Statistical Analysis Plan

Sponsor	*Mirum Pharmaceuticals, Inc.*
Protocol Title:	*Open Label Study of the Efficacy and Long Term Safety of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis*
Protocol Number:	*LUM001-501*
Premier Research PCN:	*LUME2940*
Document Version:	*Amendment 3 (Final Version 1.0)*
Document Date:	*30-Jun-2020*

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician	Print Name: Jana Steinmetz, MS Sign Name: DocuSigned by: Jana Steinmetz Signer Name: Jana Steinmetz Signing Reason: I am the author of this document Signing Time: 30-Jun-2020 | 14:04:36 EDT 9302752519E1436089832B622B6DE775	30-Jun-2020 | 14:04:50 EDT
Mirum Pharmaceuticals, Inc. Representatives	Print Name: Thomas Jaecklin, MD Sign Name: DocuSigned by: Signer Name: Thomas Jaecklin Signing Reason: I approve this document Signing Time: 30-Jun-2020 | 23:14:49 PDT 3EC09166F36D4E499498AA675BEF07BF	30-Jun-2020 | 23:14:53 PDT
	Print Name: Will Garner, PhD Sign Name: DocuSigned by: Will Garner Signer Name: Will Garner Signing Reason: I approve this document Signing Time: 30-Jun-2020 | 12:54:14 PDT 2924BA8492304DB89A4DF5C7F56C3585	30-Jun-2020 | 12:54:19 PDT

Document History

Statistical Analysis Plan (SAP) Amendment 3

Date: 30-Jun-2020

The primary reasons for this analysis plan amendment are to make updates per changes made in Protocol Amendment 4.1 (dated 08-Feb-2019), and to make clarifications and changes to planned analyses for the addendum to the final clinical study report (CSR). The final CSR was produced using the 3rd planned IA focused on data through Week 72. Analyses described in SAP Amendment 3 will be followed for the final analyses.

The following changes have been made to SAP Amendment 2:

- Reflect the change of sponsorship from Lumena Pharmaceuticals LLC (Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc) to Mirum Pharmaceuticals, Inc.
- Reflect re-naming of LUM001 as maralixibat chloride (MRX).
- An intent-to-treat (ITT) analysis population has been added for the final analysis. Each sibling pair is included in the ITT analysis population. The ITT population will be used as the analysis set for all final efficacy analyses, as described in this SAP (amendment 3).
- The per-protocol (PP) analysis population was used in the 1st interim analysis to examine efficacy outcomes. No summaries using the PP Population are planned for the final analyses.
- Efficacy analysis performed on the modified intent-to-treat (mITT) analysis population for the 3rd planned IA is considered as a sibling sensitivity analysis, and will not be repeated for the final analysis. For the 3rd planned IA, all subjects either withdrew early (prior to Week 72) or completed the study through Week 72. The LUM001-501 CSR dated 07May2020 focused on data collected or assessed through Week 72.
- Visit-based assessments have been mapped to analysis visits based on study day, where study day is relative to the date of first dose of study drug (see Section 6.1.6).
- Visit-based analyses will be performed by analysis visit, rather than clinic visit. Applicable efficacy and safety endpoints have been updated to reflect this change. Analyses of all efficacy variables, regardless of drug interruptions, will be performed using the analysis visits. For subjects with an extended drug interruption, efficacy assessments after the interruption are essentially treated as if the subject was on study drug during the period of time that the subject was off study drug. The analysis visit windows will also be used for all visit-based safety assessments that occurred before an extended (>28-day) drug interruption (due to a protocol amendment), including those subjects without such a drug interruption.

- Visit-based safety data collected or assessed after a > 28-day drug interruption period (between protocol amendments) will not be included in analysis summaries, but will be included within listings.
- The assumption of normality for primary and secondary efficacy variables will be tested using the Shapiro-Wilk test, rather than by a visual inspection of a normal Q-Q plot.
- For each primary and secondary efficacy variable (except ItchRO (Obs) 4-week morning average score), and select exploratory variables (i.e., alkaline phosphatase [ALP], total cholesterol, 7α hydroxyl-4-cholesten-3-one [C4], gamma-glutamyl transferase [GGT], and low-density lipoprotein cholesterol [LDL-C]) an analysis by PFIC2 subtype (truncating PFIC2, non-truncating PFIC2) has been added.
- A summary of ItchRO (Obs) morning scores has been added as an exploratory analysis that presents the number and percent of days the daily morning score is ≤ 1 point by time period and PFIC type. Time periods include Screening/Baseline, Day 1 - Week 8, Weeks > 8 - 13, Weeks > 13 - 24, Weeks > 24 - 36, Weeks > 36 - 48, Weeks > 48 - 72, Weeks > 72 – 124, Weeks > 124 – 204, and Weeks > 204.
- Last-observation-carried-forward (LOCF) records at Week 72 and Week 124 (Week 48 and Week 122 for ItchRO variables) have been added for visit-based assessments. Applicable efficacy and safety endpoints have been updated to reflect this change.
- "Endpoint" time points (i.e., Week 13/early termination [E]T, Week 48/ET, Week 72/LOCF, Week 122/ET, Week 124/LOCF, and end of treatment [EOT]/ET) have been replaced with the LOCF analysis time points.
- ItchRO 2-week morning and evening average scores are replaced with weekly morning and evening average scores.
- Secondary efficacy variables have been updated to include: ALP, aspartate aminotransferase [AST], bilirubin (total and direct), ItchRO (Obs) weekly average score, ItchRO (Obs) 4-week morning average score, and ItchRO (Obs) weekly morning average score. ItchRO (Pt) average scores and ALP are now considered as exploratory efficacy variables.
- Exploratory efficacy variables have been updated.
- Change from Baseline to Week 13 in ItchRO weekly morning average score and alanine aminotransferase (ALT) are considered as secondary efficacy endpoints.
- ItchRO 4-week morning and evening average scores are only derived through Week 48 (i.e., Baseline, and Weeks 4, 8, 13, 28, and 48). After Week 48 ItchRO was only collected in 2-week time periods. Change from Baseline in ItchRO (Obs) 4-week morning average score is summarized at Weeks 13, 48, and 48/LOCF.
- ItchRO responder definition based on a change from baseline of ≤ -0.5 has been replaced with a change from baseline of ≤ -1.75. Thus, ItchRO responder definitions include change from baseline of ≤ -1.0, ≤ -1.33, ≤ -1.5, and ≤ -1.75.

- Pruritus response rates as measured by ItchRO (Obs) and ItchRO (Pt) weekly morning morning average scores have been added. Pruritus response rates as measured by these weekly morning average scores will be summarized at Weeks 13, 48, 48/LOCF, 98, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Serum bile acid (sBA) responder definitions have been updated to include (a) % change from baseline of ≤ -75, (b) sBA ≤ 102 µmol/L, (c) % change from baseline of ≤ -75 or sBA ≤ 102 µmol/L, and (d) sBA ≤ 8.5 µmol/L (normalization). sBA response rates will be summarized at Weeks 13, 48, 72, 72/LOCF, 96, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Response rates for liver function lab tests (C4, AST, ALT, and total bilirubin) will be summarized at Weeks 13, 48, 72, 72/LOCF, 96, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Efficacy analysis by MRX dose has been removed, as it is no longer believed to be relevant.
- Efficacy analysis by PFIC2 subtypes (non-truncated and truncated) have been added for select efficacy variables.
- z-scores for body mass index (BMI) have been added.
- z-scores for body height, body weight, and BMI are considered as exploratory efficacy endpoints rather than safety.
- Adverse events of special interest (AESI) groups have been changed for consistency with other MRX Phase 2 analysis plans (see Section 9.2.1).
- The coding dictionary versions used to code adverse events (AEs) and medications have been changed to a more recent version, for consistency with other MRX Phase 2 studies. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1; previously v16.0. Concomitant medications will be coded using World Health Organization-Drug Dictionary (WHO-DD) (Enhanced version Sept 2019); previously Enhanced version March 1, 2013.
- AEs and exposure will be analyzed by MRX dose (≤ 280 µg/kg QD, 280 BID including 2-week dose-escalation dose of 280 plus 140 µg/kg).
- For subjects with >14 days of study drug interruption/withdrawal, the definition of a concomitant medication has been described.
- ItchRO reliability based on itch severity assessments by the patient and those by the observer/caregiver have been removed, because the ItchRO instrument has been validated under a separate analysis plan.
- Schedule of Procedures D and G: clarifying footnote added to indicate that baseline reference laboratory value for subjects re-entering in protocol amendment 3 (PA3) and protocol amendment 4 (PA4), after a dose interruption of ≥ 7 days is based on laboratory assessments collected at the re-entry visit Dose-escalation -2 Weeks.

- Analyses will be based on data pooled across investigative sites. Demographic and baseline characteristics, and disease history and baseline disease characteristics will not be presented descriptively by investigative site, as previously planned, for those sites that assigned at least 6 subjects to study drug (i.e., 25% of the total planned number of subjects assigned study drug).
- Due to a misinterpretation of the automatic dose-escalation protocol by the drug supplier, 3 of the 7 subjects enrolled and administered study drug at Site 001 were not titrated up to the 280 ug/kg/day dose per the protocol. This dosing error resulted in a "Serious Breach of GCP or the Trial Protocol", according to UK's Regulations. Subjects 001-051, 001-053, and 001-054 were dosed on 140 ug/kg/day until Week 24 at which time they were dose-escalated to 280 ug/kg/day. A sensitivity analysis excluding all Site 001 subjects was described in SAP Amendment 2. This sensitivity analysis has been removed. The study drug exposure listing (Listing 16.6.2) includes the dosing information for these subjects.
- A mixed-effects model for repeated measures analysis on each ItchRO (Obs) efficacy variable was added in SAP Amendment 2 as a sensitivity analysis. This sensitivity analysis has been removed.
- Treatment compliance overall and by PFIC type will be presented; a separate analysis presentation for treatment compliance during BID dosing has been removed.
- Figures of mean change from baseline over time are changed to present the mean ±SE, instead of mean ±SD.
- Update list of planned summary tables for 3rd planned interim analyses (see Section 14.1).
- Update list of planned summary tables, figures and listings for final analyses (see Section 14).
- Administrative/formatting changes.
- Addition of Will Garner, PhD, as a signatory.
- Format SAP according to the most recent Premier Research (Premier) SAP template.

The amended SAP (SAP Amendment 3) will be finalized and submitted to file after database lock but before final analyses are produced. As LUM001-501 is an open-label study and various interim analyses have been completed prior to database lock, based on previous finalized SAPs, the integrity of the final analysis is maintained.

Statistical Analysis Plan (SAP) Amendment 2

Date: 14-May-2018

The primary reasons for this analysis plan amendment are to make updates per changes made in PA3 (dated 02-Nov-2015) and PA4 (dated 20-Dec-2016) that include changes to study objectives, study design, inclusion/exclusion criteria, procedures/assessments, study drug administration (including twice daily dosing regimen), optional follow-up treatment periods, and subject re-entry.

The following changes have been made to SAP Amendment 1:

- Addition of study objectives specific to the Optional Follow-up Treatment Periods (After Week 72) described in Protocol Amendment 3 and Protocol Amendment 4.
- Addition of an exploratory study objective.
- The study design has been adapted to include an optional follow-up treatment period for eligible subjects who choose to stay on treatment with MRX. The optional follow-up treatment period occurs after the 4-week dose-escalation period, the 4-week stable dosing period at 140 µg/kg/day, the 5-week stable dosing period at 280 µg/kg/day, and the 59-week long-term exposure period. During the optional follow-up treatment period, subjects may have their dose of MRX increased to a maximum of 560 µg/kg/day (280 µg/kg twice-daily [BID] doses), based on ongoing efficacy as measured by sBA level and ItchRO score and safety assessment.
- Updates were made that reflect the increase in the study's duration and the addition of study visits, including endpoint time points Week 124/ET and EOT/ET and updating the Schedule of Procedures table(s).
- Addition of a planned third interim analysis, along with subsequent periodic interim analyses.
- A given subject may have been off study drug for a lengthy period of time (i.e., ≥7 days) during the course of their study treatment. The reasons for being off study drug include drug interruption (e.g., as directed by an investigator due to an AE), study drug compliance issues (e.g., missed consecutive doses), and dosing gaps due to being off study between protocol amendments 2 and 3, or 3 and 4 (e.g., a subject completing study drug under protocol amendment 2 (PA2), but before implementation of PA3 for which they subsequently provide informed consent and are reinitiated on study drug). If any visit occurs more than 7 days after the date of last dose on protocol amendments 2, 3, or 4 (referred to as "last dose"), or the date of last dose before the dose interruption, the assessments performed during that visit will not be used in analysis summaries. In this case, assessments performed at the last visit that occurred before or within 7 days of the date of "last dose" will be assigned to the appropriate endpoint or ET analysis visit (e.g., Week 13/ET and Week 72/ET).

- Similarly, ItchRO assessments that occur during non-dosing days that are more than 7 days after the date of the "last dose" will not be used for deriving ItchRO average scores. In this event, the appropriate ET average score will be based on ItchRO assessments made on the last 7 days (for weekly average scores), or last 14 days (for 2-week average scores), or last 28 days (for 4-week average scores), immediately following the date of the "last dose".
- Handling and/or derivation of analysis visits, treatment-emergent AEs (TEAEs), treatment compliance, and treatment exposure affected by subjects being off study drug during the course of their study treatment are addressed.
- Addition of clarity to definition of Per-Protocol Population.
- The subject disposition summary has been updated to include the number and percentage of subjects that consented to PA3 and completed at least 1 post-Week 72 assessment, consented to PA4 and completed at least 1 post-Week 124 assessment, completed study treatment through varying study phases (i.e., Week 72, Week 124, and EOT), and discontinued early from the study at each study phase (along with reasons for withdrawal). The number and percentage of subjects that were initiated on BID dosing and discontinued early during BID dosing (along with reasons for withdrawal) will also be summarized. The number of screen failures under the original protocol, the number of screen failures under a protocol amendment, the number of families with siblings enrolled in the study, and the total number of siblings have also been added to the subject disposition summary.
- Treatment compliance during BID dosing summary statistics have been added for subjects that initiated afternoon dose-escalation (ADE). Treatment compliance derivation for this analysis summary has been added.
- BMI has been added as a baseline characteristic to the demographics summary table, and is summarized by visit as a safety variable.
- For the baseline disease characteristics summary table, ItchRO (ItchRO Observer and ItchRO Patient) 4-week morning average and 4-week evening average scores have been added.
- All by investigative site efficacy analysis have been removed.
- At least one of the investigative sites are located in a country that does not permit the reporting of complete dates of birth. These sites only report the birth year. Complete date of birth is required, however, to derive a subject's weight and height z-scores and determine vital signs that are out-of-normal range, at each scheduled study visit. For partial birth dates, the convention for imputing missing dates for the purpose of statistical analysis has been added.
- For the secondary efficacy variable(s), ItchRO weekly average score has been replaced with 3 ItchRO average scores: weekly average score, 4-week morning average score, and 4-week-evening average score.

- Secondary evaluations will include the mean change from Baseline to Week 48/ET for ItchRO endpoints and mean change from Baseline to Week 72/ET for other efficacy endpoints.
- ItchRO 2-week morning average scores and 2-week evening average scores have been added as secondary efficacy variables for those time points during the follow-up treatment period for which the electronic diary (eDiary) was only to be completed by subjects for 2 consecutive weeks following Weeks 84, 96, 108, 120, and after each of the recurring 12-week period clinic visits. ItchRO 2-week average scores for these post-Week 48 time points will be presented in all tables, figures, and listings along with 4-week averages (rather than separately). Footnotes will be added, as applicable, to distinguish the derivations/time periods.
- For subjects enrolled in the ADE phase, analysis has been added for primary and secondary efficacy variables that include a paired t-test for change from baseline to EOT/ET (with the exception of ItchRO variables) and change from baseline by study visit summary statistics. Summary statistics for sBA levels by study visit and dose of MRX have also been added for those subjects enrolled in the ADE phase.
- For efficacy analyses, the PP Population will only be used to examine change from baseline to Week 13/ET and Week 72/ET in sBA levels and change from baseline to Week 13/ET and Week 48/ET in each ItchRO (Obs) efficacy variable.
- For each ItchRO (Obs) efficacy variable, a Mixed-effects Model for Repeated Measures (MMRM) analysis has been added as a sensitivity analysis, using the mITT Population.
- Further information with respects to the statistical model used for the MMRM analysis has been added.
- An additional ItchRO responder definition has been added using a decrease from baseline of $\geq$1 point.
- The ItchRO responder definition based on a change from baseline of $\leq$ 2.0 has been replaced with a change from baseline of $\leq$ 1.33.
- Responder definitions based on ItchRO weekly average scores have been changed to use 4-week morning average scores. Where applicable (i.e., for post-Week 48 time points), 2-week morning average scores will be used.
- The Crossover Population has been removed, along with the exploratory analysis comparing the efficacy of 140 µg/kg/day versus 280 µg/kg/day for which this analysis population was used.
- Fat-soluble vitamin tests have been excluded as exploratory efficacy variables. Fat-soluble vitamins are presented as safety endpoints.
- For select fat-soluble vitamins (FSVs), abnormalities and clinically-meaningful shifts from baseline summaries at each scheduled visit (as appropriate) have been added. For these select fat-soluble vitamins, categories may include normal, sufficient, insufficient,

possibly insufficient, indeterminate, and excess (see Section 6.1.9 for specific definitions).

- For study drug exposure summaries, the units for average daily dose have been changed from mg/day to µg/kg/day, and the units for total drug exposure has been changed from mg to µg/kg.
- The cumulative time interval categories used to summarize study drug exposure have been revised (see Section 9.1).
- A new category of AESI group has been added that combines gastrointestinal (GI)-related events and conditions associated with liver deterioration.
- Palatability questionnaire data have been added in a listing and summary shift tables.
- Due to a misinterpretation of the automatic dose-escalation protocol by the drug supplier, 3 of the 7 subjects enrolled and administered study drug at Site 001 were not titrated up to the 280 ug/kg/day dose per the protocol. This dosing error resulted 3 subjects on a dose of 140 ug/kg/day until Week 24 at which time they were dose-escalated to the 280 ug/kg/day dose. A sensitivity analysis, excluding all Site 001 subjects, has been added in the analysis of primary and secondary efficacy endpoints. Additionally, a summary of incidence of TEAEs by study phase with the exclusion of Site 001 subjects has been added, along with a listing of all AEs reported by subjects at Site 001.
- List of abbreviations have been updated.
- The Sponsor's address has been changed from "12531 High Bluff Drive, Suite 110, San Diego, CA 92130" to "300 Shire Way, Lexington, MA 02421". The following footnote has been added, "Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc.".
- The Shire Biostatistics Team Lead has been changed from Tom Tang, Ph.D. to Yi Chen, M.S.
- The Shire Medical Lead has been changed from Beatriz Caballero, MD to Thomas Jaecklin, MD.

The amended SAP will be finalized and submitted to file before the final database lock pertaining to Lumena Pharmaceuticals LLC study protocol LUM001-501.

Statistical Analysis Plan (SAP) Amendment 1

Date: 09-Aug-2016

The primary reasons for this amendment are to add secondary and exploratory efficacy variables (including new responder variables), add analyses summarizing data for Progressive Familial Intrahepatic Cholestasis (PFIC)1 and PFIC2 subjects, change the derivation of average daily ItchRO score, add 3 AE categories of special interest, redefine the timing and overall plan for the second planned interim analysis, change label of ItchRO average daily score, and make updates per changes made in Protocol Amendment 3.

This SAP amendment will not cover those changes to Protocol Amendment 3 that were impacted by the addition of the optional follow-up treatment period (after Week 72). A second amendment to the SAP will be developed, before database lock, which will cover changes impacted by this optional follow-up treatment period.

The following changes have been made to the original SAP (v1.0):

- ALP and AST have been added as secondary efficacy variables.
- High-density lipoprotein (HDL) cholesterol, triglycerides, GGT, activated partial thromboplastin time (aPTT), prothrombin time, international normalized ratio (INR), 25-hydroxyvitamin D, vitamin A, alpha tocopherol, retinol binding protein (RBP), the 15 sBA subspecies, and the ratio of cholic acid and chenodeoxycholic acid have been added as exploratory efficacy variables.
- Responder analysis based on sBA, ItchRO (Obs) scores, and liver function lab tests (7α hydroxyl-4-cholesten-3-one [C4], AST, ALT, and total bilirubin) have been defined and added as exploratory efficacy variables.
- Autotaxin, fibroblast growth factor 19 (FGF-19), and fibroblast growth factor 21 (FGF-21) have been added as exploratory efficacy variables. The clinical protocol and original SAP (v1.0) specified these tests as exploratory evaluations that may be conducted as a post hoc analysis.
- Data summaries will be presented for PFIC1 and PFIC2 subjects independently and for all subjectss combined.
- The derivation of ItchRO daily score has been changed to the average of morning and evening scores. The clinical protocol and original SAP (v1.0) define ItchRO daily score as the maximum of the morning and evening scores.
- If a Week 72/ET visit occurs more than 7 days after the date of last dose, assessments performed at the last visit that occurs before or within 7 days of the date of last dose will be assigned to the Week 72/ET analysis visit. The original SAP specified that, in this case, assessments performed at the last visit that occurs on or before the day of the date of last dose would be assigned to the Week 72/ET analysis visit.

- For early discontinued subjects whose Week 72/ET visit occurs before or within 7 days of the date of last dose, the post-baseline analysis visit windowing conventions for the ET visit will be used (see Section 6.1.6). The original SAP specified that these analysis visit windowing conventions would apply if the Week 72/ET visit occurs on or before the day of the date of last dose.
- If ItchRO assessments occur more than 7 days after the date of the Week 48 visit or last dose (if discontinuation is beforeWeek 48), the Endpoint (Week 48/ET) weekly average score will be based on assessments made on the last 7 days immediately following the date of the Week 48 visit or last dose (if discontinuation is before Week 48). The original SAP specified that, in this case, assessments made on the last 7 days immediately preceding (but not including) the Week 48 visit date or last dose (if discontinuation is before Week 48) would be the basis for the Endpoint (Week 48/ET) weekly average score.
- An algorithm for determining each scheduled visit date used in deriving weekly average ItchRO scores has been added.
- For subjects with >14 days of study drug interruption/withdrawal, the definition of a TEAE has been described.
- For demographics summaries, a subject's age at baseline will be presented. The original SAP specified age at enrollment.
- Secondary efficacy evaluations will include mean change from baseline to Week 48. The original SAP included this Week 48 analysis as a durability of effect analysis.
- TEAE presentations by study phase (i.e., Weeks 0-13, Weeks 14-48, > Week 48, and Overall) have been clarified, including the use of study day to determine each study phase (e.g., Week 0-13 represents study days 0-91).
- 3 additional AESIs (thyroid function abnormality, fat-soluble vitamin deficiency events, and growth retardation events) have been defined and added to the safety analysis.
- The second planned interim analysis has been changed to include subject activity up through Week 72 that has occurred on or before 14Jun2016. Over 90% of the enrolled subjects are expected to have completed the Week 48 assessments for this interim analysis. The clinical protocol and SAP (v1.0) described the second planned interim analysis as taking place after all enrolled subjects had completed the Week 48 (or early termination) study visit. Further, safety and efficacy analyses will be performed in the Safety Population. The original SAP (v1.0) specified the mITT and Per-Protocol populations for efficacy analyses. Details have been added to describe the analyses for the second planned interim analysis.
- For the ItchRO efficacy variable, the terminology has been changed to "ItchRO weekly average score". The terminology for this variable in the clinical protocol and original SAP (v1.0) is "ItchRO average daily score".

- The objective evaluating durability of effect of MRX was removed, along with associated analyses. Per PA3, durability of effect cannot be assessed in this study since it is not a placebo controlled trial and a treatment effect has not yet been established.
- Graphical displays are described in greater detail.
- The timing of data monitoring committee (DMC) meetings has been updated from "quarterly" to "at specified intervals" for the duration of the study.
- The Sponsor's name has been changed from "Lumena Pharmaceuticals, Inc." to "Lumena Pharmaceuticals LLC".
- The Shire Biostatistics Team Lead has been changed from Aparna Raychaudhuri, Ph.D. to Tom Tang, Ph.D.
- Jana Steinmetz, M.S. has been added as a co-author to the SAP.

The amended SAP will be finalized and submitted to file before the final database lock pertaining to Lumena Pharmaceuticals LLC study protocol LUM001-501.

Table of Contents

List of Tables

1. Overview

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Mirum Pharmaceuticals Inc. (Mirum) protocol LUM001-501, Open Label Study of the Efficacy and Long Term Safety of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis, dated 08-Feb-2019 (Amendment 4.1).

The original LUM001-501 protocol, dated 23-Oct-2013, planned for a 48-week treatment period. This treatment period included 4 parts: a 4-week dose-escalation (DE) period at doses up to 140 µg/kg/day; a 4-week stable dosing period at 140 µg/kg/day; a 5-week stable dosing period at 280 µg/kg/day, and a 35-week long-term exposure period.

There have been 5 protocol amendments to date. The summary list of changes to each of the protocol amendments are described in the final amendment, Protocol Amendment 4.1. Several of the protocol amendments included optional long-term treatment extensions and one of the later amendments added a twice-a-day (BID) dosing regimen.

Protocol Amendment 2, dated 05-Nov-2014, increased the number of subjects from 12 to approximately 24 evaluable subjects, increased the treatment period to 72 weeks, and added a 2nd interim analysis when all enrolled subjects reached the Week 48 visit.

Protocol Amendment 3, dated 02-Nov-2015, added an optional follow-up treatment period intended to offer the opportunity to eligible subjects to continue on treatment after Week 72 until the first to occur of the following: (i) up to 52 weeks of additional treatment (Week 124), or (ii) in the event that a new study opens to enrollment.

Protocol Amendment 4, dated 20-Dec-2016, allow continued participation in the Optional Follow-Up Treatment Period, beyond what was previously described in Protocol Amendment 3. Study treatment in the Optional Follow-up Treatment Period will continue until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially. This amendment also described the way in which eligible subjects who had previously discontinued from the study may re-enter and receive study treatment in the optional follow-up treatment period (After Week 72). Additional objectives for the Optional Follow-up Treatment Period were added, including the exploration of a twice daily (BID) dosing regimen (280 µg/kg BID) and higher daily dosing of LUM001.

The final protocol amendment, Amendment 4.1, dated 08Feb2019, primarily amended Protocol Amendment 4 to reflect the change of sponsorship from Lumena Pharmaceuticals LLC (Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc.) to Mirum Pharmaceuticals, Inc.

A subject may have been off study drug for an extended period of time during the course of their study treatment. The reasons for being off study drug include drug interruption (e.g., as directed by an investigator due to an AE), study drug compliance issues (e.g., missed consecutive doses), and dose interruptions due to being off study between protocol amendments. For example, a subject could complete study drug treatment through Week 72 under the Protocol Amendment 2 before implementation of Protocol Amendment 3 that extended treatment through Week 124. The subject could subsequently provide informed consent under the new amendment and be

re-initiated on study drug. Subjects with a drug interruption of at least 7 days had their study drug dose re-escalated.

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 Harmonisation (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 planned analysis identified in this SAP may be included in 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 addendum to 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 analysis plan include the study protocol and accompanying sample data collection documents.

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The amended SAP (Amendment 3) will be finalized and submitted to file before final analyses are produced.

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

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Objectives up to and Including Week 72

The objectives of this study (up to and including Week 72) are:

- To evaluate the long-term safety and tolerability of MRX in pediatric subjects with progressive familial intrahepatic cholestasis (PFIC).
- To evaluate the effect of MRX on serum bile acids in pediatric subjects with PFIC at 13 weeks of treatment.
- To evaluate the effect of MRX on biochemical markers of cholestasis and liver disease at 13 weeks of treatment.
- To evaluate the effect of MRX on pruritus in pediatric subjects with PFIC at 13 weeks of treatment.

2.1.2. Objectives of the Optional Follow-up Treatment Period (After Week 72)

Objectives of the Optional Follow-up Treatment Period (After Week 72) are:

- To offer eligible subjects in the LUM001-501 study continued study treatment beyond Week 72 until the first of the following occurs: (i) the subjects are eligible to enter another MRX study or (ii) MRX is available commercially.
- To obtain safety and efficacy data in subjects treated long-term on MRX.
- To explore a twice a day (BID) dosing regimen and higher daily dosing of MRX.
- To identify genetic indicators of treatment response, including use of exome sequencing.
- To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma.
- To assess palatability of the MRX formulation.

2.1.3. Exploratory Objective

An exploratory objective is:

- To allow the possibility of analysis of serum markers of treatment response using metabolomic and proteomic analysis on previously collected serum samples.

2.2. Study Endpoints

In addition to the time points specified in the protocol, efficacy and visit-based safety endpoints will also be analyzed in a LOCF approach at Week 72 (Week 48 for ItchRO endpoints) and Week 124 (Week 122 for ItchRO endpoints).

Subjects that did not complete at least 1 post-Week 72 assessment (Week 48 for ItchRO) will be excluded from all post-Week 72 (Week 48 for ItchRO) analyses. Subjects that did not complete at least 1 post-Week 124 assessment will be excluded from all post-Week 124 analyses.

2.2.1. Safety Endpoints

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

- Incidence of TEAEs including serious adverse events (SAEs), related to study drug, leading to withdrawal, special interest TEAEs, along with TEAEs by severity
- Change from baseline in clinical safety laboratory values at each analysis visit (where applicable)
- Observed serum AFP values at each analysis visit (where applicable)
- Physical examination findings, including body height, weight, and BMI at each analysis visit
- Vital signs at each analysis visit
- Concomitant medication usage

- Study drug exposure, including weekly average dose, total drug exposure, and treatment duration
- Plasma sample MRX concentrations at each analysis visit (where applicable)

Vital signs include heart rate (HR), respiratory rate, body temperature, and blood pressure (BP). 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.

Adverse events and study drug exposure will be summarized by PFIC type (PFIC1, PFIC2, and overall) and MRX dose (280 µg/kg QD and 280 µg/kg BID). Concomitant medications will be summarized overall and by PFIC type.

Laboratory results (with the exception of AFP) will be summarized by analysis visit as observed and change from baseline values. Percent change from baseline summaries will be included for select laboratory tests as described in Section 9.3.

For select fat-soluble vitamins, including 25-hydroxyvitamin D, alpha tocopherol / total lipids ratio, INR, retinol:RBP molar ratio, and vitamin A, abnormalities and clinically-meaningful shifts from baseline summaries will be presented for each analysis visit (as appropriate). For these FSVs, categories may include sufficient, insufficient, possibly insufficient, indeterminate, and excess (see Section 6.1.9 for specific definitions). A summary of corrected sodium abnormalities will also be presented.

Serum samples for AFP, a marker of hepatocellular carcinoma, are only drawn during the optional follow-up treatment period at every other 12-week repeating period clinic visit and at the EOT visit.

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study includes the following:

- Fasting sBA level change from Baseline (Day 0) to Week 13.

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- ALT, AST, and bilirubin (total and direct) change from Baseline (Day 0) to Week 13.
- Pruritus as measured by ItchRO (Obs) change from Baseline (Day 0) to Week 13.

ItchRO (Obs) secondary efficacy variables include: weekly average scores, 4-week morning average scores, and weekly morning average scores.

2.2.2.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study include the following:

- Change from Baseline in fasting sBA level at Weeks 4, 8, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Change from Baseline in pruritus as measured by ItchRO (Obs) weekly average score and weekly morning average score at Weeks 4, 8, 28, 48, 48/LOCF, 86, 98, 110, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Change from Baseline in pruritus as measured by ItchRO (Obs) 4-week morning average score at Weeks 13, 48, and 48/LOCF.
- Change from Baseline in ALT, AST, and bilirubin (total and direct) levels at Weeks 4, 8, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Change from Baseline in pruritus as measured by ItchRO (Obs) weekly evening average score at Weeks 4, 8, 13, 28, 48, 48/LOCF, 86, 98, 110, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Change from Baseline in pruritus as measured by ItchRO (Pt) weekly average score, weekly morning average score, and weekly evening average score at Weeks 4, 8, 13, 28, 48, 48/LOCF, 86, 98, 110, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Change from Baseline for ALP, 7α hydroxyl-4-cholesten-3-one (C4), total cholesterol, LDL-C, and GGT at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment
- Responder analysis: pruritus response rates as measured by ItchRO (Obs and Pt) weekly morning average scores at Weeks 13, 48, 48/LOCF, 98, 122, 122/LOCF, and every 12 weeks (where applicable) through the end of treatment; Responder definitions include change from baseline of ≤ -1.0, ≤ -1.33, ≤ -1.5, and ≤ -1.75.
- Responder analysis: sBA response rates at Weeks 13, 48, 72, 72/LOCF, 96, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment. Responder definitions include % change from baseline of ≤ -75, sBA ≤ 102 µmol/L, % change from baseline of ≤ -75 or sBA ≤ 102 µmol/L, and sBA ≤ 8.5 µmol/L (normalization).
- Responder analysis: sBA and ItchRO (Obs) weekly morning average scores at Weeks 13, 48, 72 (sBA only), 96 (Week 98 for ItchRO data), 120 (Week 122 for ItchRO data), 124/LOCF (Week 122/LOCF for ItchRO data), and every 12 weeks (where applicable) through the end of treatment. Responder definitions include each of the sBA responder definitions combined with an ItchRO (Obs) weekly morning average change from baseline score of ≤ -1.0 point.

- Responder analysis: liver function lab tests (C4, AST, ALT, and total bilirubin) at Weeks 13, 48, 72, 72/LOCF, 96, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment. Responder definitions include C4 % change from baseline ≥ 100, shift from >ULN (upper limit of normal) at baseline to normal in AST, shift from >ULN at baseline to normal in ALT, and shift from >ULN at baseline to normal in total bilirubin.
- Change from Baseline in the Clinician Scratch Scale (CSS) score at Weeks 2, 4, 8, 13, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment.
- Change from Baseline in height, weight, and BMI z-scores at Weeks 2, 4, 8, 12, 24, 36, 48, 60, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, and every 12 week (where applicable) through the end of treatment.
- Change from Baseline for Pediatric Quality of Life Inventory (PedsQL) Total Scale Score (parent), Multidimensional Fatigue Scale Score (parent), and Family Impact Total Scale Score at Weeks 13, 13/ET, 24, 48, 72, 72/LOCF, 84, 96, 108, 120, 124, 124/LOCF, and every 12 weeks (where applicable) through the end of treatment.

The following exploratory efficacy variables will only be presented in subject listings:

- patient impression of change (PIC)
- caregiver impression of change (CIC)
- caregiver global therapeutic benefit (CGTB)
- autotaxin
- aPTT
- prothrombin time
- INR
- triglycerides
- high-density lipoprotein cholesterol (HDL-C)
- FGF-19
- FGF-21
- sBA sub-species (taurocholic acid, taurochenodeoxycholic acid, tauroursodeoxycholic acid, taurodeoxycholic acid, taurolithocholic acid, glycocholic acid, glycoursodeoxycholic acid, glycochenodeoxycholic acid, glycodeoxycholic acid, glycolithocholic acid, cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, and lithocholic acid) and the ratio of cholic acid and chenodeoxycholic acid

2.2.2.4. Efficacy Parameter Descriptions

Itch Reported Outcome (ItchRO™)

The primary assessment of pruritus in this study will be evaluated using a newly developed Itch caregiver/patient reported outcome measure (ItchRO) administered as a twice daily eDiary. To accommodate potential cultural restrictions within the familial intrahepatic cholestasis 1 (FIC1) affected population a paper version of the ItchRO diary will be made available.

Caregivers for all subjects will complete the observer instrument: ItchRO (Obs). Children at least 9 years of age will complete the patient instrument: ItchRO (Pt). Children between the ages of 5 and 8 years of age or where the investigator has expressed concern about the subject's ability to reliably complete the data (e.g., due to developmental delay) will complete the patient instrument with the assistance of their caregiver. There will be no ItchRO (Pt) report for subjects under the age of 5. The itch score from the ItchRO (Obs) and the ItchRO (Pt) will be analyzed separately. 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.

For this instrument, the caregiver and/or subject indicate the itch severity in the morning and in the evening each day during the following periods:

- Screening through first 13 weeks of the treatment period
- 4 consecutive weeks that follow the Week 24 clinic visit
- 4 consecutive weeks including and preceding the Week 48 clinic visit
- 2 consecutive weeks that follow the Week 84, Week 96, Week 108, and Week 120 clinic visits
- 2-week periods following each recurring 12-week clinic visit during the optional extension follow-up treatment period.

ItchRO scores have a range of 0–4, with the higher score indicating increasing itch severity. For both the ItchRO (Obs) and the ItchRO (Pt), the average score between the morning and evening ItchRO reports represent the daily score: a measure of itching over the previous 24-hour period (see Section 6.1.9).

Pruritus scores as measured by the ItchRO instrument (observer and patient) include: weekly average score, weekly morning average score, weekly evening average score, 4-week average score, and 4-week evening average score. ItchRO scores will be calculated as described in Section 6.1.9.

Weekly average scores are calculated as the average of the daily scores over a defined study week consisting of the 7 days before the scheduled visit (i.e., Baseline [Day 0], Weeks 4, 8, 28, 48, 86, 98, 110, 122, and every 12 weeks thereafter). For the change from baseline calculation in weekly average ItchRO scores, baseline is defined as the weekly average ItchRO score in the week consisting of the 7 days immediately before the baseline visit date. 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.

Weekly morning and weekly evening average scores are calculated as the average of the morning/evening scores over a defined study week consisting of the 7 days before the scheduled visit (i.e., Baseline [Day 0], Week 4, 8, 28, 48, 86, 98, 110, 122, and every 12 weeks thereafter). For the change from baseline calculation in weekly morning and weekly evening average ItchRO scores, baseline is defined as the weekly morning/evening average ItchRO score in the period consisting of the 7 days immediately before the baseline visit date. Post-baseline weekly morning/evening average ItchRO scores are only computed if at least 4 of the 7 morning/evening ItchRO scores for the 7-day period are available.

4-week average scores are calculated as the average of the evening/morning scores over a defined period consisting of the 28 days before the scheduled visit (i.e., Baseline [Day 0], Weeks 4, 8, 28, and 48). For the change from baseline calculation in 4-week average ItchRO scores, baseline is defined as the weekly average ItchRO score in the period consisting of the 28 days immediately before the baseline visit date. Post-baseline 4-week average ItchRO scores are only computed if at least 20 of the 28 evening/morning ItchRO scores for the 28-day period are available.

In deriving weekly or 4-week average post-baseline ItchRO scores, each scheduled visit date will be determined based on the varying eDiary collection periods (as applicable): (A) Week 4, 8, 13, and 48, (B) Week 28, 86, 98, 110, and 122, and (C) recurring 12-week periods during the optional extension follow-up treatment period.

A. Week 4, 8, 13, and 48: The scheduled visit date is used.
B. Week 28, 86, 98, 110, and 122: Each scheduled visit date will be determined based on the date of the associated scheduled visit (i.e., Week 24, 84, 96, 108, and 120) plus 28 days for Week 28, and plus 14 days for Week 86, 98, 110, and 122.
C. Recurring 12-week periods: Each scheduled visit date will be determined based on the date of the associated scheduled visit plus 14 days.

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

Clinician Scratch Scale (CSS)

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

Caregiver Impression of Change (CIC)

The CIC is designed to assess the caregiver's perception of the subject's itching after various points of study drug treatment compared to his/her itching before 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: 1=Much better, 2=Better, 3=A little better, 4=No change, 5=A little worse, 6=Worse, 7=Much worse.

Patient Impression of Change (PIC)

The PIC is designed to assess the subject's perception of his/her itching after various points of study drug treatment compared to his/her itching before the start of treatment with study drug. The PIC is completed, by subjects who were 9 years of age or older. 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: 1=Much better, 2=Better, 3=A little better, 4=No change, 5=A little worse, 6=Worse, and 7=Much worse.

Caregiver Global Therapeutic Benefit (CGTB)

The CGTB questionnaire is designed to assess the caregiver's perception of the treatment benefits on the subject's itching compared to the side effects experienced with study drug. The questionnaire is designed for self-administration and uses a 5-point scale in which 1 designates the best outcome and 5 designates the worst outcome: 1=Definitely, 2=Somewhat, 3=About the same, 4=Maybe not, 5=Definitely not.

Pediatric Quality of Life Inventory (PedsQL)

The PedsQL™ [6] is a validated, modular instrument designed to measure health-related quality of life (HRQoL) in infants, children and adolescents. The PedsQL questionnaire is administered to subjects and/or caregivers depending on age using age-appropriate PedsQL modules. The PedsQL consists of developmentally appropriate forms for infants/children ages 1-12 months, 13-24 months, 2-4, 5-7, 8-12, and 13-18 years. Pediatric self-report is measured in children and adolescents ages 5-18 years, and parent proxy-report of child HRQoL is measured for children and adolescents ages 12 months to 18 years.

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

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

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

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

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

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

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

PedsQL scoring algorithms for scale scores are presented in Section 6.1.10.

Responder Definitions

Pruritus responder rates as measured by ItchRO (Obs) and ItchRO (Pt) weekly morning average scores are defined as:

- change from baseline average score ≤ -1.0 point
- change from baseline average score ≤ -1.33 points
- change from baseline average score ≤ -1.5 points
- change from baseline average score ≤ -1.75 points

Serum bile acid response rate endpoints are defined as:

- % change from baseline in sBA ≤ -75
- sBA ≤ 102 umol/L
- % change from baseline in sBA ≤ -75 or sBA ≤ 102 umol/L
- sBA ≤ 8.5 umol/L (normalized)

Serum bile acid and ItchRO (Observer) response rate endpoints are defined as:

- ItchRO (Observer) weekly morning average score ≤ -1.0 point and
  - % change from baseline in sBA ≤ -75
  - sBA ≤ 102 umol/L
  - % change from baseline in sBA ≤ -75 or sBA ≤ 102 umol/L
  - sBA ≤ 8.5 umol/L (normalized)

The sBA and ItchRO (Obs) response rates are summarized at Weeks 13, 48, 72 (sBA only), 96/98, and 120/122, as applicable. In general, responder definitions that are based on both sBA and ItchRO require matching visit data. The exception is for Week 96/98, where Week 96 sBA data and Week 98 ItchRO data will be used, and for Week 120/122, where Week 120 sBA data and Week 122 ItchRO data will be used.

Liver function lab test response rate endpoints are defined as:

- % change from baseline in C4 ≥ 100 (i.e., at least 2 times the baseline C4 level)
- shift in AST level from > ULN at baseline to normal
- shift in ALT level from > ULN at baseline to normal

- shift in total bilirubin level from > ULN at baseline to normal

2.2.3. Other Endpoints

2.2.3.1. Genetic Endpoints

For the purpose of this analysis plan, exploratory genetic analyses will be limited to the presentation of genotype data in a listing.

2.2.3.2. Metabolomic and Proteomic Endpoints

Exploratory responder analyses (metabolomics and proteomic investigation) is outside the scope of this analysis plan.

2.2.3.3. Palatability Endpoints

Palatability of the MRX formulation is assessed in all patients, by-proxy in patients <4 years old and by patient questionnaire in children ≥4 years old, at each clinic visit in the optional follow-up treatment period, with the exception of the DE and ADE visits.

3. Overall Study Design and Plan

3.1. Overall Design

This is an open-label study in children with PFIC designed to evaluate the safety and efficacy of MRX. The study is divided into 5 parts: a 4-week dose-escalation period, a 4-week stable dosing period at 140 µg/kg/day, a 5-week stable dosing period at 280 µg/kg/day, a 59-week long-term exposure period, and an optional follow-up treatment period for eligible participants who choose to stay on treatment with MRX. During the optional follow-up treatment period, subjects may be eligible for twice daily (BID) dosing based on efficacy as measured by sBA level and ItchRO score, and may have their dose of MRX increased to a maximum of 560 µg/kg/day (280 µg/kg BID). Subjects' participation in the optional follow-up treatment period will continue until the first of the following occurs: (i) subjects are eligible to enter another MRX study or (ii) MRX is available commercially.

A minimum of three interim analyses of key safety and/or efficacy parameters will be performed. The first interim analyses will occur after the first 12 subjects who meet the Per-Protocol (PP) population definition have completed the Week 13 study visit. The second interim analyses will occur after all enrolled subjects have completed the Week 48 (or Early Termination) study visit. The third interim analyses will be performed after all enrolled subjects have completed at least 6 months of treatment under PA4 (or the Early Termination visit). Subsequent interim analyses may be performed at periodic intervals.

3.2. Sample Size and Power

PFIC is a rare disease. The planned sample size of approximately 24 evaluable subjects with PFIC is based on practical considerations, rather than statistical considerations and desired power for a prespecified difference. As such, this study is designed to provide important information for this patient population that is needed for planning future studies.

3.3. Study Population

The study population is males and females between the ages of 12 months and 18 years, inclusive, diagnosed with PFIC and who have a gamma-glutamyl transpeptidase blood level less than 100 IU/L at screening.

3.4. Treatments Administered

All subjects will receive MRX, up to 560 µg/kg/day (given as BID doses of 280 µg/kg) or up to a maximum daily dose of 25 mg BID. Dosing will occur over a 13-week treatment period (comprised of 4-weeks dose-escalation [Dose Level 1-4], 4-weeks stable dosing at 140 µg/kg/day, and 5-weeks stable dosing at 280 µg/kg/day), followed by a 59-week long-term exposure period.

For the first 72 weeks of the study, each subject will receive either 1.0 mL (subjects weighing ≥10 kg) or 0.5 mL (subjects weighing <10 kg) of solution containing MRX orally as follows, administered as a daily morning dose:

- Dose Level 1: 14 µg/kg/day.
- Dose Level 2: 35 µg/kg/day.
- Dose Level 3: 70 µg/kg/day.
- Dose Level 4: 140 µg/kg/day.
- Dose Level 5: 280 µg/kg/day.

At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll over into the optional follow-up treatment period. Subjects eligible for the optional follow-up treatment period will continue treatment under dosing scenarios based on whether their MRX dosing will continue without interruption or interruption of <7 continuous days, or with interruption ≥7 days. Eligibility for BID dosing will be determined based on efficacy as measured by sBA level and ItchRO score.

The sBA value used for determination of ADE eligibility will be the most recent available value. The ItchRO score used for ADE eligibility will be derived from the most recent 2-week electronic diary collection period.

If a subject experiences intolerance (e.g., GI symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator in consultation with the Sponsor Medical Monitor may lower the dose for the remainder of the study. If the subject is on the BID dosing regimen, dose lowering will first be attempted with the afternoon dose. Subjects who were previously down-titrated may be re-challenged during the long-term exposure period.

3.4.1. Dose-Escalation Period

During the first 4 weeks of the study, the dose-escalation period, the dose will be increased at weekly intervals starting with Dose Level 1, up to Dose Level 4, to acclimate the subject to the study drug.

If a subject experiences intolerance (e.g., GI symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator in consultation with the

Sponsor Medical Monitor may lower the dose for the remainder of the study. In these circumstances an unscheduled visit will occur and the appropriate replacement study medication will be issued to the subject as quickly as possible.

3.4.2. Stable Dosing Period

Following the dose-escalation period (Day 0 – Week 4) subjects will continue MRX dosing through Week 8 using Dose Level 4, or the highest tolerated dose below Dose Level 4. For those subjects who tolerated Dose Level 4, at Week 8, the dose will be increased to Dose Level 5 until Week 13.

3.4.3. Long-term Exposure Period

Subjects will continue to receive MRX during the long-term exposure dosing treatment period at the highest dose achieved during the stable dosing treatment period. However, if a subject experiences intolerance due to GI symptoms, the investigator in consultation with the Sponsor Medical Monitor, may lower the dose for the remainder of the study. At the investigator's discretion and in consultation with the Sponsor Medical Monitor, subjects who were previously down-titrated may be re-challenged during the long-term exposure period.

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

3.4.4. Optional Follow-up Treatment Period (Post-Week 72)

Subjects eligible for the optional follow-up treatment period will continue treatment under dosing scenarios based on whether their MRX dosing will (1) continue without interruption or interruption of <7 continuous days, OR, (2) continue with interruption ≥7 days.

Eligibility for BID dosing will be determined based on efficacy as measured by sBA level and ItchRO score.

Subjects who enter the optional follow-up treatment period without MRX dosing interruption or with an interruption of <7 continuous days will be dosed in the following manner:

- Subjects with normal sBA level AND ItchRO score <1.5 will be maintained at the same dose level and will continue morning dosing only.
- Subjects with sBA level above normal AND/OR ItchRO 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.
  - The afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled, to a maximum dose of 280 µg/kg (or up to the maximum tolerated dose).

- The maximum daily dose will be 280 µg/kg BID, ie 560 µg/kg/day (max. 25 mg BID).

Subjects who enter the optional follow-up treatment period with a MRX dosing interruption of ≥7 days initially will receive morning dosing only and will undergo DE in the following manner:

- The morning dose will be initiated at Dose Level 2 (35 µg/kg) and doubled in weekly intervals to a maximum dose of 280 µg/kg, or up to the maximum tolerated dose.
- Once the morning dose of 280 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO score will be evaluated.
- Subjects with normal sBA AND ItchRO score <1.5 after morning dose-escalation will be maintained at the same dose level and will continue morning dosing only.
- Subjects with sBA above normal AND/OR ItchRO score ≥1.5 will begin BID dosing (afternoon dose-escalation) as outlined above.

Subjects will continue to receive study drug until they are eligible to enter another MRX study or until MRX is available commercially, whichever occurs first.

The maximum daily dose will be 280 µg/kg BID, ie 560 µg/kg/day (maximum 25 mg). If a subject experiences intolerance (e.g., GI symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician Investigator in consultation with the Sponsor Medical Monitor may lower the dose for the remainder of the study. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose.

The sBA value used for determination of ADE eligibility will be the most recent available value. The ItchRO score used for ADE eligibility will be derived from the most recent 2-week electronic diary collection period.

Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in the optional follow-up treatment period under Protocol Amendment 4.

3.4.5. End of Treatment

For subjects who did not consent to the optional follow-up treatment period, a subject is considered to have completed treatment if treatment was not permanently discontinued before the Week 72 visit. A follow-up phone contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.

For subjects who consented to the follow-up treatment period, an additional follow-up period disposition is collected in the electronic case report form (eCRF). The subject is considered to have completed treatment during the follow-up treatment period if study treatment was not permanently discontinued before the subject completing the EOT visit as defined in the most recent consent signed by the subject. A follow-up contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.

The end of study for the purposes of regulatory reporting is the point at which the last contact with the last subject during the protocol-specified scheduled follow-up treatment period is made.

3.5. Method of Assigning Subjects to Treatment Groups

This is an open-label study, and therefore all subjects will be assigned to treatment with MRX.

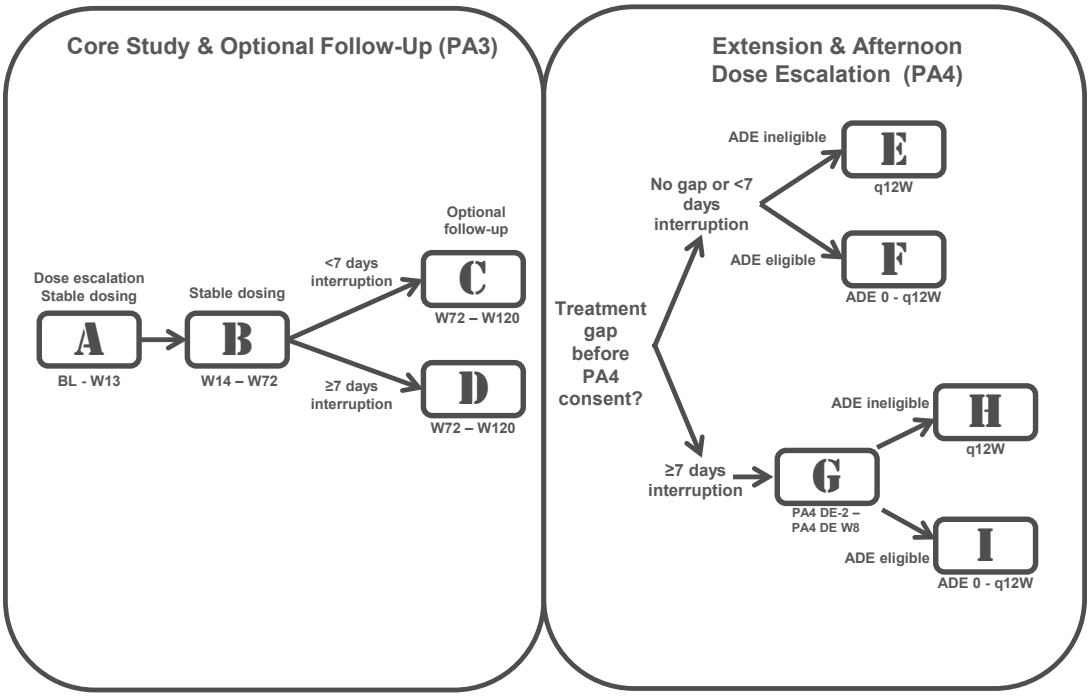
3.6. Study Period and Schedule of Procedures

For an individual subject, the study participation period will consist of a screening period of up to 6 weeks, a 13-week treatment period (including a dose-escalation period followed by two stable dose periods), and a 59-week long-term exposure period. Subjects who complete 72 weeks of treatment may be eligible to receive further treatment during the Optional Follow-up Treatment Period.

Overall Scheme and Corresponding Schedule of Procedures

The following schematic shows the study flow and corresponding Schedule of Procedures (A - I).

Study Termination and End of Treatment Procedures are outlined in Schedule J (Section 3.6.9). Any subject who completes or withdraws from the study should undergo all procedures specified for the EOT/ET visit (see Section 3.6.9).



The below sections show the schedule of procedures and the data to be collected on each study day or week.

3.6.1. Schedule of Procedures A – Dose-escalation and Stable Dosing Period: Baseline – Week 13

Study Period	Screening	Treatment Period								
		Dose-escalation					Stable Dosing Period			
Study Week			1	2	3	4	5	8	9	13
Study Day	Day -42	Day 0	7	14	21	28	35	56	63	91
Window (in days)			(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)
Informed Consent/Assent	X									
Eligibility Assessment (Inclusion/Exclusion)	X									
Demographics	X									
Medical History	X									
Physical Exam	X									
Body Weight & Height	X	X		X		X		X		X
Vital Signs [1]	X	X		X		X		X		X
Liver imaging (ultrasound) [2]	X									
Serum or Urine Pregnancy Test (if indicated)[3]	X	X		X		X		X		X
CBC with Differential [4]	X	X		X		X		X		X
Coagulation[4]	X	X		X		X		X		X
Chemistry Panel [4]	X	X		X		X		X		X
Lipid Panel [4,5,]		X		X		X		X		X
Cholestasis Biomarkers [4,5]	X	X		X		X		X		X
Fat-Soluble Vitamins [4,5,6]		X						X		X
Plasma Sample for MRX: US		X[a]		X[a]		X[a]		X[a]		X[a]
Plasma Sample for MRX: UK, EU, Australia		X[b]				X[b]				X[b]
PFIC Genotyping[7]	X									
Urinalysis [4]	X	X[c]		X[c]		X		X		X
Caregiver ItchRO/Patient ItchRO	X	X	X	X	X	X	X	X	X	X
Clinician Scratch Scale	X	X		X		X		X		X
PedsQL		X								X
Patient/ Caregiver Impression of Change										X
Caregiver Global Therapeutic Benefit										X
Enrollment	X									
Study Drug Supplied		X		X		X		X		X
Review Study Diaries & Assess Compliance		X		X		X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X

Study Period	Screening	Treatment Period								
		Dose-escalation					Stable Dosing Period			
Study Week			1	2	3	4	5	8	9	13
Study Day	Day -42	Day 0	7	14	21	28	35	56	63	91
Window (in days)			(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)
Phone Contact			X		X		X		X	

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 Screening ultrasound not required if an ultrasound completed ≤ 6 months is available.
3 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
4 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
5 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
6 Blood samples must be drawn before administration of vitamin supplementation.
7 Genotyping will be performed to provide a full characterization and documentation of the mutation type in support of the diagnosis of PFIC.

A In the US, , blood will be drawn ~4 hours post dosing for drug level analysis at Weeks 2, 8, and 13,. At Week 4, blood will be drawn ~2 hours post-dosing (fasting <4 hrs will be allowed to accommodate 2-hr post dose draw).
B In the UK, EU and AUS, , blood will be drawn ~4 hours post dosing for drug level analysis at Weeks 4 and 13.
c At indicated visits during the treatment period, oxalate will be part of UA.

	Clinic Visit
	Phone Contact

3.6.2. Schedule of Procedures B – Stable Dosing Treatment Period: Week 14 – Week 72

Study Period	Treatment Period (continued)										Study Termination	Safety Follow Up
	59 Week Long-term exposure											
Study Week	16	20	24	28	32	36	40	44	48	60	Week 72 (or Early Term[7])	30 days after final dose
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			X			X	X	X	
Body Weight & Height			X			X			X	X	X	
Vital Signs[1]			X			X			X	X	X	
CBC with Differential[2]			X			X			X	X	X	
Coagulation[2]			X			X			X	X	X	
Chemistry Panel[2]			X			X			X	X	X	
Lipid Panel[2,3]			X			X			X	X	X	
Cholestasis Biomarkers[2,3]			X			X			X	X	X	
FAT-Soluble Vitamins[2,3,4]			X			X			X	X	X	
Plasma Sample for MRX: All			X[a]			X[a]			X[a]	X[a]	X[a]	
Urinalysis[2]			X			X			X[b]	X	X[b]	
Urine Pregnancy Test [5]			X			X			X	X	X	
Clinician Scratch Scale			X			X			X	X	X	
Caregiver ItchRO/Patient ItchRO			X[c]	X[c] to Week 28				X[c]	X to Week 48			
PedsQL			X						X		X	
Patient/Caregiver Impression of Change									X		X	
Caregiver Global Therapeutic Benefit									X		X	
Study Drug Supplied			X			X			X	X	X[d]	
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
Follow-up Phone Contact[6]	X	X		X	X		X					X

Study Period	Treatment Period (continued)										Study Termination	Safety Follow Up
	59 Week Long-term exposure											
Study Week	16	20	24	28	32	36	40	44	48	60	Week 72 (or Early Term[7])	30 days after final dose
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)

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Subjects who withdraw early should complete all evaluations at this visit.

A At Weeks 24, 36, 48, 60 and 72 blood will be drawn approximately 4 hours post dosing for drug level analysis.
B At indicated visits during treatment period, oxalate will be part of the UA.
C During the long-term exposure period, daily completion of the study diary for 4 consecutive weeks will be required following the Week 24 & Week 44 clinic visits.
D For subjects entering optional Follow-up Treatment Period, once corresponding consent is signed.

	Clinic Visit
	Phone Contact

3.6.3. Schedule of Procedures C – Optional Follow-Up Treatment Period: Week 72 – Week 120

For Subjects With No Interruption in MRX Dosing or Interruption <7 Days. Includes Evaluation of Eligibility for BID Dosing Regimen.

Study Period	Treatment Period (continued)											
	Follow-up Treatment Period											
FTP Study Week	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120[c]**
Study Day	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**
Window (in days)	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Informed Consent/Assent for PA4[8]			X			X			X			X
Afternoon dose-escalation (ADE) eligibility assessment followed by shift in visit schedule[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Physical Exam			X			X			X			X
Body Weight & Height			X			X			X			X
Vital Signs[1]			X			X			X			X
CBC with Differential[2]			X			X			X			X
Coagulation[2]			X			X			X			X
Chemistry Panel[2]			X			X			X			X
Lipid Panel[2,3]			X			X			X			X
Cholestasis Biomarkers[2,3]			X			X			X			X
FAT-Soluble Vitamins[2,3,4]			X			X			X			X
Optional Genotyping[5]			X									
Exome Sequencing Sample[10]			X[10]			X[10]			X[10]			X[10]
Urinalysis[2]			X			X			X[a]			X[a]
Serum or Urine Pregnancy Test (if indicated)[6]			X			X			X			X
Clinician Scratch Scale			X			X			X			X
Caregiver ItchRO/ Patient ItchRO			X[b]	X[b] to Week 86		X[b]	X[b] to Week 98		X[b]	X[b] to Week 110		X[b]

Study Period	Treatment Period (continued)											
	Follow-up Treatment Period											
FTP Study Week	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120[c]**
Study Day	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**
Window (in days)	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
PedsQL			X			X			X			X
Patient/Caregiver Impression of Change									X			X
Caregiver Global Therapeutic Benefit									X			X
Study Drug Supplied			X			X			X			
Assess Study Drug Compliance			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
Follow-up Phone Contact[7]	X	X		X	X		X	X		X	X	

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 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 PFIC.
6 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
7 Subjects must be available to receive a phone call from study staff.
8 Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent patient for Protocol Amendment 4 at next clinic visit.
9 Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent has been signed, site will assess patient eligibility for Protocol Amendment 4. Depending on outcome of ADE eligibility assessment, patient will move into either Schedule of Procedures E or F. Of note: It is possible that subject will not necessarily complete up through Week 120 before they move to Schedule of Procedures E or F.
10 Sample will require consenting under PA4 and will be drawn once, at the time of such re-consent.

A At indicated visits during treatment period, oxalate will be part of the UA.
B During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 84, Week 96, Week 108, and Week 120 visits.
C A Week 124 (or ET) visit (Study Day 868 ± 14 days) was included in Protocol Amendment 3.

Clinic Visit
Phone Contact

3.6.4. Schedule of Procedures D – Optional Follow-Up Treatment Period: Week 72 – Week 120

For Subjects With Interruption in MRX Dosing ≥7days. Includes Evaluation of Eligibility for BID Dosing Regimen.

Study Period	Treatment Period (continued)																
	Follow-up Treatment Period Dose-escalation (DE)						Continuation of 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[c]
Study Day	-14	0	511*	518*	525*	532*	560*	588*	616*	644*	672*	700*	728*	756*	784*	812*	840*
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)
Informed Consent/Assent for study re-entry under PA3[11]	X																
Assess Eligibility for study re-entry	X	X															
Informed Consent/Assent for PA4								X			X			X			X
Afternoon dose-escalation (ADE) eligibility assessment followed by shift in visit schedule[9]								X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Physical Exam	X	X		X		X		X			X			X			X
Body Weight & Height	X	X		X		X		X			X			X			X
Vital Signs[1]	X	X		X		X		X			X			X			X
CBC with Differential[2]	X	X		X		X		X			X			X			X
Coagulation[2]	X	X		X		X		X			X			X			X
Chemistry Panel[2]	X	X		X		X		X			X			X			X
Lipid Panel[2,3]	X	X		X		X		X			X			X			X
Cholestasis Biomarkers[2,3]	X	X		X		X		X			X			X			X
FAT-Soluble Vitamins[2,3,4]	X	X		X		X		X			X			X			X

Study Period	Treatment Period (continued)																
	Follow-up Treatment Period Dose-escalation (DE)						Continuation of 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[c]**
Study Day	**-14**	**0**	**511***	**518***	**525***	**532***	**560***	**588***	**616***	**644***	**672***	**700***	**728***	**756***	**784***	**812***	**840***
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Optional Genotyping[5]	X																
Urinalysis[2]	X	X		X		X		X			X			X[a]			X[a]
Exome Sequencing Sample[10]								X[10]			X[10]			X[10]			X[10]
Serum or Urine Pregnancy Test (if indicated)[6]	X	X		X		X		X			X			X			X
Clinician Scratch Scale	X	X		X		X		X			X			X			X
Caregiver ItchRO/ Patient ItchRO								X[b]	X[b] to Week 86		X[b]	X[b] to Week 98		X[b]	X[b] to Week 110		X[b]
PedsQL		X						X			X			X			X
Patient/Caregiver Impression of Change														X			X
Caregiver Global Therapeutic Benefit														X			X
Study Drug Supplied		X		X		X		X			X			X			
Assess Compliance				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
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[7]			X		X		X		X	X		X	X		X	X	

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 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 PFIC.
6 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
7 Subjects must be available to receive a phone call from study staff.

Study Period	Treatment Period (continued)																
	Follow-up Treatment Period Dose-escalation (DE)						Continuation of 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[c]
Study Day	-14	0	511*	518*	525*	532*	560*	588*	616*	644*	672*	700*	728*	756*	784*	812*	840*
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)

8 Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent patient for Protocol Amendment 4 at next clinic visit.

9 Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent has been signed, site will assess patient eligibility for Protocol Amendment 4. Depending on outcome of ADE eligibility assessment, patient will move into either Schedule of Procedures E or F. **Of note: It is possible that subject will not necessarily complete up through Week 120 before they move to Schedule of Procedures E or F.**

10 Sample will require re-consenting under PA4 and will be drawn once, at the time of such re-consent.

11 For subjects re-entering under Protocol Amendment 3, Baseline laboratory values are considered those collected at re-entry visit DE-2 weeks

* Calculation of Study Day includes subject's participation through the first 72 weeks.

A At indicated visits during treatment period, oxalate will be part of the UA.

B During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 84, Week 96, Week 108, and Week 120 visits.

C A Week 124 (or ET) visit (Study Day 868 ± 14 days) was included in Protocol Amendment 3.

Clinic Visit
Phone Contact

3.6.5. Schedule of Procedures E – Extension of Optional Follow-Up Treatment Period, Subject Ineligible for ADE

Applicable as follows:

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

	Below study activities repeat in recurring 12 week periods[7]		
Repeating Period Week	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**4 weeks after consent under PA4**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
Physical Exam			X
Body Weight & Height			X
Vital Signs[1]			X
CBC with Differential[2]			X
Coagulation[2]			X
Chemistry Panel[2]			X
Lipid Panel[2,3]			X
Cholestasis Biomarkers[2,3]			X
FAT-Soluble Vitamins[2,3,4]			X
Urinalysis[2]			X[a]
AFP Sample			X[8]
Serum or Urine Pregnancy Test (if indicated)[5]			X
Clinician Scratch Scale			X
Caregiver ItchRO/ Patient ItchRO			X (collected for 2 week period following this visit)
PedsQL			X
Palatability Questionnaire			X
Study Drug Supplied			X

	Below study activities repeat in recurring 12 week periods[7]		
Repeating Period Week	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**4 weeks after consent under PA4**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
Assess Compliance			X
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Follow-up Phone Contact[6]	X	X	

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study or (ii) MRX is available commercially.
8 Sample will be drawn at every other clinic visit.

A At indicated visits during treatment period, oxalate will be part of the UA.

	Clinic Visit
	Phone Contact

Schedule of Procedures F – Extension of Optional Follow-Up Treatment Period, Subjects **eligible** for ADE

Applicable as follows:

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

Study Period	**Follow-up Treatment Period Afternoon Dose-escalation (ADE)**							**Study activities repeat in recurring 12 week periods after completion of the ADE period7**		
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[1]	X			X			X			X
CBC with Differential[2]	X			X			X			X
Coagulation[2]	X			X			X			X
Chemistry Panel[2]	X			X			X			X
Lipid Panel[2,3]	X			X			X			X
Cholestasis Biomarkers[2,3]	X			X			X			X

Study Period	Follow-up Treatment Period Afternoon Dose-escalation (ADE)							Study activities repeat in recurring 12 week periods after completion of the ADE period7		
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)**
FAT-Soluble Vitamins[2,3,4]	X			X			X			X
Urinalysis[2]	X			X			X			X[a]
AFP Sample										X[8]
Plasma Sample for MRX[9]	X			X			X			X[9]
Serum or Urine Pregnancy Test (if indicated)[5]	X			X			X			X
Clinician Scratch 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	X			X			X			X
Assess Compliance	X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X		X

Study Period	Follow-up Treatment Period Afternoon Dose-escalation (ADE)							Study activities repeat in recurring 12 week periods after completion of the ADE period7		
Study Week	**ADE Day 0**	**ADE Week 1**	**ADE Week 2**	**ADE Week 4**	**ADE Week 5**	**ADE Week 6**	**ADE Week 8**	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**To be scheduled as soon as ADE eligibility is confirmed and materials are on-site**							**The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.**		
Window (in days)	**N/A – see above**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±7)**	**(±7)**	**(±14)**
Adverse Events	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[6]		X	X		X	X		X	X	

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study or (ii) MRX is available commercially.
8 Sample will be drawn at every other clinic visit.
9 PK sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose-escalation period.

A At indicated visits during treatment period, oxalate will be part of the UA.

	Clinic Visit
	Phone Contact

3.6.6. ParticipantSchedule of Procedures G – Optional Follow-Up Treatment Period: Re-Entry Under Protocol Amendment 4

Applicable as follows:

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

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

Study Period	Protocol Amendment 4 Follow-up Treatment Period Dose-escalation (DE)						
PA4 DE Study Week	**PA4 DE -2**	**PA4 DE Day 0**	**PA4 DE Week 1**	**PA4 DE Week 2**	**PA4 DE Week 3**	**PA4 DE Week 4**	**PA4 DE Week 8**
Scheduling Considerations	**-14**	**0**					
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**
FAT-Soluble Vitamins[2,3,4]	X	X		X		X	
Urinalysis[2]	X	X		X		X	
Exome Sequencing Sample[7]	X						
Serum or Urine Pregnancy Test (if indicated)[5]	X	X		X		X	
Clinician Scratch Scale	X	X		X		X	
Caregiver ItchRO/ Patient ItchRO						X (collected for 2 week period following this visit)	
PedsQL		X					
Study Drug Supplied		X		X		X	
Assess Compliance				X		X	
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Follow-up Phone Contact[6]			X		X		X

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Sample will be drawn once, at the time of consent under PA4.
8 For subjects re-entering under Protocol Amendment 4, Baseline laboratory values are considered those collected at re-entry visit PA4 DE-2 weeks.

Clinic Visit
Phone Contact

3.6.7. Schedule of Procedures H – Optional Follow-Up Treatment Period: Re-Entry Under Protocol Amendment 4, Subject Ineligible for ADE

	Below study activities repeat in recurring 12 week periods[7]		
Repeating Period Week	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**The Week 4 visit of the first repeating period will take place 4 weeks after PA4 DE Week 8**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
Physical Exam			X
Body Weight & Height			X
Vital Signs[1]			X
CBC with Differential[2]			X
Coagulation[2]			X
Chemistry Panel[2]			X
Lipid Panel[2,3]			X
Cholestasis Biomarkers[2,3]			X
FAT-Soluble Vitamins[2,3,4]			X
Urinalysis[2]			X[a]
AFP Sample			X[8]
Serum or Urine Pregnancy Test (if indicated)[5]			X
Clinician Scratch Scale			X
Caregiver ItchRO/ Patient ItchRO			X (collected for 2 week period following this visit)
PedsQL			X
Palatability Questionnaire			X
Study Drug Supplied			X
Assess Compliance			X
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Follow-up Phone Contact[6]	X	X	

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

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study or (ii) MRX is available commercially.
8 Sample will be drawn at every other clinic visit.

A At indicated visits during treatment period, oxalate will be part of the UA.

	Clinic Visit
	Phone Contact

3.6.8. Schedule of Procedures I – Optional Follow-Up Treatment Period: Re-Entry Under Protocol Amendment 4, Subject Eligible For ADE

Study Period	Follow-up Treatment Period Afternoon Dose-escalation (ADE)							Study activities repeating in recurring 12 week periods after completion of the ADE period[7]		
FTP Study Week	ADE Day 0	ADE Week 1	ADE Week 2	ADE Week 4	ADE Week 5	ADE Week 6	ADE Week 8	Week 4	Week 8	Week 12
Scheduling Considerations	To be scheduled as soon as ADE eligibility is confirmed and materials are on-site							The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.		
Window (in days)	N/A – see above	(±2)	(±2)	(±2)		(±2)	(±2)	(±7)	(±7)	(±14)
Physical Exam	X			X			X			X
Body Weight & Height	X			X			X			X
Vital Signs[1]	X			X			X			X
CBC with Differential[2]	X			X			X			X
Coagulation[2]	X			X			X			X
Chemistry Panel[2]	X			X			X			X
Lipid Panel[2,3]	X			X			X			X
Cholestasis Biomarkers[2,3]	X			X			X			X
FAT-Soluble Vitamins[2,3,4]	X			X			X			X
Urinalysis[2]	X			X			X			X[a]
AFP Sample										X[8]
Plasma Sample for MRX[9]	X			X			X			X[9]
Serum or Urine Pregnancy Test (if indicated)[5]	X			X			X			X

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

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

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another MRX study or (ii) MRX is available commercially.
8 Sample will be drawn at every other clinic visit.
9 PK sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose-escalation period.

A At indicated visits during treatment period, oxalate will be part of the UA.

	Clinic Visit
	Phone Contact

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

	EOT / ET	Safety Follow Up
Scheduling Considerations	**To take place upon completion of study[7] or at the time of early withdrawal**	**Minimum of 30 days after final dose**
Physical Exam	X	
Body Weight & Height	X	
Vital Signs[1]	X	
CBC with Differential[2]	X	
Coagulation[2]	X	
Chemistry Panel[2]	X	
Lipid Panel[2,3]	X	
Cholestasis Biomarkers[2,3]	X	
FAT-Soluble Vitamins[2,3,4]	X	
Urinalysis[2]	X[a]	
AFP Sample	X	
Serum or Urine Pregnancy Test (if indicated)[5]	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[6]		X

	EOT / ET	Safety Follow Up
Scheduling Considerations	**To take place upon completion of study[7] or at the time of early withdrawal**	**Minimum of 30 days after final dose**

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 of Protocol Amendment 4 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential.
6 Subjects must be available to receive a phone call from study staff.
7 Will take place when the first of the following occur: (i) subjects are eligible to enter another MRX study or (ii) MRX is available commercially.

A At indicated visits during treatment period, oxalate will be part of the UA.

	Clinic Visit
	Phone Contact

4. Statistical Analysis and Reporting

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

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS (release 9.4 or higher).

Data summaries will be presented for PFIC1 and PFIC2 subjects independently and for all subjects combined. Select efficacy variables will also be presented by PFIC2 subtype (truncating and non-truncating).

Continuous (quantitative) variables will be summarized using descriptive statistics including number of subjects (n) with non-missing values, mean, 2-sided 95% confidence interval (CI) for the mean, standard deviation (SD), and/or standard error of the mean (SE), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the number and percentage of subjects who are in each particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis population for the PFIC type/subtype, and/or treatment phase, unless otherwise specified.

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

The minimum and maximum values for derived and select observed values will be reported as follows, with measures of location and spread following the above rules. Derived values for corrected sodium, 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, 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, RBP, retinol:RBP molar ratio, and alpha tocopherol/total lipids will be reported to 2 decimal places.

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

All statistical tests will be conducted using 2-tailed tests at the 0.05 significance level, with corresponding 95% CIs and p-values presented. A p-value of ≤ 0.10 but > 0.05 will be considered evidence of a trend.

All final, planned analyses identified in this SAP will be performed after all relevant study data have been processed and integrated into the analysis database, and the database has been locked. Any post-hoc, exploratory analysis completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in Section 9.8 of the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified as such in the text of the CSR.

4.2. Data Monitoring

A data monitoring committee (DMC) will review SAE data and other key subject safety and study data at specified intervals for the duration of the study. The DMC will be composed of at least 2 members who are otherwise independent from the conduct of the study and 1 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 the sponsor to stop or modify the trial if safety concerns are identified. Further details regarding the structure, function, and operation of the DMC are detailed in the DMC charter.

4.3. Interim and Final Analyses

A minimum of 4 analyses of the data are planned: at least 3 planned interim analyses and a final analysis. The first planned interim analysis of safety and efficacy parameters will be performed after the first 12 subjects who met the PP Population definition have completed the Week 13 study visit. This analysis will provide initial information about the safety and potential therapeutic activity of MRX in the study population. A second planned interim analysis will be performed after all enrolled subjects have completed the Week 48 (or Early Termination) study visit. This analysis includes subject activity up through Week 72 that has occurred on or before 14Jun2016 and will provide an assessment of the long-term safety and efficacy of MRX. A third planned interim analysis will be performed after all enrolled subjects have completed at least 6 months of treatment under Protocol Amendment 4 (or the Early Termination visit). This analysis will provide an assessment of the long-term safety and efficacy of MRX. A final analysis of the data will be performed after all enrolled subjects have completed their final (or Early Termination) study visit. Details of these analyses are specified below.

The results of the interim analyses may lead to changes in the study design. Staff directly involved in the conduct of the study, including the DMC, will review the results of the interim analyses. Interim study information may be shared with study investigators, investigator staff, study monitors, or sponsor employees or other personnel.

4.3.1. First Interim Analyses

The first planned interim analyses will take place after the first 12 subjects who meet the PP Population criteria have completed the Week 13 study visit. This analysis will present data on key safety and efficacy variables, and is intended to provide initial information about the potential therapeutic activity of MRX in the study population.

Safety analyses will include all available AE data from all subjects in the Safety Population. Efficacy analyses will include all available primary and secondary efficacy data through the first interim analysis cut-off (March 23, 2015) in the mITT and PP populations.

The following data will be presented for the first interim analysis:

- Demographic data (PP and Safety populations)
- Disease history and baseline disease characteristics (PP and Safety populations)
- Treatment compliance (Safety Population)
- Fasting sBA (PP and mITT populations)
- ALT (PP and mITT populations)
- Total bilirubin (PP and mITT populations)
- Direct bilirubin (PP and mITT populations)
- C4 (PP and mITT populations)
- ItchRO weekly average score (observer and patient) (PP and mITT populations)
- PedsQL Total Scale Score (Parent) (PP and mITT populations)
- AEs (Safety Population)

Data will be presented with descriptive statistics only. Efficacy variables will be tabulated by all available visits (including Week 13/ET) with changes from baseline.

Treatment compliance for ongoing subjects will be based on the date of the latest visit to have accountability data at the time of the cut. For efficacy outputs, if a subject is ongoing, the cut-off for determining if a visit is on-treatment for the Week 13/ET summaries is based on the latest visit from all domains.

See Section 14.1 for details of the tables to be included in the first interim analysis.

For the first interim analysis, subject listings will be generated for AEs, SAEs, and efficacy data, including efficacy laboratory tests, ItchRO (Pt and Obs) reported outcomes, PIC, CIC, CGTB, and CSS scores. A figure depicting individual subject exposure to study drug over the treatment period will also be provided.

4.3.2. Second Interim Analyses

The second planned interim analyses will be performed after all enrolled subjects have completed the Week 48 (or Early Termination) study visit and will include subject activity up through Week 72 that has occurred on or before 14Jun2016. This analysis will present data on key safety and efficacy variables, and is intended to provide initial information about the potential long-term therapeutic activity of MRX in the study population. For this interim analysis, over 90% of the enrolled subjects are expected to have completed the Week 48 assessments.

Safety analyses will include any AE that started on or before the 14Jun2016 analysis cut-off date. Efficacy analyses will include all available efficacy data through the second interim analysis cut-off. Safety and efficacy analyses will be performed in the Safety Population.

For this interim analysis, the last dose date will be set to 14Jun2016 for subjects that are ongoing in the study and on treatment after the cut-off date. For the interim analysis, any AE that started after the cut-off date will be excluded from the safety analyses.

Section 14 provides a complete list of tables and listings, along with a description of the figures, to be included in the second planned interim analysis. All subject listings will be sorted by PFIC type (i.e., PFIC1, PFIC2).

Analyses described in SAP Amendment 1 will be followed for the second planned interim analyses.

4.3.3. Third Interim Analyses

The third planned interim analyses will be performed after all enrolled subjects have completed at least 6 months of treatment under PA4 (or the Early Termination visit) and will thus include subject activity that has occurred on or before 20Feb2018. This analysis will provide an assessment of the long-term safety and efficacy of MRX.

Safety analyses will include any AE that started on or before the 20Feb2018 analysis cut-off date. Efficacy analyses will include all available efficacy data through the analysis cut-off date. Efficacy analyses will be performed in the mITT Population. Safety and all other analyses will be performed in the Safety Population.

For this interim analysis, the last dose date will be set to 20Feb2018 for subjects that are ongoing in the study and on treatment after the cut-off date. For the interim analysis, any AE that started after the cut-off date will be excluded from the safety analyses.

Section 14.1 provides a complete list of tables to be included in the third planned interim analysis. The following figures will also be included in this interim analysis (see Section 14.2): change from baseline in sBA levels over time (Figure 14.2.4.1), change from baseline in ItchRO (Obs) 4-week morning average score over time (Figure 14.2.9.1.2), change from baseline in CSS over time (Figure 14.2.14), study drug exposure by subject (Figure 14.3.1), and TEAEs over time and individual subject (Figure 14.3.2). A subject profile listing that includes select labs and pruritus (itch/scratch) scores (Listing 16.1.1) will also be included for this analysis (see Section 14.3).

Analyses described in SAP Amendment 2 will be followed for the third planned interim analyses. At the time of the analysis cut-off date (20Feb2018), all subjects had either withdrawn early or completed the study through Week 72. The LUM001-501 CSR, dated 07May2020, focused on data collected or assessed through Week 72.

4.3.4. Final Analysis

Safety analyses will include all subjects in the Safety Population. Efficacy analyses will include all subjects in the ITT analysis population. Analyses described in SAP Amendment 3 will be followed for the final analyses.

4.3.5. Posthoc Analyses

Additional analyses may be performed to explore both safety and efficacy measures collected during this study. The precise methods and analyses will be determined after the final analyses are performed. Thus, all such analyses will be interpreted cautiously and not used for formal inference.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population is defined as all subjects who were assigned to receive and received at least 1 dose of the study drug. The Safety Population will be used for all safety analyses.
- **Modified Intent-To-Treat Population (mITT):** The mITT Population is defined as all subjects who were assigned, received at least 1 dose of treatment, and have at least 1 post-baseline primary efficacy assessment (i.e., serum bile acid laboratory value). The mITT Population is the main population for efficacy analysis for the 3rd planned interim analysis.
- **Intent-To-Treat Population (ITT):** The ITT Population is defined as all subjects who were assigned, and received at least 1 dose of treatment. For the final analyses, the ITT Population is the analysis set used for efficacy analyses.
- **Per-Protocol Population (PP)**: The PP Population consists of all subjects in the mITT Population who do not have a major, non-evaluable protocol deviation (see Section 7.2). The PP Population was used in the 1st planned interim analysis. No summaries are planned for the final analyses using this analysis population.

Because PFIC is a rare disease, siblings were allowed to enroll in the study. The use of siblings in each analysis population is discussed in Section 6.1.11.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For all visit-based efficacy analyses, and for visit-based safety data that is collected or assessed before an extended (> 28-day) drug interruption period (between protocol amendments), the following baseline definition will be used for change from baseline values:

- Baseline (Day 0): The observation obtained at Study Day 0 (before first dose of study drug) will be used as the baseline (Day 0) observation for all calculations of change from baseline (Day 0). If Study Day 0 is not available/missing, the last value obtained during the screening period is used as the baseline (Day 0) observation.

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 (Study Day 0). For ItchRO weekly morning/evening average scores, baseline is defined as the average of morning/evening scores consisting of the 7 days immediately before the baseline visit. For the ItchRO 4-week morning/evening average scores, baseline is defined as the average of morning/evening scores in the 4-week period consisting of the 28 days immediately before the baseline visit (Study Day 0). The derivation of weekly and 4-week baseline ItchRO average scores will use up to 7 and 28 daily scores, respectively, with no minimum daily requirement applied.

Visit-based safety data collected or assessed after a > 28-day drug interruption period (between protocol amendments) will not be included in analysis summaries.

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

General

In addition to the time points specified in the protocol, efficacy and visit-based safety endpoints will also be analyzed in a LOCF approach at Week 72 (Week 48 for ItchRO endpoints) and Week 124 (Week 122 for ItchRO endpoints).

If any assessment/visit occurs more than 7 days after the date of last dose on PA2, PA3, or PA4 (i.e., “last dose”), and before dose re-initiation, the assessments performed during that visit will not be used in analysis summaries (see Section 6.1.6).

Rules for handling missing or partial AE, concomitant medication, date of birth, or original PFIC diagnosis dates are described in Section 6.1.11.

The sensitivity of efficacy and safety results to missing data assumptions are discussed in Section 8.4.

Primary and Secondary Efficacy Endpoints

Based on the intent-to-treat principle, all subjects included in the ITT Population will be included in the primary analysis of primary and secondary efficacy endpoints.

LOCF Imputation

In addition to the time points specified in the protocol, efficacy and visit-based safety variables will also be analyzed (as a sensitivity analysis) at the following LOCF time points:
Week 48/LOCF (ItchRO variables only), Week 72/LOCF (non-ItchRO variables),
Week 122/LOCF (ItchRO variables only), and Week 124/LOCF (non-ItchRO variables), where appropriate.

Subjects that did not complete at least 1 post-Week 72 assessment (Week 48 for ItchRO) will be excluded from all post-Week 72 (Week 48 for ItchRO) analyses. Subjects that did not complete at least 1 post-Week 124 assessment will be excluded from all post-Week 124 analyses.

Each LOCF time point is defined as the last post-baseline value obtained on or before the date of "last dose" plus 7 days within the defined study period (i.e., Week 48, 72, 122, or 124). For ItchRO measurements, averages scores at LOCF time points will use the last average score prior to the designated LOCF time point (i.e., Week 48 or Week 122) carried forward.

ItchRO Assessments

In the event that either the morning or evening ItchRO reports are not completed within the allowed reporting window, the completed report will represent the daily score. In the event that a subject/caregiver failed to complete both the morning and evening report, the daily score for that day will be treated as missing data.

If a subject/caregiver is not compliant with reporting ItchRO assessments during the 7-day period before a study visit, the weekly average score from the most recent, previous compliant 7-day period will be used in a LOCF format. For non-compliant 4-week ItchRO assessments (i.e., morning and evening scores), the most recent compliant 28-day period will be used, where the 28 days minus the 7 days immediately before the study visit will be used. This process will be repeated as necessary. For example, if the 28-day period before the Week 8 visit (e.g., Study Days 28-55) is non-compliant, then Study Days 21-48 would be used. If that 4-week period is non-compliant then the 4-week ItchRO morning/evening score would be missing. Additionally, the same ItchRO assessment day (morning/evening/daily score) will not be used across different weekly/4-week time periods (i.e., no overlap).

For post-baseline average ItchRO scores, on-study compliance is defined as having at least 4 of the 7 daily scores for a 7-day period, and at least 20 of the 28 daily morning/evening scores for a 28-day period. The derivation of weekly and 4-week baseline ItchRO average scores will use up to 7 and 28 daily scores, respectively, with no minimum daily requirement applied.

ItchRO assessments that occur during non-dosing days that are more than 7 days after the date of the "last dose", and before dose re-initiation, will not be used for deriving ItchRO average scores.

PedsQL Assessments

For PedsQL scale scores, if more than 50% of the items in the scale are missing, the scale score is not computed (see Section 6.1.10).

Responder Definitions

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

Adverse Event Severity and 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 reported relationship to study drug value will be considered as "potentially related" to study drug. If the severity of an AE is missing, the severity will be reported as "severe".

Fat Soluble Vitamin (FSV) Data

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

6.1.6. 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. Table 1 addresses scheduled post-baseline assessments; baseline assessments are described in Section 6.1.1. Scheduled visits will be selected over unscheduled visits.

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

The analysis visit windows in Table 1 will also be used for all visit-based safety assessments that occurred before an extended (>28-day) drug interruption (due to a protocol amendment), including those subjects without such a drug interruption. Visit-based safety data collected or assessed after a > 28-day drug interruption period (between protocol amendments) will not be included in analysis summaries.

For those subjects who discontinue early from the study, Table 1 will also be used to assign the appropriate analysis visit to the ET visit. For subjects that were dose-escalated after a drug interruption of > 28 days (between protocol amendments), the data collected/assessed during the dose-escalation period (i.e., DE Week -2 and DE Day 0 for both PA3 and PA4) will not be assigned to a post-dose analysis visit.

The study day will be calculated for each scheduled or ET post-baseline visit (and/or assessment) relative to the date of first dose of study drug, and compared to the assessment window presented in Table 1, 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 60 but a specific assessment (e.g., PedsQL or CGTB score) was not scheduled at that visit (see Section 3.6, Study Period and 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 1. For analysis visits past Week 48, ItchRO average weekly scores are based on the 2-week period following the scheduled in-clinic visit, rather than the week before the scheduled in-clinic visit. Thus, the "Analysis Visit" and "Analysis Visit Name" will be adjusted accordingly (e.g., "Week 86" rather than "Week 84").

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.

Adverse events and concomitant medications are exceptions to the above rules. The treatment of AEs and concomitant medications that start during periods of dosing gaps are discussed in Section 6.1.11.

Table 1 Analysis Visit Windows – Visit-Based 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 ─ 42
8	Week 8	56	43 ─ 74
13	Week 13	91	75 – 130
24	Week 24	168	131 – 210
36	Week 36	252	211 – 294
48	Week 48	336	295 – 378
60	Week 60	420	379 – 461
72	Week 72	504	462 – 546
84	Week 84	588	547 – 630
96	Week 96	672	631 – 704
108	Week 108	756	705 – 788
120	Week 120	840	789 – 872
132	Week 132	924	873 – 956
144	Week 144	1008	957 – 1040
156	Week 156	1092	1041 – 1124
168	Week 168	1176	1125 – 1203
180	Week 180	1260	1204 – 1287
192	Week 192	1344	1288 – 1371
204	Week 204	1428	1372 – 1450
216	Week 216	1512	1451 – 1534
228	Week 228	1596	1535 – 1618
240	Week 240	1680	1619 – 1702
252	Week 252	1764	1703 – 1792
264	Week 264	1848	1793 – 1876
276	Week 276	1932	1877 – 1950
288	Week 288	2016	1951 – 2034
300	Week 300	2100	2035 – 2118
312	Week 312	2184	2119 – 2202
324	Week 324	2268	2203 – 2286
336	Week 336	2352	2287 – 2370
348	Week 348	2436	2371 – 2454
360	Week 360	2520	2455 – 2538

[1] Study day relative to the date of first dose of study drug.

As a result of the study design, treatment extensions, and drug interruptions, study days are staggered within and between subjects across the study. To minimize the loss of data used for analysis, the assessment windows are not always equally spaced.

6.1.7. Investigative Sites

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

Analyses will be based on data pooled across investigative sites.

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

6.1.8. Variable Definitions

- "First dose" represents the first dose of study drug.
- "Last dose" represents the last dose on PA2 (i.e., through Week 72), PA3 (i.e., through Week 124), and/or PA4 (i.e., through the end of treatment).
- "End of Study" is the point at which the last contact with the last subject during the protocol-specified scheduled follow-up period is made.
- "Screen Failure" is a subject who has signed the informed consent (e.g., original or protocol amendment) but does not meet the associated eligibility criteria, or otherwise chose not to participate in the study/extension, before receiving the "first dose" of study drug.
- "Study Phase" used in compliance summaries (i.e., Weeks 0-13, Weeks 14-72, Weeks 73-124, Week >124, and Weeks 0-EOT) will be visit-based.
- "Week xx/LOCF" where xx=48 (ItchRO only), 72 (non-ItchRO variables), 122 (ItchRO only), and 124 (non-ItchRO variables). See Section 6.1.5.

6.1.9. Derived Variables

- **PFIC2 Subtype:** **Non-truncating** if genotypic severity is 'mild' or 'moderate'
  Truncating if genotypic severity is 'severe'

  Only applicable for subjects with PFIC type = 'PFIC2'.

- **Age (years) at Baseline**

  For subjects in which only the partial date of birth (i.e., year of birth) is reported, the reported age in years at baseline will be used.

  Otherwise,

  Age (years) at baseline = Integer of [(baseline visit date – date of birth) / 365.25]

- **Age (months) at Baseline**

  For subjects under 2 years of age, and in which only the year of birth is reported, the reported 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) / 30.4375]

  Partial birth dates are imputed for analysis purposes as described in Section 6.1.11.

- **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)** = Weight (kg) / [Height (cm)/100]^2

- **Time Since Original Diagnosis of PFIC (months)** = (date of first dose – date of original diagnosis of PFIC) / 30.4375

- **Baseline Value** = value obtained at baseline visit (before first dose of study drug)

  If baseline visit is not available, the last value obtained during screening is used as the baseline value.

  For weekly average ItchRO scores, baseline is defined as the weekly average ItchRO score in the week consisting of the 7 days immediately before the baseline visit date. For 4-week average ItchRO scores, baseline is defined as the 4-week average ItchRO score in the period consisting of the 28 days immediately before the baseline visit date.

  Change from Baseline = post-baseline value at time point – value at baseline

  For weekly and 4-week average ItchRO scores, "value" is the average score over a 7-day and 28-day period, respectively, as defined below.

  % Change from Baseline = 100 x change from baseline / value at baseline

- **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 subjects less than 24 months of age, the World Health Organization (WHO) growth charts[4] are recommended by the Centers for Disease Control (CDC) and will be used to derive z-scores. For subjects at least 24 months of age, the CDC growth charts[5] will be used to derive z-scores.

- **ItchRO Daily Score** = Average of morning and evening scores

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

- **ItchRO Weekly Average Score** = Sum of ItchRO Daily Scores (over a 7-day period) divided by the number of days ItchRO is completed

  The baseline weekly average score is calculated using the 7 days immediately before the baseline (Day 0) visit date. Post-baseline weekly average scores are calculated using the 7 days immediately before each select scheduled visit date. Post-baseline weekly average scores are only computed if at least 4 of the 7 ItchRO scores for the 7-day period are available.

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

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

  The baseline weekly average score is calculated using the 7 days immediately before the baseline (Day 0) visit date. Post-baseline weekly average scores are calculated using the 7 days immediately before each select scheduled visit date. Post-baseline weekly morning/evening average scores are only computed if at least 4 of the 7 morning/evening ItchRO scores for the 7-day period are available.

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

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

  The baseline 4-week average score is calculated using the 28 days immediately before the baseline (Day 0) visit date. Post-baseline 4-week average scores are calculated using the 28 days immediately before each select scheduled visit date. Post-baseline 4-week morning/evening average scores are only computed if at least 20 of the 28 morning/evening ItchRO scores for the 28-day period are available.

- **Alpha Tocopherol / Total Lipids Ratio (mg/g)** = 1000 x alpha tocopherol (mg/dL) / 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) + [0.216 x total serum lipids (g/L)]
- **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
Alpha Tocopherol / Total Lipids Ratio:	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:	Sufficient if level ≥ 135 to 148 mmol/L Insufficient if level < 135 mmol/L Excess if level > 148 mmol/L
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

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

  Where, LASTDAY = date of last dose, FIRSTDAY = date of first dose, and GAP = total # of days subject was off study between PA2 and PA3 and/or PA3 and PA4.

  280 QD Treatment Duration (days) =

  Date of last dose on QD dosing regimen – FIRSTDAY + 1 day – GAP

  280 BID Treatment Duration (days) =

  Date of last dose on BID dosing regimen – Date of first dose on BID dosing regimen + 1 day

  The 280 BID treatment duration is only derived for subjects that dose-escalated to a BID dosing regimen, and that GAP=0 during the BID dosing period.

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

  Expected treatment duration is used in deriving treatment compliance (see below), overall and by study phase. For each study phase, EXPLASTDAY = date of the last visit in the study phase (i.e., Week 13, 72, 124, or EOT) for subjects that complete study treatment for the specific study phase OR the date of last dose for subjects that ET during the specific study phase. For ET subjects, the date of last dose is considered, rather than the last visit date during the study phase in which the subject early terminated.

  For the Week 0-13 study phase, FIRSTDAY = date of first dose, and GAP = 0;

  For the Week 14-72 study phase, FIRSTDAY = date of the Week 13 visit plus 1 day, and GAP = 0;

  For the Week 73-124 study phase, FIRSTDAY = date of the Week 72 visit plus 1 day, and GAP = # days subject was off study between PA2 and PA3 (i.e., between Week 72 visit and first dose under PA3); Subjects that did not complete at least 1 post-Week 72 assessment are not included in the Week 73-124 study phase;

  For the Week >124 study phase, FIRSTDAY = date of the Week 124 visit plus 1 day, and GAP = # days subject was off study between PA3 and PA4 (i.e., between Week 124 visit and first dose under PA4); Subjects that did not complete at least 1 post-Week 124 assessment are not included in the >Week 124 study phase;

  Overall expected treatment duration is derived by summing over the expected treatment duration for each of the 4 individual study phases (Weeks 0-13, 14-72, 73-124, and >124).

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

  where,

  Number of days at least 1 dose is taken = Expected 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 determined for the following study phases: Weeks 0-13, Weeks 14-72, Weeks 73-124, Weeks >124, and Overall (Weeks 0-EOT).

- **Total Dose Received (µg/kg)** = Dose (µg/kg/day) x Treatment Duration (days), for a given constant dose level

  Total dose received does not account for dose deviations (e.g., missed dose, overdose, or underdose).

- **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 determined separately overall, during QD dosing, and during BID dosing. 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.

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

  Average daily dose is determined separately overall, during QD dosing, and during BID dosing. 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.

- **Clinically-Meaningful Shift from Baseline** *[applicable for ALT and total bilirubin laboratory tests]*

  For total bilirubin, a clinically-meaningful shift is dependent upon the baseline level: if the baseline level is ≤10 mg/dL, a clinically-meaningful shift is defined as a post-baseline level that is a ≥ 3 mg increase from baseline level; if the baseline level is > 10 mg/dL, a clinically-meaningful shift is defined as a post-baseline level that is a ≥ 5 mg increase from baseline level.

  For ALT, a clinically-meaningful shift is dependent upon the baseline level: if the baseline level is ≤ ULN, then a clinically-meaningful shift is defined as a post-baseline level >5 x ULN; if the baseline level is > ULN, then a clinically-meaningful shift is defined as a post-baseline level >3 x baseline level and >5 x ULN.

6.1.10. 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 6 in Section 13 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.

6.1.11. Data Adjustments/Handling/Conventions

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

Subject Age

The age of a subject at Study Day 0 (baseline) will be used to determine the appropriate age category for the ItchRO and PedsQL instruments, unless specified otherwise.

Siblings

Because PFIC is a rare disease, siblings were allowed to enroll in the study. Each sibling will be included in the Safety and ITT analysis populations. The data for only 1 sibling will be considered for the mITT and PP populations because of the potential for lack of independence of the observer reports. The choice of sibling to use in the efficacy analysis will be made at random, unless only 1 sibling is evaluable PP and the other sibling is not. In this case, the evaluable sibling will be considered for use in the efficacy analyses. Sibling selection for the purposes of efficacy analysis will be completed before data lock.

The efficacy analysis performed on the mITT analysis population for the planned 3rd IA (see Section 4.3.3) is considered as a sensitivity analysis. For the final analysis, no additional sensitivity analysis based on the inclusion or exclusion of sibling data will be performed.

Adverse Event and Concomitant Medication Coding

Adverse events will be coded using the MedDRA version 22.1. 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. This period of participation is from the first day of screening through the date of last contact. For subjects re-entering the study under PA3 and PA4 study extensions and experienced a study drug administration interruption, investigators were instructed not to enter concomitant medications that started and stopped during the period of time that the subject was off study since the subject was not enrolled in the study.

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

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

Treatment-Emergent Adverse Event Definition and Handling of Data

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

Any AE that started before the first dose and worsens in severity or changes from nonserious to serious on or after the first dose date will also be designated as a TEAE. If an event worsens in severity during the study, the lower grade event is marked as "Not recovered/not resolved" on the AE case report form (CRF) and an end date entered. A new event is reported on the AE CRF with a start date that matches the end date, and the term reported includes "Worsened" (e.g., "Worsened Headaches"). If an event becomes serious, the date that the event became serious is reported on the AE CRF as the End Date of that AE and the Start Date of the corresponding SAE.

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

is not used and the event results in death then, for analysis purposes, the severity of the event is considered as "Fatal (CTCAE Grade 5)".

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

An AE that does not have a reported 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 considered as "Severe".

Adverse Events of Special Interest

The following events have been defined as AESIs due to the nature of the disease under study as well as due to the mechanism of action of MRX:

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

The list of preferred terms (PTs) used to identify FSV deficiency events are provided in Appendix 3. Diarrhoea events include PTs of 'Diarrhoea', 'Diarrhoea haemorrhagic', and 'Gastroenteritis'. Elevated transaminases events include PTs of 'Alanine aminotransferase increased', 'Aspartate aminotransferase increased', Alanine aminotransferase abnormal', and 'Aspartate aminotransferase abnormal'. Elevated bilirubin events include the PTs of 'Blood bilirubin increased', 'Blood bilirubin abnormal', 'Bilirubin conjugated abnormal', 'Bilirubin conjugated increased', and 'Hyperbilirubinaemia'.

Partial Date Imputation

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

Partial PFIC Diagnosis Dates

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

Partial AE or Prior/Concomitant Medication Dates

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

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

if both the day and month are missing, and the year matches the first dose date and the end date is on or after the first dose date, then the date is assigned the first dose date; if the year does not match the first dose date or the end date is before the first dose date, then the day/month are assigned the first day of the year (01 Jan).

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

Partial Dates of Birth

At least one of the investigative sites are located in a country that does not permit the reporting of complete dates of birth. These sites only report the birth year. Complete date of birth is required, however, to derive a subject's weight and height z-scores and determine vital signs that are out-of-normal range, at each scheduled study visit. For partial birth dates, the convention for imputing missing dates for the purpose of statistical analysis is as follows:

Where available, the age in years and months at baseline will be used. If only age in years (at baseline) is reported, then 6 months will be used.

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

If the derived date of birth is later than the PFIC diagnosis date, the earliest complete medical history event start date, or the earliest complete reported prior/concomitant medication start date, then set the derived date of birth to the earliest of the 3 dates.

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.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

Subject disposition for all subjects will include tabulations of the number and percentage of subjects in each of the ITT, mITT and PP analysis populations, down-titrated during the study, consented to PA3 and completed at least 1 post-Week 72 assessment, consented to PA4 and completed at least 1 post-Week 124 assessment. The number and percentage of subjects that completed study treatment through varying study phases (i.e., Week 72, Week 124, and EOT), and discontinued early from the study at each study phase (along with reasons for withdrawal) will also be presented. The number and percentage of subjects that were initiated on BID dosing and discontinued early during BID dosing (along with reasons for withdrawal) will also be summarized. Percentages will be based on the number of subjects in the Safety Population.

The subject disposition tabulation will also include the number of subjects screened for eligibility, the number of screen failures under the original protocol, the number of screen failures under a protocol amendment, the number of subjects assigned to study treatment, the number of families with siblings enrolled in the study, the total number of siblings, and the number of subjects in the Safety Population.

The number and percentage of assigned subjects by investigative site will also be tabulated. Percentages will be based on the number of subjects assigned to study treatment.

Study drug accountability and compliance listings will be prepared for all subjects, showing when the planned dosing schedule was not followed, along with the date and type of dosing deviation. Other disposition and study conduct information, including major protocol deviations will be listed.

7.2. Protocol Violations and Deviations

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

- Informed consent form process or signature/version issue
- Violation of inclusion/exclusion criteria
- Study/protocol procedures
- Dosing error
- Excluded medication
- Visit window deviation
- 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 possible safety issue to the subject, or it has a potential impact on the statistical analysis of the protocol. 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. Protocol deviations which are deemed to be "Major" and "Non-Evaluable" (i.e., a deviation that has a potential impact on the efficacy analysis), will be classified as "Major Non-Evaluable". Subjects with at least 1 deviation classified as "Major Non-Evaluable" will be excluded from the PP analysis population (see Section 5).

Major protocol deviations will be presented in a subject listing. Major protocol deviations 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
- Use of bile acid or lipid binding resins during participation in the trial

7.3. Demographics and Other Baseline Characteristics

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

Tabulations for age group categories, defined as <2, 2–4, 5–8, 9–12, and 13–18 years of age at baseline, will also be presented. Unless otherwise noted, age is the subject's age at the baseline visit for all evaluations and presentations.

Subjects reporting more than 1 race will be counted in a "More than one race" category for purposes of tabulating summary statistics for race. A category of "Not Reported" is included for race and ethnicity.

These analyses will be conducted on the Safety Population.

7.4. Disease History and Baseline Disease Characteristics

Summary statistics will be presented for the following baseline variables by PFIC type and by PFIC2 subtype:

- time since original diagnosis of PFIC
- number of subjects having a family history of PFIC
- number of subjects using anything to treat itch in the past
- number of subjects using topical, oral, or other therapies to treat itch in the past
- number of subjects using each specific therapy to treat itch in the past
- number of subjects with a liver ultrasound
- number of subjects with liver masses detected on ultrasound
- baseline pruritus scores:
  - clinician scratch scale score
  - ItchRO (Obs) weekly morning average score
  - ItchRO (Obs) weekly evening average score
  - ItchRO (Obs) weekly average score
  - ItchRO (Pt) weekly average score
  - ItchRO (Obs) 4-week morning average score

- ItchRO (Pt) 4-week morning average score
- ItchRO (Obs) 4-week evening average score
- ItchRO (Pt) 4-week evening average score

- baseline levels of biochemical markers of cholestasis and liver disease and other important baseline laboratory tests:
  - sBA
  - ALP
  - AST
  - ALT
  - GGT
  - FGF-19
  - bilirubin (total and direct)
  - total cholesterol
  - triglycerides
  - C4
  - retinol (Vitamin A)
  - 25-hydroxyvitamin D
  - tocopherol alpha (Vitamin E)
  - INR

Tabulations of pruritus therapy medications will also be presented for categories of 1 medication, 2 medications, and at least 3 medications.

These analyses will be conducted on the Safety Population.

Medical history information and prior medications will be presented in subject listings.

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 0-13, Weeks 14-72, Weeks 73-124, Weeks >124, and overall (Weeks 0-EOT). Subjects terminated before any given study phase are not included in the analysis of that study phase.

For a given day, a subject is considered compliant with treatment 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 ITT Population.

Subjects that did not complete at least 1 post-Week 72 assessment will be excluded from all post-Week 72 analyses. Subjects that did not complete at least 1 post-Week 124 assessment will be excluded from all post-Week 124 analyses.

No adjustment for multiplicity will be made. All efficacy data will be included in subject data listings.

8.1. Primary Efficacy Variable Analysis

The primary analysis of the primary efficacy endpoint, sBA change from Baseline to Week 13, will be based on a paired t-test. The null hypothesis that the sBA mean change from baseline to Week 13 is zero will be tested. The mean change from baseline to Week 13 will be presented, along with its associated 95% confidence interval and p-value.

Secondary efficacy evaluations on sBA levels will include mean change from baseline to Week 48, Week 72, Week 72/LOCF, Week 120, and Week 124/LOCF.

The assumption of normality of the changes from baseline will be tested using the Shapiro-Wilk test. If the p-value of the test is ≤ 0.05 then the data suggests non-normality, and the null hypothesis that the median change from baseline is zero will be tested with the Wilcoxon signed rank test.

Observed and change from baseline in sBA level will also be summarized by analysis visit, using summary statistics including the number of observations, the mean and associated 95% confidence interval, median, standard deviation, standard error of the mean, minimum and maximum, and the p-value for testing if the mean change from baseline is zero (based on a paired t-test).

The above-described analysis will be performed overall and by PFIC type. The analysis on observed and change from baseline values by analysis visit, will also be performed by PFIC2 subtype.

8.2. Secondary Efficacy Variable Analysis

Secondary efficacy variables include ALT, AST, bilirubin (total and direct), ItchRO (Obs) weekly average score, ItchRO (Obs) weekly morning average score, and ItchRO (Obs) 4-week morning average score. Secondary efficacy variables will be analyzed similar to the primary efficacy variable, as described in the previous section.

The paired t-test analysis will be performed on mean change from baseline to Week 13, Week 48, Week 48/LOCF (for ItchRO variables only), Week 72 (for non-ItchRO variables only), Week 72/LOCF (for non-ItchRO variables only), Week 120 (Week 122 for ItchRO variables), and Week 124/LOCF (Week 122/LOCF for ItchRO variables) for each secondary efficacy variable.

With the exception of ItchRO (Obs) 4-week morning average score, the analysis on observed and change from baseline values by analysis visit will also be performed by PFIC2 subtype.

ItchRO (Obs) morning scores will also be summarized by time period and PFIC type, as the number and percent of days the daily morning score is ≤ 1 point. Time periods include Screening/Baseline, Day 1 - Week 8, Weeks > 8 - 13, Weeks > 13 - 24, Weeks > 24 - 36, Weeks > 36 - 48, Weeks > 48 - 72, Weeks > 72 – 124, Weeks > 124 – 204, and Weeks > 204. No inferential statistical tests will be performed.

8.3. Exploratory Efficacy Variable Analysis

The following exploratory efficacy variables will be presented by analysis visit with descriptive statistics: ALP, total cholesterol, C4, GGT, LDL-C, ItchRO (Obs) weekly evening average score, CSS score, height z-score, weight z-score, BMI z-score, PedsQL total scale score (parent), PedsQL multidimensional fatigue scale score (parent), PedsQL family impact total scale score, and ItchRO (Pt) weekly, weekly morning, and weekly evening average scores.

For ALP, total cholesterol, C4, GGT, and LDL-C, an analysis on observed and change from baseline values by PFIC2 subtype and analysis visit will also be included.

The above-described summaries will also include the p-value for paired t-tests.

8.4. Sensitivity Analysis

For post-baseline sBA levels, ItchRO (Obs and Pt) weekly morning average scores, and liver function lab test responder analyses, using various responder definitions (see Section 2.2.2.4), will be conducted as sensitivity analyses.

Analyses of efficacy data will include LOCF analysis values (see Section 6.1.5).

Data summaries will be presented for PFIC1 and PFIC2 subjects independently and for all subjects combined. Select efficacy variables will also be presented by PFIC2 subtype (truncating and non-truncating).

For subjects who discontinue early from the study, either before Week 72 (i.e., PA2), Week 124 (i.e., PA3), or PA4, the reason for withdrawal and effect on safety and efficacy results will be discussed in the CSR.

9. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety Population.

Safety measures of MRX including study drug exposure, AEs and SAEs, clinical laboratory values, concomitant medication usage, and plasma levels of MRX will be summarized descriptively. TEAEs of special interest (see Section 9.2.1) will be summarized separately. Vital signs and physical examination findings will be provided in subject listings.

Study drug exposure and AEs will be summarized descriptively by MRX dose (280 QD vs. 280 BID) and PFIC type (PFIC1, PFIC2, and overall).

For the AE and study drug exposure summaries, MRX dose is based on the dose at the onset of the event. The 280 QD dose includes all QD doses ≤ 280 µg/kg. The 280 BID dose includes the dose of 420 µg/kg daily for 2 weeks as part of a dose-escalation.

For visit-based safety data (i.e., safety labs and plasma levels of MRX), 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 included in subject listings.

Concomitant medications will be summarized descriptively overall and by PFIC type.

9.1. Exposure to Treatment

The average daily dose (µg/kg/day), total drug exposure (µg/kg), and treatment duration (days) will be summarized overall and by PFIC type and MRX dose (280 QD, 280 BID). Study drug exposure estimates exclude dosing gaps due to subject being off study (between protocol amendments).

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 - # days subject was off study between PAs) will also be summarized categorically, overall and by PFIC type and MRX dose, using the following cumulative time intervals:

≤ 13 weeks (≤ 86 days)
> 13 weeks (> 86 days)
> 48 weeks (> 322 days)
> 72 weeks (> 490 days)
≥ 124 weeks (≥ 854 days)

Note these categories are not mutually exclusive. The number of days may not be exactly 7 x the number of weeks to allow for permitted visit windows.

9.2. Adverse Events

In general, TEAEs are AEs with a start date on or after the first dose date of study drug and a start date before the last dose of study drug plus 14 days. For subjects with >14 days of study drug interruption/withdrawal, the definition of a TEAE considers both the date of the last dose before drug interruption and the actual last dose (see Section 6.1.11).

A summary of TEAEs will be presented overall, by PFIC type (PFIC1, PFIC2), and by MRX dose group (280 µg/kg QD, 280 µg/kg BID). The summary will include the total number and percent of subjects reporting:

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

For each MRX dose group, the percent of subjects will be derived using a denominator based on the number of subjects that received the given dose. For example, overall there are 10 subjects that were dose-escalated to BID dosing, while all 33 subjects received a QD dose.

The number and percent of subjects with reported TEAEs, grouped by MedDRA system organ class (SOC) and PT, will be tabulated overall and by maximum severity. These AE summaries

will be repeated for treatment-related AEs. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term.

Adverse events will be summarized overall and by PFIC type and MRX dose (280 QD, 280 BID). In presenting AEs by MRX dose, events will only be counted in the MRX dose group in which the start of the event occurred. For example, if an event starts while a subject is administered a 280 µg/kg QD dose and continues into the dose-escalation period of the BID dosing period, the event will only be counted in the '280 QD' dose group.

All AEs will be coded using MedDRA version 22.1. All TEAEs summarized by SOC and PT will be sorted in alphabetical order of the SOC and by descending frequency order of the PT 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 6.1.11.

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, MRX dose (µg/kg/day) received at the start of the event (or the last dose received if the AE started after the last dose or during dose interruption), 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 of Special Interest

Due to the nature of the disease under study, as well as due to the mechanism of action of MRX, the following events have been defined as AESIs: diarrhoea events, FSV deficiency events, elevated transaminases, and elevated bilirubin. For each of the AESI events, the PTs are described in Section 6.1.11.

The incidence of TEAEs of special interest for FSV deficiency events will be summarized separately in the same manner as AEs that lead to permanent discontinuation of study drug. Each group of AESIs will be presented in subject listings.

9.2.2. Deaths and Serious Adverse Events

Treatment-emergent SAEs, and treatment-emergent SAEs potentially related to study drug, will be tabulated by SOC and PT.

All deaths that occur during the study, including the post treatment follow-up period, will be presented in a subject listing. Subject listings of SAEs and SAEs related to study drug will also be presented.

9.2.3. Life Threatening Adverse Events

Life threatening AEs and severe or life-threatening AEs will be provided in separate subject listings in the same manner as SAEs.

9.2.4. Adverse Events Leading to Withdrawal

Treatment-emergent AEs that lead to permanent discontinuation of study drug will be summarized and provided in subject listings in the same manner as SAEs.

9.3. Clinical Laboratory Evaluations

Clinical laboratory variables (chemistry panel, hematology, coagulation, lipid panel, cholestasis biomarkers, and fat-soluble vitamins) will be summarized using descriptive statistics by analysis visit as both observed values and change from baseline values. For analysis, all laboratory values will be presented in conventional (US) units, with the exception of serum bile acid which will be reported in units of μmol/L.

Percent change from baseline will be added for the laboratory parameters listed in Appendix 2: Laboratory Tests for % Change from Baseline Presentation.

Laboratory values of all subjects who change (baseline to post-baseline) from normal to abnormal (low/high) or from abnormal (low/high) to normal during the course of the study will be presented in a listing. A subject listing of fat-soluble vitamin levels that demonstrate significant shifts from baseline will be presented separately. These listings will include all analysis visits for a given subject and lab test if there is a shift from baseline at any time over the course of the study.

For select FSVs (i.e., 25-hydroxyvitamin D, alpha tocopherol/total lipids ratio, INR, retinol:RBP molar ratio, and vitamin A), abnormalities and clinically-meaningful shifts from baseline summaries will be presented at each analysis visit (as appropriate). For these fat-soluble vitamins, categories may include sufficient, insufficient, possibly insufficient, indeterminate, and excess (see Section 6.1.9 for specific definitions). A summary of corrected sodium abnormalities will also be presented.

A tabulation of the number of subjects with clinically meaningful shifts (see Section 6.1.9 for definition) in bilirubin and ALT will be presented by visit. Clinically meaningful shifts in those variables will also be listed.

All laboratory variables will be presented by panel, including urinalysis, in subject listings. A separate subject listing for efficacy laboratory variables will also be presented.

9.4. Vital Signs

Vital signs (BP, HR, body temperature, and respiration rate) will be presented in subject listings.

9.5. Physical Examination

Abnormal physical examination findings at screening and indications of clinically significant abnormal findings that were newly diagnosed or worsened since the screening visit will be provided in a subject listing. Body height, body weight, and BMI, along with associated z-scores for each, will also be included in subject listings.

9.6. Concomitant Medications

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

Concomitant medications will be summarized descriptively overall and by PFIC type, using the number and percentage of subjects by ATC class and preferred term.

Concomitant medications will also be presented in subject listings. Medications that are ongoing at time of informed consent will be indicated in the data listing.

9.7. Pharmacokinetic Analysis

Due to poor absorption of MRX very low systemic exposure and plasma drug levels are expected. Blood sampling for plasma levels of MRX are collected periodically throughout the study period. Sampling at United States sites and those at non-US sites (i.e., United Kingdom, Europe, and Australia) follow a somewhat different schedule (see Section 3.6). Additionally, blood samples are taken approximately 4 hours post-dose, except at week 4 for US sites, when they are taken approximately 2 hours post-dose.

MRX plasma concentrations will be summarized using descriptive statistics by analysis visit and dose of MRX received at the specified analysis visit. Week 4 plasma levels will be presented separately for US and non-US sites because of the difference in timing of blood sampling post-dose.

Plasma MRX concentrations will also be presented in subject listings.

10. Other Planned Analysis

10.1. Quality of Life

Quality of life will be assessed on Total Scale Score (Parent), Multidimensional Fatigue Scale Score (Parent), and Family Impact Total Scale Score as efficacy parameters using the appropriate PedsQL module(s). The change from baseline to each post-baseline analysis visit (i.e., Week 13, 24, 48, 72, 72/LOCF, 84, 96, 108, 120, 124/LOCF, 132, and every 12 weeks thereafter) will be presented with descriptive statistics.

Analyses for the quality of life variables are performed on the ITT Population.

PedsQL scoring algorithms for scale scores are provided in Section 6.1.10. All individual item and total/summary scale scores will be presented in subject listings.

10.2. Palatability Analysis

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

10.3. Genetic Endpoints

For the purpose of this analysis plan, exploratory genetic analyses will be limited to the presentation of genotype data in a listing.

10.4. Additional Analyses

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. 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.

11. Changes from Protocol Planned Analyses

The protocol states that missing data imputation will not be done for efficacy endpoints. However, based on the intent-to-treat principle, visit-based efficacy and safety endpoints will include Week 72/LOCF (Week 48/LOCF for ItchRO variables) and Week 124/LOCF (Week 122/LOCF for ItchRO variables) analysis time points.

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

The protocol states that safety data will be summarized by study phase (Weeks 0-13, 14-48, 49-72, and 73-120) and over the entire study duration (Weeks 0-EOT Visit). However, AEs and study drug exposure will be summarized by PFIC type (PFIC1, PFIC2, and overall) and MRX dose (280 QD and 280 BID). Laboratory results (including AFP) will be summarized by analysis visit. Vital signs will only be presented in subject listings.

In general, subjects that did not complete at least 1 post-Week 72 assessment will be excluded from all post-Week 72 analyses. Subjects that did not complete at least 1 post-Week 124 assessment will be excluded from all post-Week 124 analyses.

Body height, body weight, and BMI z-scores have been moved from safety variables to exploratory efficacy variables.

AST have been added as a secondary efficacy variable.

For the secondary efficacy variable(s), ItchRO weekly average score has been replaced with 3 ItchRO (Obs) average scores: weekly average score, weekly morning average score, and 4-week morning average score.

The protocol defines the ItchRO daily score as the maximum of the morning and evening scores. The definition of the daily score has been changed to the average of morning and evening scores.

The protocol specifies that exploratory efficacy variables will be analyzed similarly to the primary efficacy variables. However, owing to the small sample size and the limitations of the uncontrolled design of the study, only descriptive statistics will be presented for: ALP, GGT, C4, total cholesterol, LDL-C, select PedsQL variables (total scale score [parent], multidimensional fatigue scale score [parent], and family impact total scale score), and select exploratory ItchRO variables. For CSS, PIC, CIC, CGTB, HDL-C, triglycerides, INR, aPTT, prothrombin time, select ItchRO and PedsQL variables, and the sBA sub-species, will only be presented in subject listings.

The protocol also specifies that exploratory evaluations may be conducted on the change from baseline in lysophosphatidic acid (LPA) at Weeks 4, 8, 13, 36, 48, 60, and 72. The method for assaying LPA has not been validated, thus LPA data will not be available for this analysis.

The protocol specifies that pattern of change in serum bile acids from baseline (Day 0) to EOT will be evaluated and its appropriate analysis methodology will be outlined in the SAP. This "pattern of change" endpoint will not be pursued as described in the protocol.

The protocol states that the additional questions included in the ItchRO instrument that are not scored will be tabulated. This data consists of morning and evening daily records, and will not be tabulated but rather presented in a subject listing.

The protocol states that the definition for the PP Population "will consist of all subjects in the MITT population who did not have a major protocol violation, inclusive of violation of entry the criteria"; however, this has been changed to all subjects in the mITT Population who did not have a major, non-evaluable protocol deviation.

The protocol includes a PP Population for efficacy analysis. The PP analysis population was used in the 1st interim analysis to examine efficacy outcomes. No summaries using the PP Population are planned for the final analyses.

The protocol states that "where sample size allows, treatment effects over time will be examined using methods appropriate for repeated observations". A repeated-measures analysis has not been included for the final analyses.

12. Additional Exploratory Analyses

Additional exploratory analyses generally referred to but not specifically described in the protocol, include:

- For ALT and total bilirubin, the number and percentage of subjects demonstrating a clinically-meaningful shift from their baseline level will be presented at each post-baseline analysis visit.
- For select fat-soluble vitamins, abnormalities and clinically-meaningful shifts from baseline will be presented at each analysis visit (as appropriate). For these select fat-soluble vitamins, categories may include sufficient, insufficient, possibly insufficient, indeterminate, and excess (see Section 6.1.9 for specific definitions).

- Quality of life will be assessed by examining changes from baseline in select summary and total scale scores using the appropriate PedsQL module(s).

Additional exploratory analyses may or may not be included in the clinical study report.

13. 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.
2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016.w.amstat.org/about/ethicalguidelines.cfm
3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014.w.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
4. 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)
5. 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**)
6. The PedsQL Measurement Model for the Pediatric Quality of Life Inventory – Scoring Instructions (www.pedsql.org)

14. Planned Tables, Figures, and Listings

All tables, figures, and listings will have a header showing the sponsor company name, protocol number, and output version, and a footer showing the filename and path, and date of output generation. All tables and figures will have a "SOURCE: Listing(s) XXXX" line that indicates which data listing(s) contains the underlying data.

14.1. Planned Table Descriptions

The following are planned summary tables for protocol number LUM001-501. The table numbers and page numbers are place holders only and will be determined when the tables are produced. All the tables listed below will be presented for the final analyses, but only a subset will be presented for each interim analyses. The table below indicates which tables will appear in the first, second, and third planned interim analyses.

Table Number	Table Title for Final Analysis	Include in 1st IA	Include in 2nd IA	Include in 3rd IA	Final Analysis
14.1.1	Subject Disposition (All Subjects)			A	✓
14.1.2	Number of Enrolled Subjects by Investigative Site				✓
14.1.3	Demographics and Baseline Characteristics (Safety Population)	✓	✓	✓	✓
---	Demographics and Baseline Characteristics (Per-Protocol Population)	✓			
14.1.4	Disease History and Baseline Disease Characteristics (Safety Population)	✓	✓	✓	✓
---	Disease History and Baseline Disease Characteristics (Per-Protocol Population)	✓			
14.1.5	Summary of Prior Pruritus Therapy Medications (Safety Population)				✓
14.1.6	Treatment Compliance (Safety Population)	✓	✓	✓	✓
---	Treatment Compliance During BID Dosing for Subjects that Initiated Afternoon Dose-escalation (ADE) (Safety Population)			✓	
14.2.1	Primary and Secondary Efficacy Variables: Change from Baseline by PFIC Type and Select Analysis Visits (Intent-to-Treat Population)				✓
---	Primary and Secondary Efficacy Endpoints: Change from Baseline to EOT/ET for Subjects Enrolled in the ADE Phase - Paired t-tests (Modified Intent-to-Treat Population)			✓	
---	Primary and Secondary Efficacy Variables: Change from Baseline by Study Visit for Subjects Enrolled in the ADE Phase (Modified Intent-to-Treat Population)			✓	
---	Change from Baseline Serum Bile Acid Level (umol/L) by Study Visit – QD Dosing Only (Modified Intent-to-Treat Population)			A	
---	Change from Baseline Serum Bile Acid Level (umol/L) by Study Visit – BID Dosing Only (Modified Intent-to-Treat Population)			A	
14.2.2.1	Change from Baseline sBA (umol/L) by PFIC Type and Analysis Visit (Intent-to-Treat Population)	✓	✓ (SP)	S	✓
14.2.2.2	Change from Baseline sBA (umol/L) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.3.1.1	Change from Baseline ItchRO (Observer) Weekly Average Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.3.1.2	Change from Baseline ItchRO (Observer) Weekly Average Score by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.3.2.1	Change from Baseline ItchRO (Observer) Weekly Morning Average Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.3.2.2	Change from Baseline ItchRO (Observer) Weekly Morning Average Score by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓

Table Number	Table Title for Final Analysis	Include in 1st IA	Include in 2nd IA	Include in 3rd IA	Final Analysis
14.2.3.2.3	Percent of Days ItchRO (Observer) Morning Score is ≤ 1 Point by PFIC Type and Time Period (Intent-to-Treat Population)				✓
14.2.3.3	Change from Baseline ItchRO (Observer) Weekly Evening Average Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.4.1	Change from Baseline ItchRO (Patient) Weekly Average Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.4.2	Change from Baseline ItchRO (Patient) Weekly Morning Average Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.4.3	Change from Baseline ItchRO (Patient) Weekly Evening Average Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
---	Change from Baseline ItchRO (Patient) Pruritus Average Score by Study Visit (Modified Intent-to-Treat Population)	✓	✓ (SP)	S	
---	Change from Baseline ItchRO (Observer) Pruritus Average Scores by Study Visit (Modified Intent-to-Treat Population)	✓	✓ (SP)	S	
14.2.5.1	Change from Baseline ALT (U/L) by PFIC Type and Analysis Visit (Intent-to-Treat Population)	✓	✓ (SP)	S	✓
14.2.5.2	Change from Baseline ALT (U/L) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.6.1	Change from Baseline Total Bilirubin (mg/dL) by PFIC Type and Analysis Visit (Intent-to-Treat Population)	✓	✓ (SP)	S	✓
14.2.6.2	Change from Baseline Total Bilirubin (mg/dL) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.7.1	Change from Baseline Direct Bilirubin (mg/dL) by PFIC Type and Analysis Visit (Intent-to-Treat Population)	✓	✓ (SP)	S	✓
14.2.7.2	Change from Baseline Direct Bilirubin (mg/dL) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.8.1	Change from Baseline ALP (U/L) by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)		✓
14.2.8.2	Change from Baseline ALP (U/L) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.9.1	Change from Baseline AST (U/L) by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)		✓
14.2.9.2	Change from Baseline AST (U/L) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.10.1	Change from Baseline Total Cholesterol (mg/dL) by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)	S	✓

Table Number	Table Title for Final Analysis	Include in 1st IA	Include in 2nd IA	Include in 3rd IA	Final Analysis
14.2.10.2	Change from Baseline Total Cholesterol (mg/dL) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.11.1	Change from Baseline C4 (ng/mL) by PFIC Type and Analysis Visit (Intent-to-Treat Population)	✓	✓ (SP)	S	✓
14.2.11.2	Change from Baseline C4 (ng/mL) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.12.1	Change from Baseline GGT (U/L) by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)		✓
14.2.12.2	Change from Baseline GGT (U/L) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.13.1	Change from Baseline LDL-C (mg/dL) by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)	S	✓
14.2.13.2	Change from Baseline LDL-C (mg/dL) by PFIC2 Subtype and Analysis Visit (Intent-to-Treat Population)				✓
14.2.14.1	Pruritus Responder Rates as Measured by ItchRO (Observer) Morning Average Scores by PFIC Type and Analysis Visit Using Various Responder Definitions (Intent-to-Treat Population)			✓	✓
14.2.14.2	Pruritus Responder Rates as Measured by ItchRO (Patient) Morning Average Scores by PFIC Type and Analysis Visit Using Various Responder Definitions (Intent-to-Treat Population)			✓	✓
14.2.14.3	Serum Bile Acid and ItchRO (Observer) Responder Analysis by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)	✓	✓
14.2.14.4	Liver Function Lab Test Responder Analysis by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)	✓	✓
14.2.15	Change from Baseline Clinician Scratch Scale Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)	S	✓
14.2.16.1	Change from Baseline in Height Measurement z-Scores by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.16.2	Change from Baseline in Weight Measurement z-Scores by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.16.3	Change from Baseline in BMI z-Scores by PFIC Type and Analysis Visit (Intent-to-Treat Population)				✓
14.2.17.1	Change from Baseline PedsQL Total Scale Score (Parent) by PFIC Type and Analysis Visit (Intent-to-Treat Population)	✓	✓ (SP)	S	✓
14.2.17.2	Change from Baseline PedsQL Multidimensional Fatigue Scale Score (Parent) by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)	S	✓
14.2.17.3	Change from Baseline PedsQL Family Impact Total Scale Score by PFIC Type and Analysis Visit (Intent-to-Treat Population)		✓ (SP)		✓

Table Number	Table Title for Final Analysis	Include in 1st IA	Include in 2nd IA	Include in 3rd IA	Final Analysis
---	Change from Baseline PedsQL Psychosocial Health Summary Score (Parent) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)		
---	Change from Baseline PedsQL Total Scale Score (Child) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline PedsQL Multidimensional Fatigue Scale Score (Child) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline PedsQL Physical Health Summary Score (Parent) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)		
---	Change from Baseline PedsQL Physical Health Summary Score (Child) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)		
---	Change from Baseline PedsQL Psychosocial Health Summary Score (Child) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)		
---	Change from Baseline PedsQL Parent Functioning Summary Score by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)		
---	Change from Baseline PedsQL Family Impact Summary Score by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Patient Impression of Change (PIC) Score by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	✓	
---	Caregiver Impression of Change (CIC) Score by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	✓	
---	Caregiver Global Therapeutic Benefit (CGTB) Score by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	✓	
---	Change from Baseline Autotaxin Level (ng/mL) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline Fibroblast Growth Factor 19 (FGF-19) Level (pg/mL) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline Fibroblast Growth Factor 21 (FGF-21) Level (pg/mL) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)		
---	Change from Baseline HDL Cholesterol Level (mg/dL) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline Triglycerides Level (mg/dL) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline International Normalized Ratio (INR) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline Activated Partial Thromboplastin Time (aPTT) (sec) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	

Table Number	Table Title for Final Analysis	Include in 1st IA	Include in 2nd IA	Include in 3rd IA	Final Analysis
---	Change from Baseline Prothrombin Time (PT) (sec) by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)	S	
---	Change from Baseline Serum Bile Acid Subspecies by Study Visit (Modified Intent-to-Treat Population)		✓ (SP)		
---	Pruritus Responder Rates as Measured by ItchRO (Observer) by Study Visit (Modified Intent-to-Treat Population)			✓	
---	Pruritus Responder Rates as Measured by ItchRO (Patient) by Study Visit (Modified Intent-to-Treat Population)			✓	
14.3.1	Study Drug Exposure by PFIC Type and MRX Dose (Safety Population)			✓	✓
14.3.2.1	Summary of Treatment-Emergent Adverse Events by PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.2	Incidence of Treatment-Emergent Adverse Events by PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.3	Incidence of Treatment-Emergent Adverse Events by Maximum Severity, PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.4	Incidence of Treatment Related Adverse Events by PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.5	Incidence of Treatment Related Adverse Events by Maximum Severity, PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.6	Incidence of Treatment-Emergent Serious Adverse Events by PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.7	Incidence of Treatment Related Serious Adverse Events by PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.8	Incidence of Adverse Events Leading to Permanent Treatment Discontinuation by PFIC Type and MRX Dose (Safety Population)	✓	✓ (SP)	✓	✓
14.3.2.9	Incidence of Treatment-Emergent Adverse Events of Special Interest - Fat-Soluble Vitamin Deficiency Events by PFIC Type and MRX Dose		✓ (SP)	✓	✓
14.3.2.10	Listing of Deaths	✓	✓ (SP)	✓	✓
---	Incidence of Treatment-Emergent Adverse Events of Special Interest - Gastrointestinal Related Events by Study Phase (Safety Population)	✓	✓ (SP)	✓	
---	Incidence of Treatment-Emergent Adverse Events of Special Interest – Conditions Associated with Liver Deterioration by Study Phase (Safety Population)	✓	✓ (SP)	✓	
---	Incidence of Treatment-Emergent Adverse Events of Special Interest – GI-Related Events and Conditions Associated with Liver Deterioration by Study Phase (Safety Population)			✓	

Table Number	Table Title for Final Analysis	Include in 1st IA	Include in 2nd IA	Include in 3rd IA	Final Analysis
---	Incidence of Treatment-Emergent Adverse Events of Special Interest - Thyroid Function Events by Study Phase (Safety Population)		✓ (SP)		
---	Incidence of Treatment-Emergent Adverse Events of Special Interest - Growth Retardation Events by Study Phase (Safety Population)		✓ (SP)		
14.3.3.1	Summary of Clinical Laboratory Data: Clinical Chemistry (Safety Population)			✓	✓
14.3.3.2	Summary of Clinical Laboratory Data: Hematology (Safety Population)			✓	✓
14.3.3.3	Summary of Clinical Laboratory Data: Fat-Soluble Vitamins (Safety Population)			✓	✓
14.3.3.4	Summary of Clinical Laboratory Data: Lipid Panel (Safety Population)			✓	✓
14.3.3.5	Summary of Clinical Laboratory Data: Cholestasis Biomarkers (Safety Population)			✓	✓
14.3.3.6	Summary of Clinical Laboratory Data: Coagulation (Safety Population)			✓	✓
14.3.3.7	Listing of Laboratory Parameter Levels with Significant Shifts from Baseline Over the Study (Safety Population)			✓	✓
14.3.3.8	Listing of Fat-Soluble Vitamin Levels with Significant Shifts from Baseline Over the Study (Safety Population)			✓	✓
14.3.3.9.1	Summary of Clinically Meaningful Shifts in Bilirubin and ALT (Safety Population)			✓	✓
14.3.3.9.2	Listing of Clinically Meaningful Shifts in Bilirubin and ALT (Safety Population)			✓	✓
14.3.3.10	Summary of Clinical Laboratory Data: Hepatocellular Carcinoma Marker (Safety Population)			✓	✓
14.3.3.11	Summary of Corrected Sodium and Fat-Soluble Vitamin Level Abnormalities (Safety Population)			✓	✓
14.3.3.12	Summary of Clinically-Meaningful Shifts from Baseline in Fat-Soluble Vitamins (Safety Population)			✓	✓
---	Summary of Weight Measurement z-Scores (Safety Population)			✓	
---	Summary of Height Measurement z-Scores (Safety Population)			✓	
14.3.4	Summary of Concomitant Medications (Safety Population)				✓
14.3.5	Summary of Plasma Sample MRX Concentrations (ng/mL) by Analysis Visit (Safety Population)				✓
14.4	Summary of Palatability Data by Analysis Visit (Safety Population)				✓

Note: The 1st and 3rd interim analysis (IA) use the Modified Intent-to-Treat Population for all efficacy summary tables. The 2nd IA is performed on the Safety Population. For each IA, TEAEs were summarized by study phase, instead of MRX dose. SP = Safety Population; A = table was added to the 3rd IA after SAP Amendment 1 was approved; S = summary table was split into 2 tables: QD Dosing Only and BID Dosing Only

14.2. Planned Figure Descriptions

Figures for select efficacy variables will depict trends over time for PFIC1 and PFIC2 subjects independently and overall using the ITT analysis population. Mean (± SE) observed values and/or change from baseline (Day 0) for select efficacy variables will be displayed graphically by study week over the treatment period. For these line plots over time, study week will be based on the analysis visit mapping described in Table 1.

Study drug exposure will be displayed as a swimmer plot that includes a horizontal bar showing treatment duration for each subject in the study. Each bar will be color coded in a manner that displays the time periods in which each subject was on the varying daily doses (i.e., 14 µg/kg/day, 35 µg/kg/day, 70 µg/kg/day, 140 µg/kg/day, 280 µg/kg/day, 420 µg/kg/day, and 560 µg/kg/day). Gaps in line segments will indicate a drug interruption or missed dose for any reason. Vertical reference lines will be included at study day 336 (Week 48), 504 (Week 72), and 868 (Week 124) to represent treatment periods associated with the original protocol, and protocol amendments 2 and 3.

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.

The following are planned summary figures for protocol number LUM001-501. The figure numbers and page numbers are place holders only and will be determined when the figures are produced. Additional graphical displays may be included in the clinical study report.

Listing of Planned Figures

14.2.2.1.1 ✓	Plot of Mean (SE) Change from Baseline in sBA (umol/L) by PFIC Type Over Time – Intent-to-Treat Population
14.2.2.1.2	Plot of Mean (SE) sBA (umol/L) by PFIC Type Over Time – Intent-to-Treat Population
14.2.3.2.1.1	Plot of Mean (SE) Change from Baseline in ItchRO (Obs) Weekly Average Morning Score by PFIC Type Over Time - Intent-to-Treat Population
14.2.3.2.1.2	Plot of Mean (SE) ItchRO (Obs) Weekly Average Morning Score by PFIC Type Over Time - Intent-to-Treat Population
14.2.5.1	Plot of Mean (SE) Change from Baseline in ALT (U/L) by PFIC Type Over Time – Intent-to-Treat Population
14.2.6.1	Plot of Mean (SE) Change from Baseline in Total Bilirubin (mg/dL) Over Time - Intent-to-Treat Population

14.2.7.1 Plot of Mean (SE) Change from Baseline in Direct Bilirubin (mg/dL) Over Time - Intent-to-Treat Population

14.2.9.1 Plot of Mean (SE) Change from Baseline in AST (U/L) by PFIC Type Over Time – Intent-to-Treat Population

14.2.11.1 Plot of Mean (SE) Change from Baseline in C4 (ng/mL) by PFIC Type Over Time – Intent-to-Treat Population

14.2.16.1 Plot of Mean (SE) Change from Baseline in Height z-Score by PFIC Type Over Time - Intent-to-Treat Population

14.2.16.2 Plot of Mean (SE) Change from Baseline in Weight z-Score by PFIC Type Over Time - Intent-to-Treat Population

14.3.1 ✓ Study Drug Exposure Over Time by Subject – Safety Population

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

For the second planned interim analysis, data presented in all graphical displays will be based on the Safety Population. Figures checked (✓) are included in the third planned interim analysis using the mITT population (refer to SAP Amendment 2).

14.3. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number LUM001-501.

In general, listings produced will include the subject data collected on associated CRF pages. All listings will be sorted by PFIC type, site and subject number. PFIC type, which will be displayed at the top of each page in a listing, includes PFIC1, PFIC2 (non-truncating), and PFIC2 (truncating).

The study drug accountability and compliance subject listing will include percent compliance estimates for each subject and study phase (Weeks 0-13, Weeks 14-72, Weeks 73-124, >Week 124, and overall).

For ItchRO (Obs and Pt) weekly morning and evening average scores, clinical scratch scale score, total sBA listings, and efficacy laboratory listings, change from baseline values will be included.

For AE listings, study day relative to the date of first dose of study drug will be provided along with stop and start dates. For partial event dates, study day will be derived using an imputed date as described in Section 6.1.11. Subject listings of AEs will include the dose level the subject was receiving at the start of the event and the duration of the event (days).

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

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

In addition to presenting subject listings of raw scores for each of the PedsQL module items, listings with total scale and summary scores will also be presented for PedsQL Total Scale Score, Physical Health Summary Score, Psychosocial Health Summary Score, Multidimensional Fatigue Scale Score, Family Impact Total Scale Score, Parent Functioning Summary Score, and Family Impact Summary Score.

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

The order of the listings will be as follows:

16.1.1*✓	Subject Profile: Select Labs and Pruritus Scores
16.1.2*	Subject Profile: Serum Bile Acid Subspecies
16.1.3*✓	Subject Profile: Pediatric Quality of Life Inventory – Total Scale and Summary Scores
16.1.4*✓	Subject Profile: Efficacy and Safety Labs (Serum Bile Acid, Lipids, Fat-Soluble Vitamins, and Coagulation)

16.1.5	Subject Profile: Fat-Soluble Vitamin Level Abnormalities
16.2.1✓	Analysis Populations and Treatment
16.2.2.1	Subject Disposition: Screen Failure
16.2.2.2✓	Subject Disposition: All Subjects Assigned Treatment
16.3.1	Inclusion and Exclusion Criteria
16.3.2✓	Major Protocol Deviations
16.3.3	Subjects Excluded from Efficacy Analysis
16.4.1✓	Demographics and Informed Consent
16.4.2✓	Medical History
16.4.3✓	PFIC Disease History
16.4.4*✓	Prior and Concomitant Medications
16.5	Liver Imaging
16.6.1✓	Study Drug Accountability and Compliance
16.6.2✓	Study Drug Exposure
16.7.1*✓	Total Serum Bile Acid
16.7.2*✓	Clinician Scratch Score
16.7.3.1*✓	Itch Reported Outcomes (Subject and Caregiver)
16.7.3.2*✓	Itch Reported Outcomes (Subject and Caregiver) Morning and Evening Average Scores
16.7.3.3*✓	Itch Reported Outcomes (Subject and Caregiver) Weekly Average Scores
16.7.4*✓	PIC, CIC, and CGTB
16.7.5*✓	Efficacy Laboratory Tests
16.7.6	Height, Weight, and BMI z-Scores
16.7.7.1*	Pediatric Quality of Life Inventory (Parent Report) – Total Scale and Summary Scores
16.7.7.2*	Pediatric Quality of Life Inventory (Subject Report) – Total Scale and Summary Scores
16.7.8.1.1	Pediatric Quality of Life Inventory (Parent Report for Infants) – Physical Functioning
16.7.8.1.2	Pediatric Quality of Life Inventory (Parent Report for Children 2–18 Years) – Physical Functioning

16.7.8.2 Pediatric Quality of Life Inventory (Parent Report for Infants) – Physical Symptoms

16.7.8.3.1 Pediatric Quality of Life Inventory (Parent Report for Infants) – Emotional Functioning

16.7.8.3.2 Pediatric Quality of Life Inventory (Parent Report for Children 2–18 Years) – Emotional Functioning

16.7.8.4.1 Pediatric Quality of Life Inventory (Parent Report for Infants) – Social Functioning

16.7.8.4.2 Pediatric Quality of Life Inventory (Parent Report for Children 2–18 Years) – Social Functioning

16.7.8.5 Pediatric Quality of Life Inventory (Parent Report for Infants) – Cognitive Functioning

16.7.8.6 Pediatric Quality of Life Inventory (Parent Report for Children 2–18 Years) – Nursery/Day Care/School Functioning

16.7.8.7.1 Pediatric Quality of Life Inventory (Subject Report) – Physical Functioning

16.7.8.7.2 Pediatric Quality of Life Inventory (Subject Report) – Emotional Functioning

16.7.8.7.3 Pediatric Quality of Life Inventory (Subject Report) – Social Functioning

16.7.8.7.4 Pediatric Quality of Life Inventory (Subject Report) – School Functioning

16.7.8.8.1 Multidimensional Fatigue Scale (Parent Report) – General Fatigue

16.7.8.8.2 Multidimensional Fatigue Scale (Parent Report) – Sleep/Rest Fatigue

16.7.8.8.3 Multidimensional Fatigue Scale (Parent Report) – Mental Fatigue

16.7.8.9.1 Multidimensional Fatigue Scale (Subject Report) – General Fatigue

16.7.8.9.2 Multidimensional Fatigue Scale (Subject Report) – Sleep/Rest Fatigue

16.7.8.9.3 Multidimensional Fatigue Scale (Subject Report) – Cognitive Fatigue

16.7.8.10.1 Family Impact Module (Parent Report) – Physical Functioning

16.7.8.10.2 Family Impact Module (Parent Report) – Emotional Functioning

16.7.8.10.3 Family Impact Module (Parent Report) – Social Functioning

16.7.8.10.4 Family Impact Module (Parent Report) – Cognitive Functioning

16.7.8.10.5 Family Impact Module (Parent Report) – Communication

16.7.8.10.6 Family Impact Module (Parent Report) – Worry

16.7.8.10.7 Family Impact Module (Parent Report) – Daily Activities

16.7.8.10.8 Family Impact Module (Parent Report) – Family Relationships

16.8.1*✓ Adverse Events

16.8.2.1*✓	Adverse Events of Special Interest: Fat-Soluble Vitamin Deficiency Events
16.8.2.2	Adverse Events of Special Interest: Diarrhoea Events
16.8.2.3	Adverse Events of Special Interest: Elevated Transaminases Events
16.8.2.4	Adverse Events of Special Interest: Elevated Bilirubin Events
16.8.3.1*✓	Serious Adverse Events
16.8.3.2	Serious Related Adverse Events
16.8.4.1*✓	Adverse Events Leading to Study Drug Discontinuation
16.8.4.2	Adverse Events Leading to Dose Reduction
16.8.5.1	Severe or Life Threatening Adverse Events
16.8.5.2✓	Life Threatening Adverse Events
16.8.6*✓	Adverse Events Causing Death
16.9.1*✓	Vital Signs
16.9.2✓	Physical Examination
16.10.1✓	Clinical Laboratory Tests: Clinical Chemistry
16.10.2	Clinical Laboratory Tests: Hematology
16.10.3	Clinical Laboratory Tests: Urinalysis
16.10.4	Clinical Laboratory Tests: Fat-Soluble Vitamins
16.10.5	Clinical Laboratory Tests: Lipid Panel
16.10.6	Clinical Laboratory Tests: Cholestasis Biomarkers
16.10.7✓	Clinical Laboratory Tests: Coagulation
16.10.8	Clinical Laboratory Tests: Hepatocellular Carcinoma Marker – Alpha-Fetoprotein (AFP)
16.10.9	Clinical Laboratory Tests: Timing of Sample Collection, Last Dose and Last Meal
16.10.10	Pregnancy Tests
16.11	Telephone Contact Log
16.12	Genotype Data
16.13	Plasma Sample MRX Concentrations
16.14	Palatability Questionnaire

Listings marked with an asterisk (*) were included in the second planned interim analysis.
Listings marked with a check mark (✓) were included in the third planned interim analysis.

AESIs for the final analysis include fat-soluble vitamin deficiency events, diarrhoea events, elevated transaminases events, and elevated bilirubin events. AESIs defined in previous, approved SAPs and were presented in interim analyses included fat-soluble vitamin deficiency events, GI related events, conditions associated with liver deterioration, GI related events and conditions associated with liver deterioration, thyroid function events, and growth retardation events.

15. Tables, Listings, and Listing Shells

15.1. 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
ADE	afternoon dose-escalation
AE	adverse event
AESI	adverse event of special interest
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPTT	activated partial thromboplastin time
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical; classification for drugs
BID	twice a day
BMI	body mass index
C4	7α hydroxyl-4-cholesten-3-one
BP	blood pressure
CBC	complete blood count
CDC	Center for Disease Control
CGTB	caregiver global therapeutic benefit
CIC	caregiver impression of change
CRF	case report form

Abbreviation	Definition
CSR	clinical study report
CSS	clinician scratch scale
CTCAE	Common Terminology Criteria for Adverse Events
DE	dose-escalation
DMC	data monitoring committee
eCRF	electronic case report form
eDiary	electronic diary
EMA	European Medicines Agengy
EOT	end of treatment
ET	early termination
FGF-19	fibroblast growth factor 19
FGF-21	fibroblast growth factor 21
FIC1	familial intrahepatic cholestasis 1
FDA	Food and Drug Administration
FSV	fat-soluble vitamins
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HDL-C	high-density lipoprotein cholesterol
HR	heart rate
HRQoL	health related quality of life

Abbreviation	Definition
ICH	International Conference on Harmonisation
INR	nternational normalized ratio
ItchRO™	Itch Reported Outcome
ItchRO (Obs)™	Itch Reported Outcome observer instrument
ItchRO (Pt)™	Itch Reported Outcome patient instrument
ITT	Intent-to-Treat
INR	international normalized ratio
IU	international unit(s)
LDL-C	low-density lipoprotein cholesterol
LLOQ	lower limit of quantitation
LOCF	last-observation-carried-forward
LPA	lysophosphatidic acid
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MRX	maralixibat chloride
PA2	protocol amendment 2
PA3	protocol amendment 3
PA4	protocol amendment 4
PedsQL	Pediatric Quality of Life Inventory
PFIC	progressive familial intrahepatic cholestasis

Abbreviation	Definition
PIC	patient impression of change
PP	Per-Protocol
PT	preferred term
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantitation
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

Appendix 2: Laboratory Tests for % Change from Baseline Presentation

CBC with Differential
- Hemoglobin
- Hematocrit
- Platelets
- White blood cells
- WBC Differential
  (absolute ONLY)
  - Neutrophils
  - Basophils
  - Lymphocytes
  - Monocytes
  - Eosinophils

Clinical Chemistry
- Bicarbonate
- Albumin
- Total bilirubin
- Direct bilirubin (conjugated)
- Indirect bilirubin (uncongugated)
- ALP
- AST (SGOT)
- ALT (SGPT)
- GGT

Lipid Panel
- Total cholesterol
- LDL-C (direct)
- HDL-C
- Triglycerides

Cholestasis Biomarkers
- Serum bile acids
- 7α hydroxy-4-colesten-3-one (C4)

Urinalysis
- Oxalate

Coagulation
- INR

Appendix 3: Listing of 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