report
CSS	clinician scratch score
CTCAE	common terminology criteria for adverse events
DMC	data monitoring committee
eDiary	electronic diary
EMA	European medicines agency
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
GGT	gamma glutamyl transferase
GI	gastrointestinal
HR	heart rate
HRQoL	health-related quality of life
IA	interim analysis
ICH	international council for harmonization

Abbreviation	Definition
ID	identification
ItchRO	itch reported outcome
LLOQ	lower limit of quantification
LOCF	last-observation-carried-forward
MedDRA	medical dictionary for regulatory activities
MRX	maralixibat
NDA	new drug application
PBO	placebo
PedsQL	pediatric quality of life
PT	preferred term
RBP	retinol binding protein
RSS	royal statistical society
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD	standard deviation
SE	standard error
SOC	system organ class
SOP	standard operating procedure

Abbreviation	Definition
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

Serum βhCG (if indicated)	Clinical Chemistry	Lipid Panel[1]	Urinalysis
CBC with Differential	Sodium	Total cholesterol	pH
Red blood cells	Potassium	LDL-C (direct)	Specific gravity
Hemoglobin	Chloride	HDL-C	Protein
Hematocrit	Bicarbonate	Triglycerides (TG)	Glucose
MCV, MCH, MCHC	Total protein		Ketones
Platelets	Albumin	Cholestasis Biomarkers[1]	Bilirubin
White blood cells	Calcium	Serum bile acids	Occult blood and cells
WBC Differential (% and absolute)	Phosphate	7α hydroxy-4-colesten-3-one (C4)	Nitrite
• Neutrophils	Glucose		Urobilinogen
• Eosinophils	Blood urea nitrogen (BUN)	Fat Soluble Vitamins[1]	Leukocyte esterase
• Basophils	Creatinine	25-hydroxy vitamin D	Microscopic examination[2]
• Lymphocytes	Uric Acid	Retinol	Oxalate[3]
• Monocytes	Total bilirubin	Retinol binding protein	LUM001 Drug Levels
Coagulation	Direct bilirubin (conjugated)	Tocopherol (α)	LUM001 in plasma
Activated partial thromboplastin time (aPTT) (sec)	Indirect bilirubin (unconjugated)	Marker of hepatocellular carcinoma	
Prothrombin time (PT) (sec)	Alkaline phosphatase (ALP)	Alpha-fetoprotein (AFP)	
INR	AST (SGOT)		
	ALT (SGPT)		
	GGT		

1 Blood samples for the analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation and approximately 4 hours after food or formula. Other biomarkers [eg, autotaxin, lysophosphatidic acid (LPA), FGF-19, FGF-21] may be measured. At the discretion of the sponsor, samples will be collected and appropriately stored for subsequent analysis, as needed.
2 Will be performed on abnormal findings unless otherwise specified.
3 At the specified time points on the Schedule of Procedures (Section 16.1), oxalate will be part of the urinalysis.

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