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CLINICAL PROTOCOL

PROTOCOL NUMBER: LUM001-305

IMAGINE-II STUDY

A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Protocol Amendment 6.2: 13 May 2019

Protocol History

Original Protocol:	14 Apr 2014
Protocol Amendment 1:	29 Jan 2015
Protocol Amendment 2:	12 Feb 2015
Protocol Amendment 3:	27 Apr 2016 (not published)
Protocol Amendment 4:	27 Apr 2016*
Protocol Amendment 5:	13 Nov 2017*
Protocol Amendment 6:	25 Jun 2018
Protocol Amenment 6.1	08 Feb 2019

Developed in Collaboration with ChiLDReN

***NIDDK DSMB Approval Date: 13 May 2019**

THE CHILDHOOD LIVER DISEASE RESEARCH NETWORK

Mirum Pharmaceuticals, Inc.
70 Willow Road, Suite 200
Menlo Park, California 94025
USA

SPONSOR SIGNATURE PAGE

LUM001-305

IMAGINE-II STUDY

A MULT**I**CENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LU**M**001, AN **A**PICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALA**GI**LLE SY**N**DROM**E**

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*NIDDK DSMB Approval Date: 13 May 2019

Sponsor:
Mirum Pharmaceuticals, Inc.
70 Willow Road, Suite 200
Menlo Park, California 94025
USA

TITLE PAGE

Study Drug:	LUM001
Protocol Number:	LUM001-305
Amendment Number:	6.2
Date:	13 May 2019
IND No:	119917
Study Phase:	Phase 2
Protocol Title:	A Multicenter Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects with Alagille Syndrome
Sponsor:	Mirum Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, California 94025 USA
Medical Monitor:	Cagil Ozen, MD Premier Research Office: +1 215 282 5406 Cell: +1 267 838 2380 Email: medmonitorLUM501@premier-research.com
Medical Lead:	Thomas Jaecklin, MD Mirum Pharmaceuticals AG Innere Margarethenstrasse 5 4051 Basel Switzerland Phone: +41(0) 79 850 77 18 Email: tjaecklin@mirumpharma.com
Compliance Statement:	This study will be conducted in accordance with all applicable clinical research guidelines including the International Conference on Harmonization (ICH) Guidelines for current Good Clinical Practice (GCP). Study documents will be maintained in accordance with applicable regulations.

PROTOCOL SIGNATURE PAGE

Sponsor's (Mirum) Approval

Signature:	**Date:**
Thomas Jaecklin, MD SVP Clinical Development	23 May 19

I agree to conduct this study in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- Declaration of Helsinki (Oct 2008)
- Established principles of Good Clinical Practice (ICH E6; GCP) (Harmonized)
- US Code of Federal Regulations (CFR); Food and Drug Administration (FDA) (where applicable)

Clinical Study Title:

A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Protocol Number:	LUM001-305
Amendment Number:	6.2
Date:	13 May 2019
IND No:	119917
Sponsor:	Mirum Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, California 94025 USA

As Agreed:

Investigator's Signature **Date**

Investigator's Name (Please print)

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or email the Premier Research Serious Adverse Event Form within 24 hours to the Premier Research Pharmacovigilance Department. Applicable fax numbers and email address can be found on the form (sent under separate cover) and below.

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Fax: 215-972-8765, or

Email: GlobalPV-US@premier-research.com

For all urgent protocol- or safety-related issues during and outside of business hours, the investigator must contact the Premier Research Medical Monitor:

Cagil Ozen, MD, Medical Director

North America sites:
Central phone number: +1-512-686-1256 (US)

For non-emergencies, the Premier Research Medical Monitor may be contacted by e-mail: medmonitorLUM305@premier-research.com

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- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

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European Union and Rest of World	medinfo@mirumpharma.com

Telephone numbers (provided for reference if needed):

Mirum, Menlo Park, CA (USA)

1-650-667-4085

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Protocol Number: LUM001-305

Protocol Title: A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Amendment: **6.2**

Date: **13 May 2019**

The LUM001-305 protocol is being amended to reflect the date of the DSMB approval (13May2019) of changes made per Amendment 6.1 which was never operationalized.

1. STUDY SYNOPSIS

Sponsor	Mirum Pharmaceuticals, Inc
Protocol Number	LUM001-305
Protocol Title	A Multicenter Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects with Alagille Syndrome
Study Phase	2
Indication	Treatment of cholestatic liver disease in Alagille syndrome (ALGS)
Objectives	The primary objective of the study is to: • Evaluate the long-term safety and tolerability of LUM001 in pediatric subjects with ALGS. Secondary objectives of the study are to: • Evaluate the long-term effect of LUM001 on serum bile acid levels associated with ALGS. • Evaluate the long-term effect of LUM001 on pruritus associated with ALGS. • Explore the long-term effect of LUM001 on other biochemical markers of cholestasis and liver disease. • Evaluate the long-term effect of LUM001 on xanthomas associated with ALGS. • Explore an expanded dosing range to identify the doses necessary to achieve the optimal benefit-to-risk ratio for this patient population. Exploratory objective of the study is to: • Evaluate the long term effect of LUM001 on weight in pediatric subjects with ALGS.
Study Design	This is a multicenter, double-blind study of LUM001 in children ≥12 months of age diagnosed with ALGS who have completed participation in the LUM001-301 protocol. All subjects will receive active drug (LUM001) in the study. The study is divided into 6 parts: a dose escalation period, a dose optimization period, a stable dosing period, a safety monitoring period, and 2 long-term optional follow-up treatment periods. Dose Escalation Period All subjects entering the extension study will participate in a 4-week double-blind dose escalation period during which: • Subjects randomized to receive placebo during the LUM001-301 protocol will receive weekly dose increases of LUM001 up to a target dose of 140 µg/kg/day. • Subjects randomized to active drug during the LUM001-301 protocol will continue to receive the dose of LUM001 that they were taking at Week 13 of the LUM001-301 study. The LUM001 doses for these subjects will remain blinded and will not be altered during the dose-escalation period. A minimum period of 7 days must elapse between increases in dose. Dose Optimization Period Following completion of the 4-week dose escalation period, subjects will enter an 8-week dose-optimization period. During this period, the investigator will have the option to adjust LUM001 dosing with the objective of achieving optimal control of pruritus at a dose level that is

	tolerated by the subject and up to a maximum daily dose of 280 µg/kg LUM001 or 20 mg total dose. Study drug dose will be increased or decreased in a double-blind manner. Increases in dose will be based on effect on pruritus. Reductions in dose will be based on tolerability. At the investigator's discretion, the doses for subjects who were previously down-titrated may be re-challenged during the dose optimization period. Each subject will receive one of the following dose levels: • LUM001 35 µg/kg/day. • LUM001 70 µg/kg/day. • LUM001 140 µg/kg/day. • LUM001 280 µg/kg/day. A minimum period of 7 days must elapse between increases in dose. <u>Stable Dosing and Safety Monitoring Periods</u> Following completion of the 8-week dose optimization period, all subjects will enter the stable dosing period lasting 36 weeks followed by a safety monitoring period lasting up to 48 weeks. During the stable dosing and safety monitoring periods, subjects will be dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose. However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the ChiLDReN protocol chair and Medical Monitor, may lower the dose to a previously tolerated dose for the rest of the study. <u>Long-term Optional Follow-up Treatment Period:</u> The long-term optional follow-up treatment period is for eligible subjects who choose to remain on treatment with LUM001 following the initial 96 weeks of treatment. During this long-term optional follow-up treatment period, subjects with LUM001 dosing interruptions ≤7 days will remain on the same dose they were taking at Week 96. Subjects with LUM001 dosing interruptions >7 consecutive days will require dose escalation upon resumption of study drug. The dose of LUM001 will be increased at weekly intervals up to the subject's previously achieved highest tolerated dose. Study drug for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occur: (i) subjects complete 48 weeks of additional treatment (after Week 96 [safety monitoring period]), or (ii) the subjects are eligible to enter another LUM001 study. <u>Long-term Optional Follow-up Treatment Period-2:</u> The long-term optional follow-up treatment period-2 is for eligible subjects who choose to remain on treatment with LUM001 for an additional 72 weeks. During this long-term optional follow-up treatment period-2, subjects will remain on the same dose they were taking at Week 144. Study drug for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occur: (i) subjects complete 72 weeks of additional treatment (after Week 144 [Long-term Optional Follow-up Treatment Period]), or (ii) the subjects are eligible to enter another LUM001 (SHP625) study.
Number of Subjects	Approximately 36 subjects meeting the study's inclusion and exclusion criteria will be enrolled in the study.
Study Population	<u>Original Inclusion and Exclusion Criteria (through Protocol Amendment 4)</u> <u>Inclusion Criteria</u>

	To participate in this study, subjects must meet all of the following criteria: 1. Male or female, 12 months to 18 years of age. 2. Competent to provide informed consent and assent (per IRB/EC), as appropriate. 3. Completed participation in the LUM001-301 protocol. 4. Females of childbearing potential must have a negative urine pregnancy test [β human chorionic gonadotropin (β-hCG)] at the Baseline Visit. 5. Sexually active females must be prepared to use an effective method (≤ 1% failure rate) of contraception during the trial. Effective methods of contraception are considered to be: a. Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or b. Barrier method, eg, (a) condom with spermicide, or (b) diaphragm, with spermicide; or c. Intrauterine device (IUD). 6. Subjects above the age of assent and caregivers and children must be able to read and understand English or Spanish. 7. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site. 8. Caregivers (and age appropriate subjects) must be willing and able to complete a daily electronic diary (ItchRO) during the first consecutive 12 weeks of the study and then for 4 consecutive weeks following the Week 24 and Week 44 visits. 9. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the ItchRO electronic diary software at the outset of the study. 10. Eligible subjects must be able to adhere to local Ethics Committee (EC)or Institutional Review Board (IRB) blood volume limits for laboratory testing. <u>Exclusion Criteria</u> Subjects will be excluded from the study if they meet any of the following criteria: 1. Experienced an adverse event (AE) or serious adverse event (SAE) related to the study drug during the LUM001-301 protocol that led to the discontinuation of the subject from the LUM001-301 treatment study. 2. Any conditions or abnormalities (including laboratory abnormalities) which, in the opinion of the Investigator or Medical Monitor or ChiLDReN Protocol Chair, may compromise the safety of the subject, or interfere with the subject participating in or completing the study. 3. History or known presence of gallstones or kidney stones. 4. History of non-adherence during the subject's participation in the LUM001-301 protocol. Non-adherence is defined by dosing compliance of less than 80% in the LUM001-301 protocol. 5. Unlikely to comply with the study protocol, or unsuitable for any other reason, as judged by the investigator. <u>Protocol Amendment 5 Inclusion and Exclusion Criteria: Eligible subjects for the long-term optional follow-up treatment period</u> <u>Inclusion Criteria:</u>

	1. The subject has completed the protocol either through Week 96, or the ET visit, or has received permission from the sponsor and the ChiLDReN protocol chair to re-enter the study in the long-term, optional, follow-up treatment period. 2. Female subjects of child-bearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) at the time of entry into the long-term optional, follow-up treatment period. 3. Male and female subjects of child-bearing potential who are sexually active, or are not currently sexually active, but become sexually active during the study or for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study. 4. Informed consent and assent (per IRB/EC) as appropriate. 5. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site. 6. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study. <u>Exclusion Criteria:</u> All exclusion criteria for the original LUM001-305 study apply upon re-entry into the long-term, optional follow-up treatment period. <u>Protocol Amendment 6 Inclusion and Exclusion Criteria: Eligible subjects for the long-term optional follow-up treatment period-2</u> <u>Inclusion Criteria:</u> 1. The subject has completed the protocol through either Week 144, or the ET visit, or has received permission from the sponsor and the ChiLDReN protocol chair to re-enter the study in the long-term optional follow-up period-2. 2. Females of child-bearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) at the time of entry into the long-term optional follow-up treatment period-2. 3. Males and females of child-bearing potential who are sexually active, or are not currently sexually active, but become sexually active during the study or for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study. 4. Informed consent and assent (per IRB/EC) as appropriate. 5. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site. 6. Caregivers (and age appropriate subjects) must be willing to follow the rules of eDiary completion. <u>Exclusion Criteria:</u> All exclusion criteria for the original LUM001-305 study apply upon re-entry into the long-term optional follow-up treatment period-2.
Treatment Groups	Based on tolerability and effect on pruritus each subject will receive one of the following dose levels during the stable dosing, safety monitoring, and long-term, optional, follow-up treatment periods: • LUM001 35 μg/kg/day (up to a maximum daily dose of 2.5 mg). • LUM001 70 μg/kg/day (up to a maximum daily dose of 5 mg). • LUM001 140 μg/kg/day (up to a maximum daily dose of 10 mg).

<table>
<tr><td></td><td>

- LUM001 280 µg/kg/day (up to a maximum daily dose of 20 mg).

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<tr><td>Study Drug Dosage and Administration</td><td>

Study drug will be prepared by a central pharmacy based on the subject's weight. During the study, weight will be monitored at each visit. A change from baseline in a subject's weight that is greater than 10% will require a dose adjustment. Each subsequent 10% increase in weight will be considered the new baseline for determination of future dose adjustments. Weight-based dose adjustments will be made by the central pharmacy at the time of the subject's next LUM001 preparation.

Study drug will be dispensed to subjects/caregivers at the study site. The appropriate amount of study drug will be dispensed at the Study Day 0 visit and daily dosing will begin on Study Day 1. Subjects who weigh 10 kg or more will receive a 1.0 mL grape-flavored solution containing LUM001. Subjects who weigh less than 10 kg will receive 0.5 mL grape flavored solution containing LUM001. The volume, either 1.0 mL or 0.5 mL administered will not change during the course of the study. Dosing will occur up to 216 weeks of treatment. Each daily dose will be administered in the morning at least 30 minutes before breakfast (qAM, ac). Study drug should be administered approximately at the same time every day.

<u>Dose Escalation Period</u>

For subjects randomized to placebo in the LUM001-301 protocol, or those who complete the core study more than 7 days prior enrollment into this study, the LUM001 dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose)**.** For subjects who were randomized to receive active drug in the LUM001-301 protocol. LUM001 doses will remain the same as the dose being taken at Week 13 of the core study. Study treatment for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to a specified dose-escalation regimen. This regimen will represent a *real* dose escalation for subjects previously randomized to placebo and a *mock* dose escalation for subjects previously randomized to active study treatment.

The dosing regimen for each treatment group during the dose escalation period is summarized in the following table.

LUM001-301 Protocol	**Extension Study Protocol LUM001-305 Dose Escalation Period**			
Week 13 (µg/kg/day)	**Week 1 Days 1 - 7 (µg/kg/day)**	**Week 2 Days 8 - 14 (µg/kg/day)**	**Week 3 Days 15 - 21 (µg/kg/day)**	**Week 4 Days 22 - 28 (µg/kg/day)**
Placebo [1]	14	35	70	140
35 [2]	35	35	35	35
70 [3]	70	70	70	70
140 [4]	140	140	140	140
280 [5]	280	280	280	280

[1] For subjects randomized to placebo in the LUM001-301 protocol, or those who complete the core study more than 7 days prior enrollment into this study, the LUM001 dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose)**.**

[2] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 35 µg/kg/day will remain stable at 35 µg/kg/day, or to a maximum daily dose of 2.5 mg/day.

[3] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 70 µg/kg/day will remain stable at 70 µg/kg/day, or to a maximum daily dose of 5 mg/day.

[4] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 140 µg/kg/day will remain stable at 140 µg/kg/day, or to a maximum daily dose of 10 mg/day.

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[5] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 280 µg/kg/day will remain stable at 280 µg/kg/day, or to a maximum daily dose of 20 mg/day.

The primary anticipated adverse reaction or intolerance is gastrointestinal in nature (eg, diarrhea, abdominal pain, cramping, etc.). In the absence of GI intolerance, escalation to the next dose level for an individual patient may occur at the investigator's discretion, following a scheduled phone call or visit (see Schedule of Procedures, Section 16.1).

If a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the ChiLDReN protocol chair and Medical Monitor, may lower the dose to a previously tolerated dose for the remainder of the study.

Dose Optimization Period

Following the dose escalation period, the LUM001 dose for each subject may be increased and decreased by the investigator as clinically indicated for the control of pruritus at a dose level that is tolerated by the subject. Dose optimization will occur in a blinded, titrated manner with four dose levels available as treatment options: 35, 70, 140 or 280 µg/kg/day. Adjustments may occur at weekly intervals. Once an optimal LUM001 dose is achieved, the dose will be fixed for the duration of the study.

The maximum daily dose of LUM001 in this study is 280 µg/kg/day, up to a maximum daily dose of 20 mg. Blinded investigators may request dose adjustment for any subject based on an assessment of tolerability and effect on pruritus. Caregivers and age-appropriate subjects will be asked whether they wish to take a higher dose of the study medication to achieve greater relief of itching. If so, the dose may be adjusted upward, within the permitted dose range. However, the patient, caregiver, physician investigator, or the Medical Monitor may recommend against further escalation if there are safety or tolerability concerns. Doses of LUM001 will not be increased above 280 µg/kg/day or 20 mg per day at any time.

Stable Dosing and Safety Monitoring Periods

At the end of the dose optimization period, subjects will continue dosing to complete the stable dosing and safety monitoring periods for up to 96 weeks of cumulative LUM001 exposure in this study.

Subjects who completed the 48-week study prior to the implementation of Protocol Amendment #4 may be re-contacted and re-consented for participation in the safety monitoring period of the study.

If, at any time during the study, a subject experiences intolerance due to gastrointestinal symptoms, the physician investigator may lower the dose to a previously tolerated dose.

Long-term Optional Follow-up Treatment Period:

At Week 96, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll over into the long-term optional follow-up treatment period. Following the completion of the Week 96 study visit, subjects who choose to participate in the long-term optional follow-up treatment period will be maintained at the same Week 96 dose level. Subjects with dose interruptions >7 consecutive days prior to implementation of Protocol Amendment 5 will be rescreened and require dose escalation upon resumption of study drug. The dose of LUM001 will be increased at weekly intervals up to the subject's previously tolerated dose under Protocol Amendment 4. Subjects who do not wish to enter the long-term, optional follow-up treatment period will be contacted via telephone by the study site approximately 30 days after the last dose of the study drug.

Subjects who either completed the 96-week study prior to the implementation of Protocol Amendment 5, or have received permission from the ChiLDReN protocol chair and the Medical Monitor, may be recontacted and reconsented for participation in the long-term, optional follow-up treatment period of the study.

Study drug administration under Protocol Amendment 5 will not change from Protocol Amendment 4.

Long-term Optional Follow-up Treatment Period-2:

At Week 144, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll over into the long-term optional follow-up treatment period-2. Following the completion of the Week 144 study visit, subjects who choose to participate in the long term optional follow-up treatment period-2 will be maintained at the same Week 144 dose level. Subjects who do not wish to enter the long term optional follow up treatment period-2 should complete the in-clinic Week 148 Visit 30 days after the last dose of study drug.

Subjects who either completed the 144-week study prior to the implementation of Protocol Amendment 6, or have received permission from the ChiLDReN protocol chair and the Medical Monitor, may be recontacted and reconsented for participation in the long-term, optional follow-up treatment period-2 of the study.

Study Drug Administration under Protocol Amendment 6 will not change from Protocol Amendment 5.

Dose Escalation Following Dose Interruptions

Subjects with interruptions in LUM001 dosing of more than 7 consecutive days during the stable dosing, safety monitoring, and long-term optional follow-up treatment periods, will require dose escalation upon resumption of the study drug. The dose of LUM001 will be increased at weekly intervals up to the subject's previously achieved highest tolerated dose. Study drug for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen.

Dose Escalation Regimen for Resumption of LUM001 Dosing When Dosing Interruption is Greater Than 7 Consecutive Days

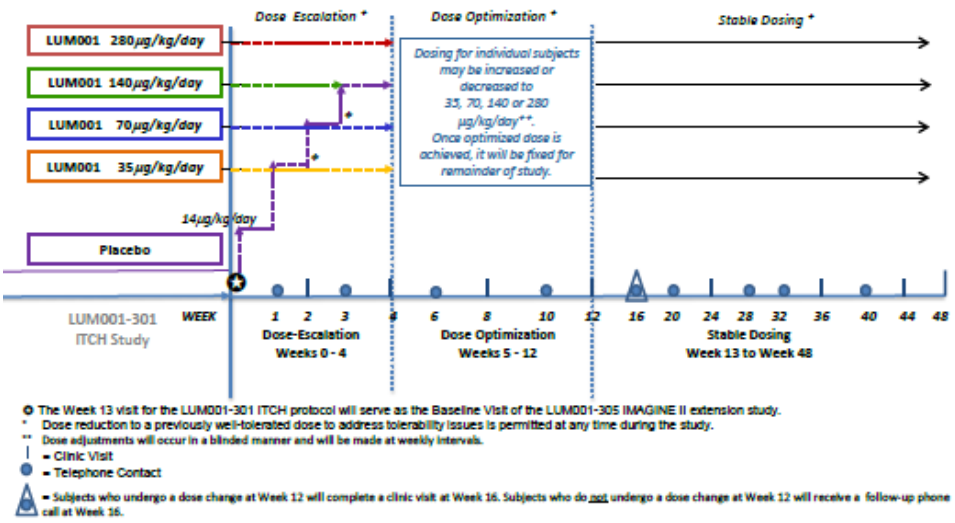
Week 1 (µg/kg/day)	Week 2 (µg/kg/day)	Week 3 (µg/kg/day)	Week 4 (µg/kg/day)
35	70 [1]	140 [1]	280 [1]

[1] Weekly dose escalations will end once the highest tolerated dose achieved prior to the subject's LUM001 dosing interruption is reached.

Rationale for Dose and Schedule Selection	The dosage of LUM001 for the first studies in pediatric cholestatic subjects was based upon prior experience with this investigational product in healthy volunteers and subjects with hypercholesterolemia. In these subjects, with normal bile flow and without liver disease, tolerability was limited above 10 mg daily by an increase in gastrointestinal (GI) AEs. These signs and symptoms are believed to be related to increased bile acid excretion and a concomitant increase in the concentration of free bile acids in the lower colon. Subjects with cholestatic liver disease have reduced bile flow compared to healthy volunteers and hypercholesterolemic subjects. LUM001 is likely to produce a smaller increase in free bile acids in the lower colon. There is also evidence in subjects with cholestasis to suggest that ASBT expression may be upregulated and higher LUM001 concentrations may be required to achieve the desired target inhibition of ASBT. Dosing in pediatric subjects will be based on subject weight. Earlier studies in healthy volunteers and hypercholesterolemic subjects demonstrated that doses of 10 mg daily, equivalent to 140 µg/kg/day for a 70 kg subject, led to a decrease in serum bile acids by >50% following 2 weeks of treatment. In previous studies with LUM001, GI AEs were generally recorded in the first week of LUM001 dosing. After 2 to 3 weeks of continuous dosing the observed rates of events was similar to those in the placebo group. In a 4-week dose finding study in healthy volunteers, a dose escalation regimen was evaluated to mitigate the risk of loose stools and diarrhea. When the LUM001 dose was increased after each 7-day dosing period, to a maximum of 5 mg daily, the incidence of GI-associated AEs in the LUM001 treated arm was reduced to rates comparable to those reported in the placebo group. The starting dose in this clinical trial may be as low as 14 µg/kg/day, is equivalent to less than the well-tolerated 1 mg dose (~17 µg/kg, 60 kg body weight) used in a previous study (Study 014), where LUM001 was tested at doses up to 5 mg/day for 14 days in 40 hyperlipidemic pediatric subjects (n=5, children ages 10-11; n=35, adolescents ages 12-17), At the 1 mg dose in Study 014, only two out of eight subjects reported moderate or severe GI-associated AEs during 14 days. On a weight basis, 23 subjects received a dose ≥14 µg/kg/day. The highest starting dose in Study 014 was 168 µg/kg/day. To reduce the risk of loose stools and diarrhea in the current study, escalation of LUM001 doses for LUM001-naïve subjects will occur at 7-day intervals starting at 14 µg/kg/day and increasing to 35 µg/kg/day, 70 µg/kg/day, and 140 µg/kg/day. Thereafter, the dose of LUM001 may be adjusted for all study subjects during the dose-optimization period. A minimum period of 7-days must elapse between increases in dose. Dose adjustments will be made at the investigator's discretion with the goal of reaching a dose optimized for maximum efficacy and tolerability of 35, 70, 140 or 280 µg/kg/day. The dose may also be down-titrated, at the investigator's discretion and in consultation with the ChiLDReN protocol chair and the Medical Monitor, for subjects experiencing intolerance to a given dose.
Study Visit Schedule and Procedures	For an individual subject, the study participation period will consist of a 4-week dose escalation period, followed by 8-weeks of dose optimization, a 36-week stable dosing period, a 48-week safety monitoring period, a 48-week long-term optional, follow-up treatment period, and a 72-week long-term optional, follow-up treatment period-2. Planned participation for each subject enrolled in the extension study is a maximum of 220 weeks, inclusive of the safety follow-up contact approximately 30 days after the last dose of LUM001. Study activities will be conducted as described in the Schedule of Procedures (Section 16.1).

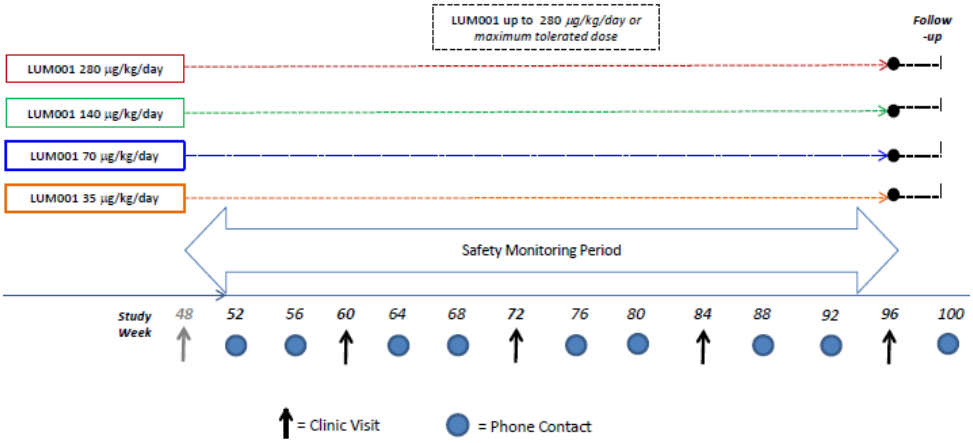
Study Scheme (as described below):

Day 0-Week 48



The Week 13 visit for the LUM001-301 ITCH protocol will serve as the Baseline Visit of the LUM001-305 IMAGINE II extension study.
* Dose reduction to a previously well-tolerated dose to address tolerability issues is permitted at any time during the study.
** Dose adjustments will occur in a blinded manner and will be made at weekly intervals.
= Clinic Visit
= Telephone Contact
= Subjects who undergo a dose change at Week 12 will complete a clinic visit at Week 16. Subjects who do not undergo a dose change at Week 12 will receive a follow-up phone call at Week 16.

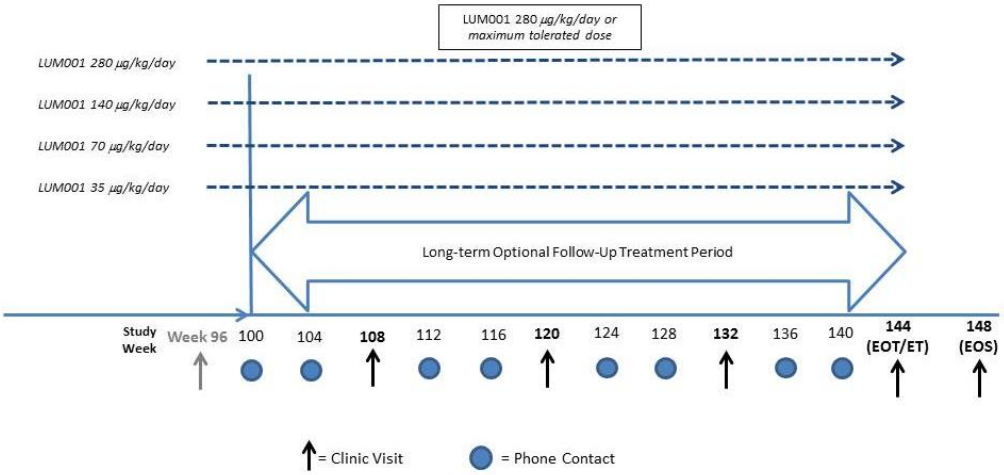
Week 49 – Week 96



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

Week 96 – Week 148

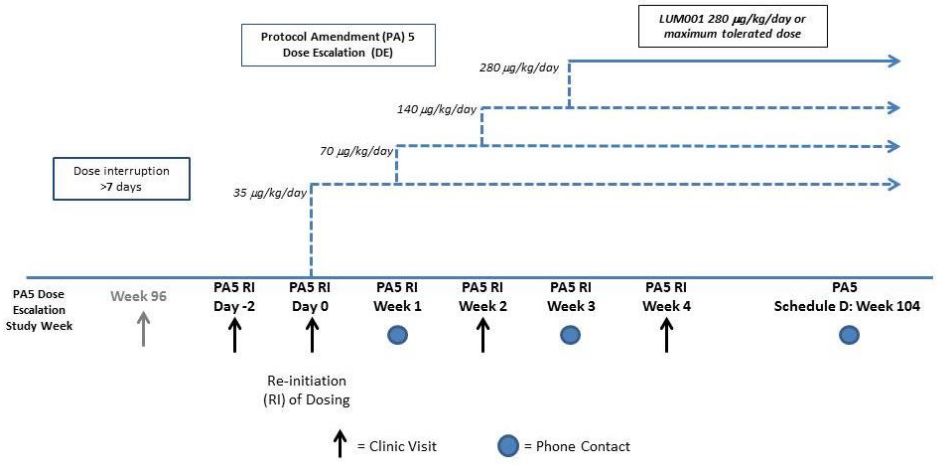
(no interruption in LUM001 dosing, or interruption ≤7 days between Week 96 and Week 100)



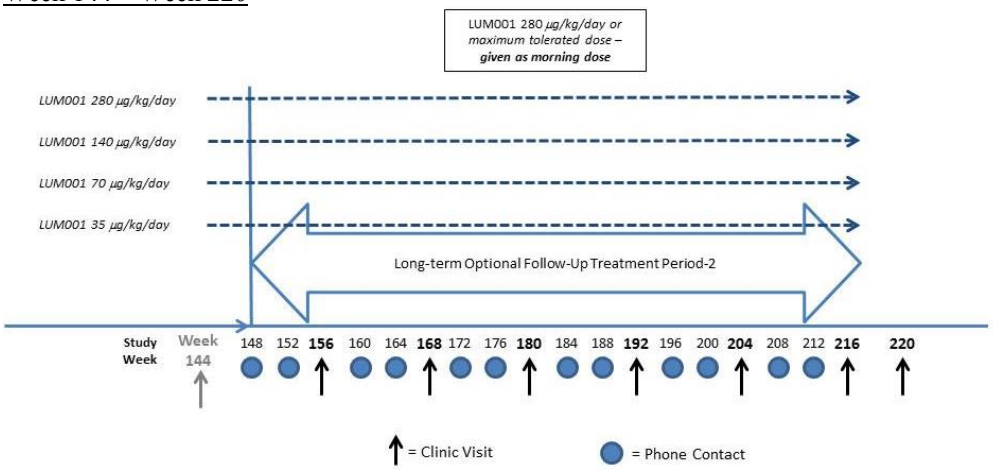
In consultation with the ChiLDReN protocol chair and the Sponsor Medical Monitor, the dose may be lowered to a previously well-tolerated dose to address tolerability issues at any time during the study

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

Week 96 – Week 148
(interruption >7 days between Week 96 and Week 100)



Week 144 – Week 220



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

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

Baseline (Day 0): Evaluations and procedures completed for the Week 13 Visit of the LUM001-301 study will also serve as the evaluations for the Baseline Visit for the extension study. Informed consent and/or assent for participation in the extension study must be obtained for all participating subjects and their parents or legal guardians, as appropriate. At the Baseline visit (Week 0), subjects will be assessed to confirm continued study eligibility including a review of medical history and will undergo a physical examination including body weight, height, and vital signs. Blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers as well as for PK analysis (plasma levels of LUM001). The clinician scratch scale will be administered, as well as the PedsQL. Female subjects of childbearing potential will have a urine pregnancy test and concomitant medications and any AEs will be recorded. The degree and severity of xanthomatosis will be evaluated for all subjects by the clinician xanthoma scale. Study drug for Weeks 1 and 2 will be supplied at the Baseline visit to eligible subjects.

Dose Escalation Period (Week 0 to Week 4): Double-blind dosing in the dose escalation period will be initiated on the morning after the Baseline Visit. Caregivers and age appropriate subjects will be instructed to complete their ItchRO electronic diary twice daily (morning and evening). Subjects will return to the clinic at Weeks 2, and 4, and will receive follow-up phone calls at Weeks 1 and 3. On clinic visit days, safety and clinical laboratory evaluations will be performed. The clinician scratch scale will be administered, adherence to study drug will be assessed and additional dosing instructions will be supplied. Study diary compliance will be assessed and concomitant medications and any AEs will be recorded at clinic visits and at scheduled telephone contacts. Additional study drug will be supplied at Weeks 2 and 4.

Dose Optimization Period (Week 5 to Week 12): During the dose optimization period, the dose for each subject may be increased or decreased at the investigator's discretion in a double-blind manner. The purpose of the dose optimization period is to allow the investigator to adjust the subject's LUM001 dose to a level that is both tolerable to the subject and maximizes the potential effect of LUM001 on pruritus. Once an optimal dose is achieved, the dose will be fixed for the duration of the study.

Electronic diaries will be completed twice daily by age-appropriate subjects and caregivers through Week 12 and then collected. Subjects will return to the clinic at Weeks 8 and 12 and will receive follow-up telephone calls at Weeks 6 and 10. At the clinic visits, safety and clinical

	laboratory evaluations will be performed and vital signs, height and weight measurements will be collected. The clinician scratch scale will be administered and a review of study diary and medication compliance will be completed. Concomitant medications and any AEs will be assessed and recorded at each visit and at scheduled telephone contacts. Additional study drug will be supplied at Weeks 8 and 12. Stable Dosing Treatment Period (Week 13 to Week 48): Subjects will continue to receive study drug during the stable dosing treatment period according to the dose achieved during the dose optimization period. However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the ChiLDReN protocol chair and Medical Monitor, may lower the dose to a previously tolerated dose for the remainder of the study. During the stable dosing period, subjects will return to the clinic at Weeks 24, 36, 44 and 48. Subjects who undergo a dose change at the Week 12 visit will also return to the clinic at Week 16 (see below). With the exception of Week 44, safety and clinical laboratory evaluations, blood sampling for study drug determination, and a physical exam (including collection of vital signs, height and weight measurements) will be completed at each clinic visit. In addition, the clinician scratch scale and clinician xanthoma scale will be administered and study drug compliance will be assessed. The PedsQL will be completed at Weeks 24 and 48 the Caregiver Impression of Change (CIC) will be completed at Week 48. Subjects/caregivers will receive follow-up phone calls at Weeks 16, 20, 28, 32 and 40. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts. Subjects who undergo a dose change at the Week 12 visit will complete an on-site clinic visit at Week 16. Subjects who do not undergo a dose change at Week 12 will receive a follow-up phone call at Week 16. The study activities that will be conducted at the Week 16 clinic visit are described in the Schedule of Procedures (Section 16.1). Electronic diaries will be completed by age-appropriate subjects and caregivers following the Week 24 and Week 44 visits. The diaries will be redistributed at Week 24 and completed twice daily for 4 weeks before being collected at Week 28. The diaries will then be redistributed at Week 44 and completed twice daily until the end of the study (Week 48). Re-training on the use of the diary will occur as appropriate at the Week 24 and Week 44 visits. At the physician investigator's discretion, tapering or withdrawal of concomitant medications used for the treatment of pruritus may occur during the stable dosing period. With the exception of Week 44, additional study drug will be supplied at each clinic visit during the stable dosing period.

	Safety Monitoring Period (Week 49 to Week 96): During the safety monitoring period, subjects will return to the clinic every 3 months, at Weeks 60, 72, 84, and 96. Safety and clinical laboratory evaluations and a physical exam (including collection of vital signs, height, and weight measurements) will be completed at each clinic visit. The clinician scratch scale will also be completed at each clinic visit and study drug compliance will be assessed. The PedsQL, CIC, and the Clinician Xanthoma scale will also be administered at Weeks 60, 72, 84, and 96. Subjects/caregivers will receive follow-up phone calls at Weeks 52, 56, 64, 68, 76, 80, 88, and 92. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts. Twice daily completion of the ItchRO electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, 84, and 96 clinic visits. Review of electronic diary data and assessment of compliance will occur during scheduled telephone contacts at Week 64, 76, and 88 and during the Week 96 clinic visit. Electronic diaries will be provided to subjects and caregivers at these visits and re-training on the use of the diary will occur, as appropriate. At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the safety monitoring period. Additional study drug will be supplied at each clinic visit during the follow-up treatment period. Week 96: Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the long-term, optional follow-up treatment period. This will include a formal reassessment of the Protocol Amendment 5 inclusion and exclusion criteria and consenting of the subject at Week 96 per Schedule C. Eligible subjects must have documented consents in order to continue in the long-term, optional follow-up treatment period. A physical exam (including collection of vital signs, height and weight measurements) will be performed. Blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis (plasma levels of LUM001). The clinician scratch scale and PedsQL will be administered and the degree and severity of xanthomatosis will be evaluated for all subjects using the clinician xanthoma scale. Review of the ItchRO electronic diary data and assessment of compliance will occur during the Week 96 clinic visit. The electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Twice daily completion of the diary will be required during the 2 weeks following the Week 96 clinic visit. Female subjects of childbearing potential will have a urine pregnancy test and concomitant medications and any AEs will be recorded. Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected. Study drug will be discontinued at this visit if the subject chooses not to participate in the long-term, optional follow-up treatment period. Subjects will be encouraged to complete all study activities and visits. Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week 96 visit, with the exception of the ItchRO assessment. For safety reasons, efforts must be made to follow subjects for at least 30 days following their last dose of study drug. Follow-up Phone Call (30 days after Last Dose): For subjects who do not roll over into the long-term, optional follow-up treatment period, a safety follow-up phone call will be made 30 days after the last dose of study drug for subjects participating in all versions of the protocol up through Protocol Amendment 4. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and any AEs noted during this phone call will be recorded. For subjects who participate in the

long-term, optional follow-up treatment period, this phone call will be replaced by the Week 148 end of study (EOS) clinic visit. For subjects who participate in the long-term, optional follow-up treatment period-2, this phone call will be replaced by the Week 220 (EOS) clinic visit.

Long-term, Optional Follow-up Treatment Period (Week 96-148): Once Protocol Amendment 5 is implemented at the site, subjects who are eligible and consent for entry into the long-term, optional follow-up treatment period will continue to receive study drug until the first of the following occurs:

(i) The subjects complete 48 weeks of additional treatment after Week 96 (safety monitoring period)

(ii) The subjects are eligible and consent to enter another LUM001 study

Subjects with no LUM001 dosing interruptions or interruptions ≤7 days will continue to receive the same LUM001 dose they last received during LUM001-305 (Week 96 dose). Study activities will proceed as outlined in Schedule D.

Subjects with LUM001 dosing interruptions >7 days will be rescreened and dose escalated up to 280 µg/kg/day or the highest tolerated dose over 4 weeks beginning at 35 µg/kg/day (see Figure 6). Study activities will proceed as outlined below and in Schedule E.

- Protocol Amendment (PA) 5 Re-initiating (RI) Day -2 Clinic Visit: Consent (and/or assent as applicable) are obtained; eligibility criteria are confirmed. Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Concomitant medications and AEs will be recorded.
- PA5 RI Day 0 Clinic Visit: Eligibility criteria are confirmed. Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Clinician scratch scale, clinician xanthoma scale, and PedsQL are completed. Concomitant medications and AEs will be recorded. Study drug is dispensed and subject begins dosing at 35 µg/kg/day dose level.
- PA5 RI Week 1 Telephone Contact: Concomitant medications and AEs will be recorded. Subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated.
- PA5 RI Week 2 Clinic Visit: Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Clinician scratch scale, clinician xanthoma scale, and PedsQL are completed. Concomitant medications and AEs will be recorded. Study drug is dispensed and subject escalates to 140 µg/kg/day dose, if prior dose level was tolerated.
- PA5 RI Week 3 Telephone Contact: Concomitant medications and AEs will be recorded. Subject escalates to 280 µg/kg/day dose level or previous maximum tolerated dose, if prior dose level was tolerated.
- PA5 RI Week 4 Clinic Visit: Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Clinician scratch scale, clinician xanthoma scale, and PedsQL are completed. The ItchRO electronic diaries will be provided to subjects and caregivers and re-training on the use of the diary will occur, as appropriate. Twice daily completion of the electronic diary will be required during the 2 weeks following this visit. Concomitant medications and AEs will be recorded. Study drug is dispensed and subject continues dosing at 280 µg/kg/day dose level or on maximum tolerated dose.

	• PA5 Schedule D Week 104 Telephone Contact (4 weeks after PA5 RI Week 4 Clinic Visit): Concomitant medications and AEs will be recorded. Subjects will then follow study activities as outlined in Schedule D. Per Schedule D, subjects will return to the clinic every 12 weeks at Weeks 108, 120, 132, 144, (end of treatment/early termination [EOT/ET]), and at Week 148 (EOS). During the clinic visits, physical exam, body weight and height, vital signs, urine samples, and blood samples for clinical laboratory testing including fasting lipid panel and fat soluble vitamins, bile acids, and other cholestasis biochemical markers will be collected. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale and the clinician xanthoma scale will be assessed at every clinic visit. The PedsQL questionnaire and CIC will be administered at Weeks 108, 144 and 148. Review of the ItchRO electronic diary data and assessment of compliance will occur during the Week 112, 124, and 136 telephone contacts. The ItchRO electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Twice daily completion of the electronic diary will be required during the 2 weeks following the Week 96, 108, 120, and 132 clinic visits and during the 4 weeks following the Week 144 visit. Subjects rolling over into the long-term optional follow-up treatment period-2 will complete the electronic diary for 2 weeks following the Week 144 visit. Female subjects of childbearing potential will have a urine pregnancy test at each clinic visit prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and AEs will be collected. Telephone Contact will occur at Weeks 100, 104, 112, 116, 124, 128, 136, and 140 where collection of concomitant medications and any AEs will be recorded. Week 144: Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the long-term, optional follow-up treatment period-2. This will include a formal reassessment of the Protocol Amendment 6 inclusion and exclusion criteria and consenting of the subject at Week 144, per Schedule D. Eligible subjects must have documented consents in order to continue in the long-term, optional follow-up treatment period-2. Subjects who withdraw from the study prior to completion of the long-term, optional follow-up treatment period, should also undergo the procedures specified for the EOT/ET visit (Week 144). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis plasma levels of LUM001). In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL and the clinician xanthoma scale. The CIC assessment will be completed. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded. Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected. Study drug will be discontinued at this visit if the subject chooses not to participate in the long-term, optional treatment period-2. Review of the ItchRO electronic diary data and assessment of compliance will occur during the Week 144 clinic visit. The electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Twice daily completion of the diary will be required for 2 weeks following the Week 144 clinic visit for subjects rolling over into the long-term, optional follow-up treatment period-2. Subjects not rolling over into long-term, optional follow-up treatment period-2 will be asked to complete the diary for 4 weeks following Week 144. Week 148: Subjects who either elect not to participate in, or who are not eligible to participate in the long-term, optional, follow-up treatment period-2 will return to the study site 30 days after the last dose of study drug and undergo the procedures specified for the EOS visit (Week 148). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and

	other cholestasis biochemical markers, as well as for PK analysis plasma levels of LUM001). In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL, the clinician xanthoma scale, and the CIC. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded. Long-term Optional Follow-up Treatment Period-2 (Week 144 - 220): Once Protocol Amendment 6 is implemented at the site, subjects who are eligible and consent for entry into the long-term, optional follow-up treatment period-2 will continue to receive study drug until the first of the following occurs: (i) The subjects complete 72 weeks of additional treatment after Week 144 (long-term, optional follow-up treatment period) (ii) The subjects are eligible and consent to enter another LUM001 (SHP625) study Subjects rolling over into the long-term optional follow-up treatment period-2 will continue to receive the same LUM001 dose they last received during LUM001-305 (Week 144 dose) (refer to Figure 7). Study activities will proceed as outlined in Schedule of Procedures F. Subjects with dose interruptions after Week 48 and prior to Week 96, or who early terminated, may re-enter the study with the permission from the sponsor and the ChiLDReN protocol chair. These subjects will initiate dose escalation at visit PA5 RI -2 (per Schedule of Procedures E) and then will follow study activities beginning at Week 104 (per Schedule of Procedures D). Per Schedule of Procedures F, subjects will return to the clinic every 12 weeks at Weeks 156, 168, 180, 192, 204, 216 (EOT/ET visit) and at Week 220 (EOS visit). During the clinic visits, physical exam, body weight and height, vital signs, urine samples, and blood samples for clinical laboratory testing including fasting lipid panel and fat soluble vitamins, bile acids, and other cholestasis biochemical markers will be collected. The clinician scratch scale and clinician xanthoma scale will be assessed at every clinic visit. The PedsQL questionnaire and the CIC will be administered at Weeks 156, 216 and 220 clinic visits. The ItchRO electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Caregivers are not required to complete the eDiary (ItchRO[Obs]) if the subject is living separately from the ItchRO observer; however, subjects ≥9 years of age will be required to complete ItchRO(Pt). Twice daily completion of the electronic diary will be required during the 2 weeks following the Week 144, 156, 168, 180, 192, and 204 clinic visits and during the 4 weeks following the Week 216 (EOT/ET) visit. Review of the ItchRO electronic diary data and assessment of compliance will occur during scheduled telephone contacts at Week 148, 160, 172, 184, 196, 208 and during the Week 220 clinic visit. Female subjects of childbearing potential will have a urine pregnancy test at each clinic visit prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and AEs will be collected. Telephone Contact will occur at Weeks 148, 152, 160, 164, 172, 176, 184, 188, 196, 200, 208 and 212 where collection of concomitant medications and any AEs will be recorded. Week 216 (EOT/ET): Subjects who either complete the long-term optional follow-up treatment period-2 or who withdraw from the study prior to completion should undergo the procedures specified for the EOT/ET visit (Week 216). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis of LUM001 plasma levels In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL, the clinician xanthoma scale, and the CIC. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded. Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected. Study drug will be discontinued at this visit.

	Week 220 (EOS): All subjects will return to the study site 30 days after the last dose of study drug and undergo the procedures specified for the EOS visit (Week 220). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis plasma levels of LUM001). In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL, the clinician xanthoma scale, and the CIC. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded.
Drug Level Evaluations	Plasma levels of LUM001 will be evaluated at Baseline and Weeks 2, 4, 8, 12, 24, 36, 48, 96, 216 (EOT/ET) and 220 (EOS). Blood will be drawn approximately 4 hours post-dosing for drug level analysis**.**
Safety and Tolerability Evaluations	The safety and tolerability of LUM001 will be assessed by determining the incidence, relationship to study drug, severity and seriousness of treatment-emergent AEs, withdrawals due to AEs, and changes in vital signs, laboratory and other safety parameters. Alterations in liver parameters assessed for the purposes of safety monitoring will be relative to the baseline (Day 0) of the LUM001-301 protocol in which the subject was enrolled. A Data Safety Monitoring Board (DSMB) will review SAE data, other key subject safety and study data at specified intervals for the duration of the study.
Efficacy Evaluations	The primary evaluation will be the mean change from baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 to Week 48 in: • Fasting serum bile acid level. Secondary evaluations will be the mean change from baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 through Week 216/EOT in: • Biochemical markers of cholestasis and liver disease (eg, alanine aminotransferase [ALT], alkaline phosphate [ALP], gamma-glutamyltransferase [GGT] and bilirubin [total and direct]). • Pruritus as measured by the electronic diary ItchRO instruments (ItchRO(Obs)™, caregiver instrument/ItchRO(Pt) ™ patient instrument). • During the first 12 weeks of the study, the electronic diary (ItchRO) will be completed twice daily (AM & PM). During the stable dosing period (Weeks 13-48), twice daily completion of the electronic diary (ItchRO) for 4 consecutive weeks will be required following the Week 24 and Week 44 clinic visits. For subjects who continue in the safety monitoring period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 60, 72, and 84 clinic visits. For subjects who continue in the long-term optional follow-up treatment period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 96, 108, 120 and 132 clinic visits and for 4 weeks following the Week 144 visit. For subjects who continue in the long-term optional follow-up treatment period-2, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 144, 156, 168, 180, 192, and 204 clinic visits, and for 4 weeks following the Week 216 visit. • Xanthomas as measured by clinician xanthoma scale. • Clinician scratch scale • Fasting serum bile acid levels The exploratory evaluation will be the mean change in weight z-score from baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 through Week 216 (EOT/ET).

	Exploratory evaluations will include the mean change from baseline in ItchRO, fasting sBA, and biochemical markers of cholestasis and liver disease at Week 144, Week 216 (EOT/ET), and at Week 220 (EOS). Additional exploratory evaluations will be specified in the statistical analysis plan and may include analyses between Week 144 (EOT/ET) and Week 148 (EOS) for subjects who complete Protocol Amendment 5 and between Week 216 (EOT/ET) and Week 220 (EOS) for subjects who complete Protocol Amendment 6.
Statistical Considerations	Sample Size Approximately 36 subjects meeting the study's inclusion and exclusion criteria will be enrolled in the study. The number of subjects enrolled in this study will be determined by the number of subjects who roll-over from the LUM001-301 protocol. Because this is an extension study for the LUM001-301 protocol, the sample size is not based on statistical considerations. Safety All safety analyses will be performed on the Safety Population, defined as all subjects who received at least one dose of the study drug during the extension study. Adverse Events will be examined over the entire treatment period, and for the dose escalation and optimization periods. Adverse events for each study period will be summarized overall by treatment group based on the treatment group at enrollment in the extension study at baseline (Study Day 0). Adverse events for the stable dosing period will also be summarized overall and by treatment group based on the stable dosing group. Other safety measures including clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation and range will be given for the values themselves and by their mean changes from pre-defined reference points (see below) at each visit. Qualitative variables will be summarized using counts and percentages by baseline treatment group at each study visit. Drug Level Analysis Descriptive statistics analysis of LUM001 concentrations will be carried out on the plasma concentration data. Efficacy All efficacy analyses will also be performed on the Safety Population, defined as all subjects who received at least one dose of the study drug during the extension study. Secondary efficacy measures will be analyzed similarly as above. Details of the analysis methods will be outlined in the SAP. All data will be included in data listings.

2. LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
µg	microgram
µM	micromolar
7αC4, C4	7α-hydroxy-4-cholesten-3-one; an indirect method of bile acid synthesis
AE	adverse event
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPTT	activated partial thromboplastin time
ASBT	apical sodium-dependent bile acid transporter
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase (SGOT)
ATC	Anatomic Therapeutic Chemical; classification for drugs
β-hCG	beta-subunit of human chorionic gonadotropin; pregnancy test
BA	bile acid
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
cholesterol 7α-hydroxylase	rate-limiting enzyme in the synthesis of bile acid from cholesterol
CIC	Caregiver Impression of Change
CMV IgM	cytomegalovirus IgM antibody
CRF	case report form
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
dL	deciliter
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor 19; regulates carbohydrate, lipid and bile acid metabolism
FGF-21	fibroblast growth factor 21; modulates hepatic metabolism

Abbreviation	Definition
G	gram
GCP	good clinical practices
GGT	gamma-glutamyltransferase
GGTP (γGTP)	gamma-glutamyl transpeptidase
GI	gastrointestinal
HAV IgM	Hepatitis A virus IgM antibody
HbsAg	surface antigen of the hepatitis B virus
HCV	Hepatitis C virus
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HR	heart rate
HRQoL	health related quality of life
IAF	informed assent form
IB	Investigator's Brochure
IBAT	ileal bile acid transporter
IBATi	ileal bile acid transporter inhibitor
ICF	informed consent form
ICH	International Conference on Harmonization
INR	international normalized ratio
IRB	institutional review board
ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Itch Reported Outcome observer instrument
ItchRO(Pt)™	Itch Reported Outcome patient instrument
IUD	intrauterine device
Kg	kilogram
L	liter
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LPA	lysophosphatidic acid
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mmol	millimole
MRI	magnetic resonance imaging

Abbreviation	Definition
NBD	nasobiliary drainage
NCS	not clinically significant
ObsRO	observer reported outcome
PA	Protocol amendment
PBC	primary biliary cirrhosis
PEBD	partial external biliary diversion
PedsQL	Pediatric Quality of Life Inventory
PFIC	progressive familial intrahepatic cholestasis
PI	principal investigator
PK	pharmacokinetic
PROM	patient reported outcome measure
Pt	patient
PT	prothrombin time
q.s.	quantity sufficient
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SD-5613	original designation for LUM001
Sec	second
SLC10A2	solute carrier family 10 member 2; gene that encodes ASBT protein
SUSAR	suspected unexpected serious adverse reaction
TG	triglycerides
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
US, USA	United States of America
WBC	white blood cell
WHO	World Health Organization
WMA	World Medical Association

3. STUDY OBJECTIVES

The primary objective of the study is to:

- Evaluate the long-term safety and tolerability of LUM001 in pediatric subjects with Alagille syndrome (ALGS).

Secondary objectives of the study are to:

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

Exploratory objective of the study is to:

- Evaluate the long-term effect of LUM001 on weight in pediatric subjects with ALGS.

4. BACKGROUND AND RATIONALE

LUM001 is an inhibitor of the ileal bile acid transporter/apical sodium-dependent bile acid transporter/soluble carrier family 10 member 2 (IBAT/ASBT/SLC10A2), initially developed as a lipid lowering agent (SD-5613). At this time, further development for this indication is not planned. By virtue of its ability to inhibit bile acid absorption, LUM001 is being developed as a therapeutic agent for signs and symptoms of cholestatic liver disease.

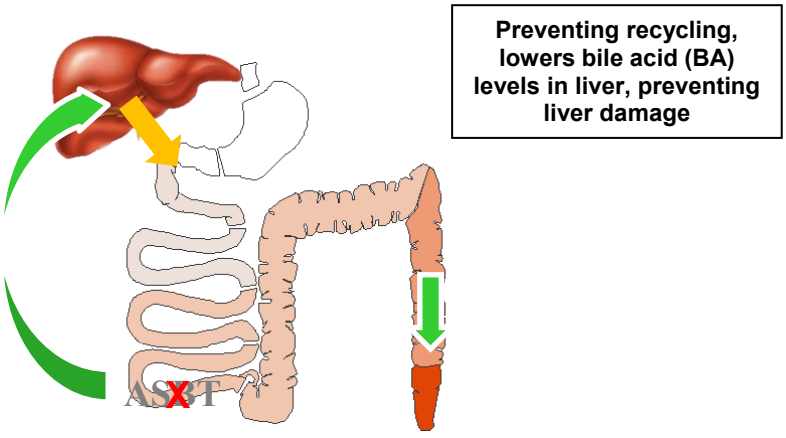
4.1 Therapeutic Rationale

Alagille syndrome (ALGS) is an example of cholestatic liver disease in children. In patients with ALGS, impairment of the egress of bile acids from the liver leads to cholestasis, hepatocellular injury and damage, and progressive liver disease that may ultimately lead to the need for liver transplantation. Itch is the archetypal symptom of cholestasis, occurring at all stages of cholestatic liver disease, with or without jaundice.

Surgical interruption of the enterohepatic circulation in patients with cholestatic liver disease has been shown to be beneficial. However, complications do occur and many patients and their families are reluctant to accept a permanent external ostomy in spite of the expected benefits. Pharmacological diversion of bile acids to the distal gut with an ASBTi/IBATi could be an attractive alternative to surgical intervention in ALGS.

LUM001 is a potent inhibitor of ASBT/IBAT. The ASBT/IBAT is present in the terminal 25% of the small intestine. This transporter mediates the uptake of conjugated bile acids across the brush border membrane of the enterocyte. Additional proteins and transporters carry bile acids from the enterocyte through the intestinal wall into the blood stream, where they are circulated to the liver via the portal vein and then re-secreted into the intestine in a system known as the enterohepatic circulation. Ninety-five percent of bile acids that enter the gut lumen are recycled to the gallbladder where they are stored for future release to the duodenum.

Figure 1: Interruption of Enterohepatic Circulation with an ASBT/IBAT Inhibitor



ASBT/IBAT expression is under negative feedback regulation by bile acids; thus in the setting of cholestasis, ASBT/IBAT is maladaptively upregulated (Neimark et al., 2004) (Hofmann, 2003). Therefore, inhibiting the reuptake of bile acids may represent an ideal treatment for cholestatic disease. In the current study, ALGS will serve as models for generalized cholestasis. By inhibiting the intestinal reabsorption of bile acids, LUM001 could interrupt the enterohepatic circulation and mimic the effects of partial external biliary diversion (PEBD) or ileal exclusion. The current extension study will test this hypothesis.

4.2 Alagille Syndrome

Alagille syndrome (ALGS) is an autosomal dominant with variable penetration multisystem disorder. The clinical diagnosis is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities and characteristic facial features. Fewer than 200 patients with ALGS are born each year in the United States. The estimated prevalence in Europe is 1.4/100,000 (Orphanet: The portal for rare diseases and orphan drugs). Elevations of serum bilirubin up to 30 times normal and serum bile salts up to 100 times normal are not uncommon. Levels of markers of bile duct damage, including gamma-glutamyltransferase (GGTP or GGT) and alkaline phosphatase (ALP), usually are significantly elevated. Cholesterol levels may exceed 25.9–51.7 mmol/L. Multiple xanthomas are common sequelae of severe cholestasis. The pruritus seen in patients with this condition is among the most severe of any chronic liver disease and it is present in most children by the third year of life. Although surgical interruption of the enterohepatic circulation has been successfully employed in the treatment of cholestasis and hypercholesterolemia in ALGS (Emerick and Whitington, 2002) (Modi et al., 2007), the management of cholestasis in ALGS remains largely supportive at this time. As cholestasis tends to improve over the first 5 to 10 years of life, therapies that ameliorate the complications of cholestasis, without a commitment to liver transplantation, are particularly attractive (Emerick et al., 1999).

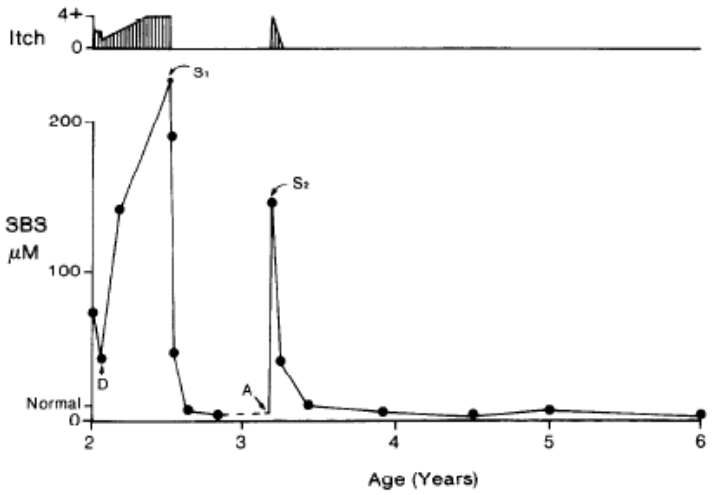
4.3 Pruritus

Patients with cholestatic liver disease frequently present with pruritus, which can be severe, even in the absence of jaundice. Elevation of serum bile acids is frequently accompanied by pruritus, and a causal association between pruritus and bile acids is suggested by the following: (1) pruritus can been induced in volunteers by applying topical unconjugated bile acids, deoxycholate and chenodeoxycholate to the skin; and (2) pruritus can be relieved by surgical interruption of the enterohepatic circulation, which dramatically lowers serum bile acids. Nevertheless, the correlation between the levels of serum and skin bile acids and the degree of pruritus is poor.

Intractable and pharmacologically recalcitrant pruritus is one of the major morbidities afflicting children with ALGS or progressive familial intrahepatic cholestasis (PFIC). Treatment with antipruritics and bile salt resins may provide partial relief of itching for children with ALGS, but

currently available pharmacologic approaches are of limited value. It has been shown that removing bile with surgical procedures such as partial external biliary diversion and nasal biliary drainage (NBD) substantially reduces pruritus in ALGS (Emerick and Whitington, 2002), PFIC, and primary biliary cirrhosis (PBC). Almost complete resolution of pruritus has been observed in children with PFIC disease in a period of as little as two to four weeks following the procedure. The rapid resolution of itch in response to therapy can be seen in Figure 2 extracted from the original description of this procedure by Whitington and Whitington (1988). Rapid lowering of bile acids, bilirubin and ALT has also been observed (Table 1).

Figure 2: Serum Bile Salt Concentration and Degree of Itch



Patient SR- serum bile salt concentration and degree of itch over a 4-yr course. Nasoduodenal drainage (D) resulted in reduced serum bile salt concentration and itch. When medical management failed, a cholecystostomy tube was placed (S_1), resulting in a reduction in serum bile salt concentration to normal and the disappearance of itching. When the cholecystostomy tube was accidentally pulled out (A), the serum bile salt concentration and itching increased rapidly. The construction of a permanent cholecystostomy (S_2) resulted in a quick return to normal, a state that has been maintained since. (Whitington and Whitington, 1988).

Table 1: Improvement in Biochemical Markers and Pruritus After Partial External Biliary Diversion in PFIC Disease and Alagille Syndrome Subjects

Diagnosis	Age at Surgery (yrs)	Pruritus Score (0-4 Scale)*		Serum Bile Acids (μM)		Conjugated Bilirubin (μM)		Alanine Aminotransferase (IU/L)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
PFIC	3	4	0	226	2	24	0	140	30
PFIC	9	4	0	225	3	80	0	193	13
PFIC	3	4	0	275	9	17	0	155	69
PFIC	3	4	0	218	5	68	10	141	64
Alagille	12	4	1 - 2	153	37	164	77	198	168
Alagille	6	4	1	317	25	50	15	248	305

* 0 = no itching; 4 = itching with cutaneous mutilation and bleeding (Whitington and Whitington, 1988)

4.4 LUM001

4.4.1 Nonclinical Studies

4.4.1.1 Pharmacology

LUM001 is a potent selective inhibitor of the ileal apical sodium-dependent bile transporter, a transmembrane protein localized on the luminal surface of ileal enterocytes, commonly referred to as ASBT/IBAT. The drug is a competitive inhibitor for bile acid substrate with a high affinity for the transporter. Nonclinical studies indicate that selective inhibition of ASBT by LUM001 results in increased fecal bile acid excretion, inhibition of the postprandial rise in serum bile acids, and decrease in serum total cholesterol. It also increases the activity of hepatic cholesterol 7α-hydroxylase and 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, consistent with inhibition of bile acid reabsorption as the mechanism of action.

4.4.1.2 Pharmacokinetics

Because of its large molecular weight and the presence of a quaternary nitrogen atom, LUM001 is poorly absorbed from the gut. In rats and dogs, oral bioavailability was < 0.4% at all doses tested. LUM001 is metabolically stable after oral administration. After intravenous administration, the majority of drug is excreted in the feces, with approximately 5% excretion in the urine.

4.4.1.3 Toxicology

A comprehensive assessment of LUM001 has been conducted in vitro and in animals. LUM001 is not toxic at doses far higher than those that are pharmacologically active in mice, rats, dogs, and monkeys. The most significant effect observed in rodents is a prolongation of coagulation time considered secondary to malabsorption of vitamin K, which in turn is related to inhibition of bile acid absorption, the pharmacologic effect of LUM001. Reversible prolongation of coagulation times was observed primarily in male rats that are especially sensitive to agents that alter vitamin K absorption and may not be an appropriate model for predicting vitamin K malabsorption in humans. Acute oral doses up to 200 mg/kg LUM001 were well tolerated in dogs, with emesis as the primary dose-limiting toxicity. There was no evidence of mutagenic activity in vitro and no clastogenic activity in vitro or in vivo. Results from rat and rabbit embryo/fetal development studies with doses up to 1000 and 250 mg/kg/day, respectively, showed no adverse effects on fetal growth and development. Additional toxicology information can be found in the Investigator's Brochure (IB).

4.4.2 Previous Clinical Experience

Detailed information concerning the clinical studies conducted with LUM001 can be found in the Investigator's Brochure. A summary is included below.

The overall objective of the initial clinical development plan was to evaluate the safety and efficacy of chronic, oral administration of LUM001 (tablet and capsule formulations) for the

reduction of serum LDL-C in subjects with hypercholesterolemia. The efficacy, pharmacokinetics, tolerability, and safety of LUM001 in humans have been evaluated in a total of 12 clinical studies, including 2 studies that also tested sustained release formulations. Phase 1 studies included a single and two multiple dose tolerability studies, an adsorption, distribution, metabolism, and excretion (ADME) study, a statin co-administration study, a statin interaction study, and a food composition study. Phase 2 studies included two dose-ranging studies in adult subjects, a tolerability study in adolescents and children, and a multiple dose tolerability and efficacy study of three sustained release formulations, compared with the immediate release formulation. More than 1,400 human subjects have been exposed to LUM001 (immediate release) for up to 10 weeks.

In previous clinical studies, LUM001 inhibited the postprandial increase in serum total bile acids concentrations and increased fecal total bile acids excretion, consistent with the mechanism of action of inhibiting ASBT. LUM001 administration resulted in reductions of serum LDL-C in healthy volunteers and subjects with elevated cholesterol. These findings confirm that LUM001, a minimally absorbed inhibitor of ASBT, is effective in blocking enterohepatic recirculation of bile acids with the expected consequences on bile acid and cholesterol metabolism. With LUM001 administration, there was also a trend toward increases in high-density lipoprotein cholesterol (HDL-C) and total triglycerides relative to placebo.

Administration of LUM001 at doses up to 100 mg once daily over a four-week period was generally safe in healthy volunteers and at doses up to 40 mg once daily for up to 10 weeks in subjects with hypercholesterolemia. The most commonly reported adverse drug reactions in LUM001-treated subjects were abdominal cramping (pain) and diarrhea and loose stools. With the exception of a single serious adverse event (SAE) of cholecystitis no other SAEs possibly related or related to LUM001 have been reported, (over 1,400 subjects exposed).

The majority of orally administered LUM001 was excreted intact in the feces along with a few minor metabolites. LUM001 exposure in adolescents and children (Study 014) was low and consistent with a drug that is minimally absorbed. Pharmacokinetic parameters in adolescent and children subjects did not significantly differ from those seen in adult subjects.

No clinically significant laboratory abnormalities were documented in LUM001-treated subjects. LUM001 was associated with mild, often transient elevations of serum ALT in a small percentage of subjects. Clinically significant (CS) reductions of serum fat-soluble vitamin levels were not observed with LUM001 treatment in humans; however, levels of the carotenoid β-carotene were mildly reduced. No alterations in coagulation parameters were observed, indicating no functional changes in vitamin K status. Fecal fat excretion was not increased compared to placebo after four weeks of LUM001 treatment at doses up to 100 mg.

One Phase 2 randomized, double-blind, placebo-controlled study has been completed in pediatric subjects from 12 months to 18 years with ALGS (LUM001-302 – IMAGO). This study evaluated the safety and efficacy of maralixibat in the treatment of cholestatic liver disease. All

subjects suffered from intractable pruritus explainable only by liver disease. The primary efficacy endpoint for this study, the change from baseline to Week 13/ET in fasting serum bile acid levels for maralixibat treatment in comparison with placebo treatment, was not met. Despite nominal improvements at some time point assessments, there were no significant differences in the serum bile acid level from baseline values to Week 13/ET in either the 140 µg/kg/day or the 280 µg/kg/day treatment groups. Nominally significant improvements in Observer ItchRO average daily itch scores from baseline values to the Week 13/ET visit were noted in the 140 µg/kg/day treatment group and in the overall maralixibat treatment group. Additionally, the Peds QL Scale (Parent) score compared with placebo treatment showed a significant improvement at Week 13/ET in the maralixibat 140 ug/kg/day and in the overall maralixibat treatment groups. There were no SAEs or deaths reported during the conduct of the study. Generally similar percentages of subjects experienced TEAEs in the active treatment groups (in the maralixibat 140 µg/kg/day treatment group, 6/6 subjects [100.0%] and in the maralixibat 280 µg/kg/day treatment group, 7/8 subjects [87.5%]) versus 4/6 subjects (66.7%) who experienced a TEAE in the placebo group. The majority of TEAEs reported in the overall maralixibat group were mild or moderate in severity (9/14 subjects [64.3%] and 4/14 subjects [28.6%], respectively). Reported events were generally consistent with the expected TEAEs including GI events and conditions associated with liver deterioration.

4.5 Rationale for Dose and Schedule of Administration

The dosage of LUM001 chosen for the first studies in cholestatic subjects is based upon prior experience with this product in healthy volunteers and subjects with hypercholesterolemia and in the completed Phase 2 study completed in pediatric subjects with ALGS (LUM001-302, see Section 4.4.2). In these subjects, with normal bile flow and without liver disease, tolerability was limited above 10 mg daily by an increase in GI AEs. These signs and symptoms were believed to be related to increased bile acid excretion and a concomitant increase in the concentration of free bile acids in the lower colon. In subjects with cholestatic liver disease it is likely that bile flow is reduced compared to healthy volunteers and hypercholesterolemic subjects and that LUM001 will produce a correspondingly smaller increase in free bile acids in the lower colon, and could potentially lead to the drug being better tolerated at the same dose level.

Ideally, dosing in pediatric subjects should be scaled from that in adults based on intestinal length, ie, mg of drug per cm of intestine. Differing relationships between intestinal mucosal surface area, age, and body weight have been reported in the literature. Weaver, Austin, & Cole (1991) provided data indicating that the average length of the small intestine increases with age from birth through 20 years; this relationship followed a curve that is similar to the height and weight growth curves. However, a plateau had not been reached at the maximum age examined (20 years), precluding predictions of intestinal length for older adults and thus scaling to infants and children based on estimated intestinal length. An analysis of intestinal length as a function of age, weight, and height in adult cadavers was conducted by Hounnou, Destrieux, Desme, Bertrand, & Velut (2002). Their analysis demonstrated that age had a negative and body weight a

positive correlation with intestinal length. Taken as a whole, the existing analyses are inconclusive with respect to the dependent variables that predict intestinal length. Consequently, the most reasonable approach is to calculate doses in pediatric subjects from those in adults based using a direct mg/kg scaling. For reference in an average adult subject, weighing 70 kg, a 10 mg daily dose is equivalent to 140 µg/kg/day.

Sample daily exposure (mg/day) across proposed dose levels for subjects ranging in weight from 10-30 kg is depicted in Table 2.

Table 2: Sample Daily Exposure (mg/day) in Pediatric Subjects

Weight (kg)	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)
10	0.1	0.4	0.7	1.4	2.8
15	0.2	0.5	1.1	2.1	4.2
20	0.3	0.7	1.4	2.8	5.6
25	0.4	0.9	1.8	3.5	7.0
30	0.4	1.1	2.1	4.2	8.4

In a previous study (Study 014), LUM001 was administered to 40 hyperlipidemic pediatric subjects (n=5, children ages 10-11; n=35, adolescents ages 12-17), up to a maximum tested dose of 5 mg/day for 14 days. The average subject weight in Study 014 was 60 kg and a 5 mg/day dose of LUM001 was approximately equivalent to 83 µg/kg/day. Plasma LUM001 exposure in adolescents and children was low (non-detectable <0.25cng/mL to 1.13 ng/mL) and consistent with a drug that is minimally absorbed. Detection of LUM001 in plasma samples was sporadic, both within and among subjects. In addition there does not appear to be a relationship with either subject age or gender. These data do not differ from the extensive pharmacokinetic data collected in adults to date. Although the bioavailability of LUM001 has not yet been characterized in children younger than 10 years of age, the GI systems are functionally mature in children by about 1 year of age (Walthall et al., 2005) (van den Anker et al., 2011). This study will enroll children ages 12 months to 18 years.

In Study 014, as with all other studies of LUM001, no drug related serious AEs were observed. The most frequently reported AEs in all treatment groups (LUM001 and placebo) were diarrhea, abdominal pain, loose stools and nausea. Most AEs were assessed with a probable or uncertain relationship to study medication and were generally characterized as mild or moderate in severity, except for those in six subjects who experienced severe nausea, diarrhea or abdominal pain. These GI events usually resolved during continued treatment. Thirty-nine (39) out of 40 subjects randomized to receive LUM001 completed the 14-day treatment period. One subject in the 0.3 mg group experienced severe diarrhea and abdominal pain that resulted in withdrawal from the study after 4 days of treatment. It is noteworthy that the AEs in Study 014 were generally recorded in the first seven days of LUM001 dosing, and observed at a four-fold lower frequency from Days 8 to 14. This is consistent with the extensive adult dosing experience,

where GI events were observed at levels similar to those in the placebo group after two weeks of continuous dosing.

To assess the effects of dose titration to mitigate dose-limiting adverse effects, LUM001 was evaluated in a 28-day once-daily dosing study in healthy volunteers (Study 003). In one arm, the dose was increased after each 7-day dosing period, to a maximum of 5 mg daily (equivalent to a dose of 67 µg/kg/day, using the average subject weight). Using this dosing regimen, the incidence of GI-associated AEs was lower than those observed in the placebo group (Table 3) and in other treatment arms with constant dosing above and below 5 mg daily.

Table 3: GI-associated Adverse Events in Study 003

GI Adverse Events	Placebo (n=20)	1 mg qAM (n=8)	2.5 mg qAM (n=25)	5 mg qAM (n=26)	0.5-5 mg qAM* (n=16)
Abdominal pain	2 (10%)	3 (37%)	4 (16%)	5 (17%)	1 (6.3%)
Constipation	2 (10%)	0	3 (12%)	0	0
Diarrhea	1 (5%)	1 (12%)	5 (20%)	2 (7%)	0
Nausea	0	0	1 (4%)	1 (4%)	0
Pruritus Ani	0	0	6 (24%)	4 (15%)	0

*Escalation regimen: 0.5 mg qAM (7 µg/kg/day) on Days 1-7, 1 mg qAM (13 µg/kg/day) on Days 8-14, 2.5 mg qAM (33 µg/kg/day) on Days 15-21, 5 mg qAM (67 µg/kg/day) on Days 22-28. Average body weight 75 kg.

The appropriate efficacious dose of LUM001 for the lowering of bile acid concentrations and the reduction of pruritus in cholestatic populations is not known. However, earlier studies demonstrated that doses of 10 mg daily (equivalent to 140 µg/kg/day for a 70 kg subject) led to a decrease in serum bile acids in healthy volunteers by >50%. In the PFIC population, there is some evidence that ASBT is upregulated, suggesting that higher doses may be required to saturate transporters and reach the desired effect in PFIC disease.

In the current LUM001 development program, the safety, tolerability and efficacy of LUM001 is being assessed for the first time in children with cholestatic liver disease associated with ALGS, 12 months to 18 years. The starting dose in these clinical trials, 14 µg/kg/day, is equivalent to less than the well-tolerated 1 mg dose (~17 µg/kg, 60 kg body weight) used in Study 014, where LUM001 was tested at doses up to 5 mg/day for 14 days in 39 hyperlipidemic pediatric subjects. At the 1 mg dose in Study014, only two out of eight subjects reported moderate or severe GI-associated AEs during 14 days. On a weight basis, 23 subjects received a dose ≥14 µg/kg/day. The highest starting dose in Study 014 was 168 µg/kg/day.

To reduce the risk of loose stools and diarrhea in the current study, escalation of LUM001 doses for LUM001-naïve subjects will occur at 7-day intervals starting at 14 µg/kg/day and increasing to 35 µg/kg/day, 70 µg/kg/day, and 140 µg/kg/day. Thereafter, the dose of LUM001 may be adjusted for all study subjects during the dose-optimization period. A minimum period of 7-days

must elapse between increases in dose. Dose adjustments will be made at the investigator's discretion with the goal of reaching a dose optimized for maximum efficacy and tolerability of either 35, 70, 140 or 280 μg/kg/day.

The dose may also be down-titrated, at the investigator's discretion and in consultation with the ChiLDReN protocol chair and the Medical Monitor, for subjects experiencing intolerance to a given dose.

5. INVESTIGATIONAL PLAN

5.1 Study Design

This is a multicenter, double-blind study of LUM001 in children >12 months of age diagnosed with ALGS who have completed participation in the LUM001-301 protocol. All subjects will receive active drug (LUM001) in the study. The study is divided into 6 parts: a dose escalation period, a dose optimization period, a stable dosing period, a safety monitoring period, and 2 long term, optional treatment periods.

Dose Escalation Period

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

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

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

Dose Optimization Period

Following completion of the 4-week dose escalation period, subjects will enter an 8-week dose-optimization period. During this period, the investigator will have the option to adjust LUM001 dosing with the objective of achieving optimal control of pruritus at a dose level that is tolerated by the subject and up to a maximum daily dose of 280 µg/kg LUM001 or 20 mg total dose. Study drug dose will be increased or decreased in a double-blind manner. Increases in dose will be based on effect on pruritus. Reductions in dose will be based on tolerability. At the investigator's discretion, the doses for subjects who were previously down-titrated may be re-challenged during the dose optimization period. Each subject will receive one of the following dose levels:

- LUM001 35 µg/kg/day.
- LUM001 70 µg/kg/day.
- LUM001 140 µg/kg/day.
- LUM001 280 µg/kg/day.

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

Stable Dosing and Safety Monitoring Periods

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

Long-term Optional Follow-up Treatment Period

The long-term, optional follow-up treatment period is for eligible subjects who choose to remain on treatment with LUM001 following the initial 96 weeks. During this long-term, optional follow-up treatment period, subjects with dosing interruptions ≤7 days will remain on the same dose they were taking at Week 96. Subjects with LUM001 dosing interruptions >7 consecutive days will require dose escalation upon resumption of study drug. The dose of LUM001 will be increased at weekly intervals up to the subject's previously achieved highest tolerated dose. Study drug for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen. Subjects' participation in the long-term, optional follow-up treatment period will continue until the first of the following occur: (i) subjects complete 48 weeks of additional treatment (after Week 96 [safety monitoring period]), or (ii) the subjects are eligible to enter another LUM001 study.

Long-term Optional Follow-up Treatment Period-2

The long-term optional follow-up treatment period-2 is for eligible subjects who choose to remain on treatment with LUM001 for an additional 72 weeks. During this long-term optional follow-up treatment period-2, subjects will remain on the same dose they were taking at Week 144. Study drug for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occur: (i) subjects complete 72 weeks of additional treatment (after Week 144 [Long-term Optional Follow-up Treatment Period]), or (ii) the subjects are eligible to enter another LUM001 (SHP625) study.

5.2 Data Monitoring Board

A Data Monitoring Board (DMB) will review adverse event (AE) data, other key subject safety and study data at specified intervals for the duration of the study. The DMB will be composed of at least 2 members who are otherwise independent from the conduct of the study: one or more

physicians and at least one biostatistician. The DMB's primary responsibility is to review the progress of the study, particularly with regard to safety and risk/benefit, and make recommendations to Sponsor to stop or modify the trial if safety concerns are identified. Further details regarding the structure, function and operation of the DMB will be detailed in the DMB charter.

5.3 Number of Study Centers

This will be a multicenter study in approximately 12 clinical centers that participated in Study LUM001-301.

5.4 Number of Subjects

Approximately 36 subjects meeting the study's inclusion and exclusion criteria may be enrolled in the study.

5.5 Overall Study Duration and Follow-up

For an individual subject, the study participation period will consist of a 4-week dose escalation period, followed by 8-weeks of dose optimization, a 36-week stable dosing period, a 48-week safety monitoring period, a 48-week long-term, optional follow-up treatment period, and a 72-week long-term, optional follow-up treatment period-2. Planned participation for each subject enrolled in the long-term, optional follow-up treatment period-2 is a maximum of 220 weeks, inclusive of the safety follow-up contact approximately 30 days after the last dose of LUM001.

Study activities will be conducted as described in the Schedule of Procedures (Section 16.1).

Figure 3: Study Design for LUM001-305 (Day 0-Week 48)

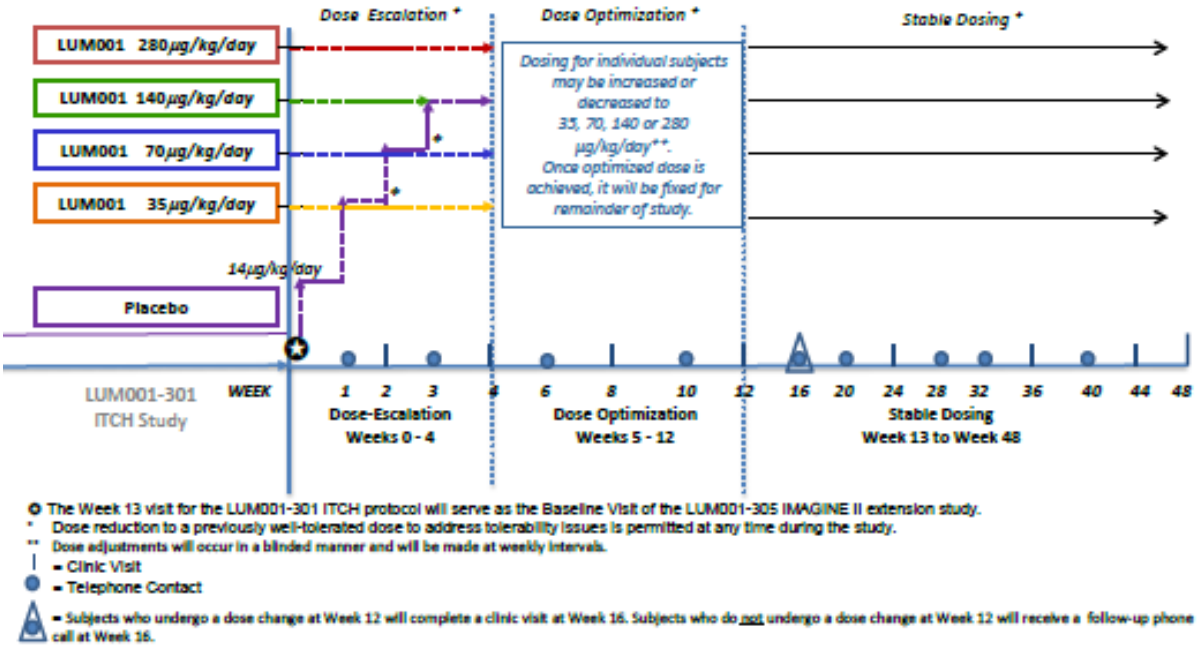
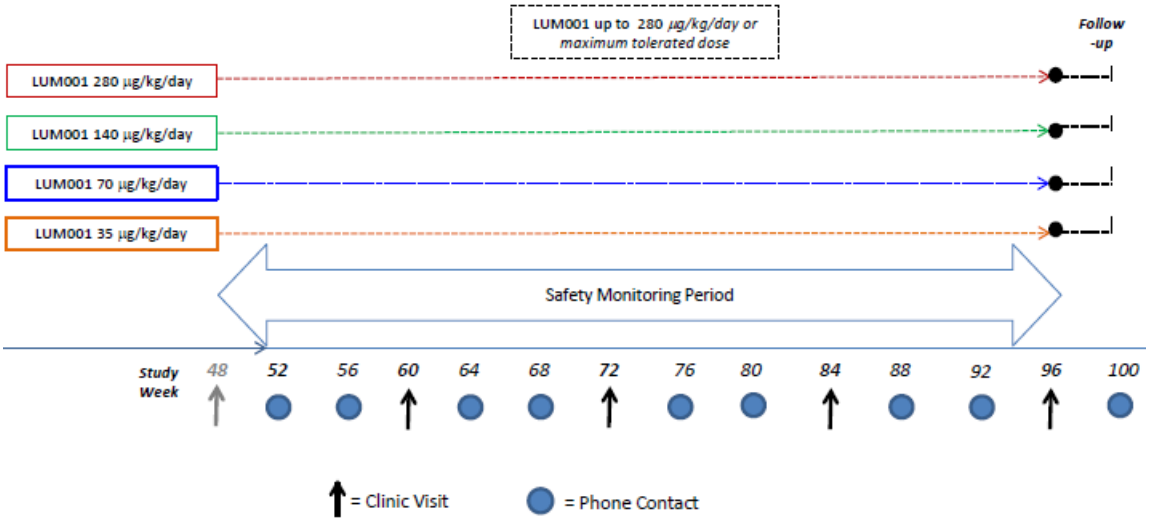


Figure 4: Safety Monitoring Period (Week 49-Week 96)

***for subjects not rolling over into Protocol Amendment 5**



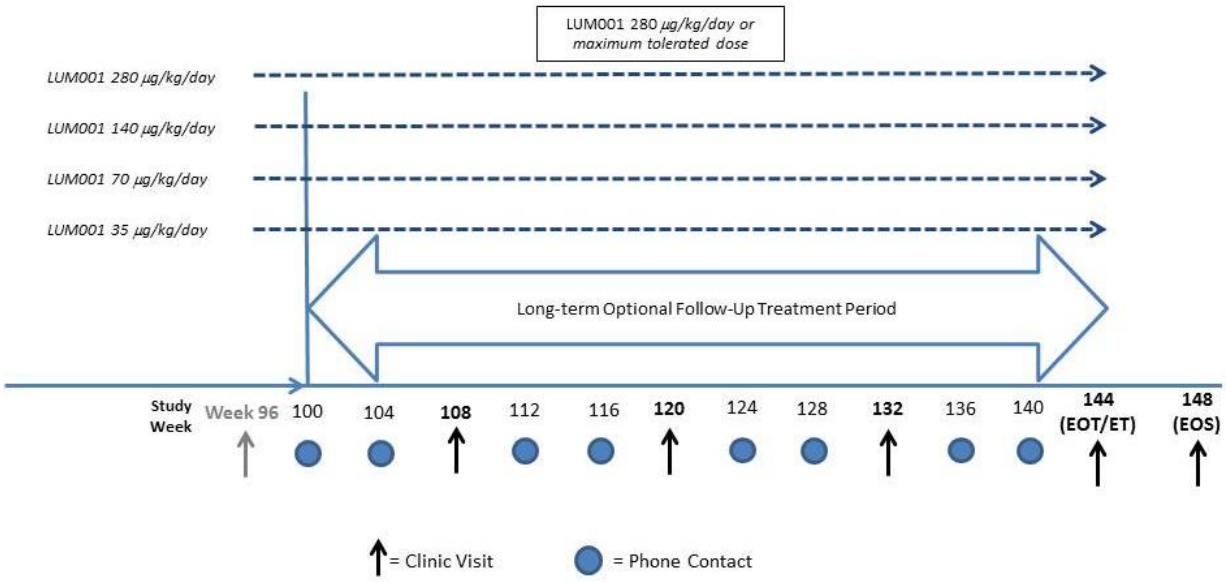
In consultation with the Protocol Chair and the Medical Monitor, the dose may be lowered to a previously well-tolerated dose to address tolerability issues at any time during the study

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

Figure 5: Long-term Optional Follow-up Treatment Period (Week 96-Week 148)

Applies to the following population:

- Subjects with no interruption in LUM001 dosing or interruption ≤7 days between Week 96 and Week 100)



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

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

Figure 6: Long-term Optional Follow-up Treatment Period (Week 96-Week 148)

Applies to the following population:

- Subjects who experienced an interruption in LUM001 dosing >7 consecutive days between Week 96 and Week 100

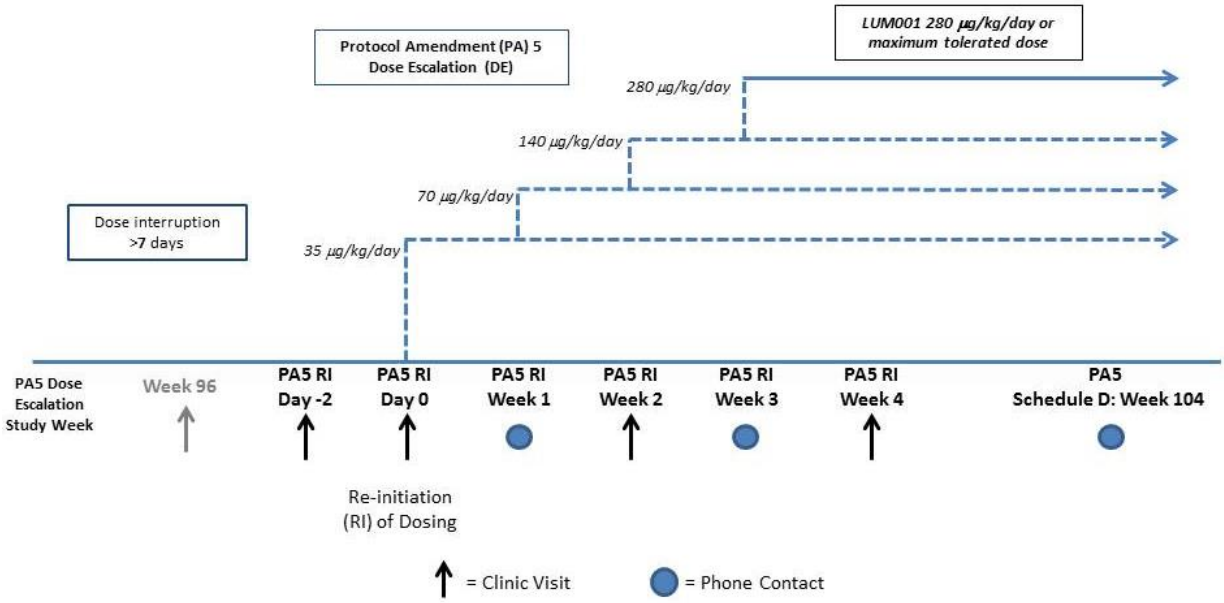
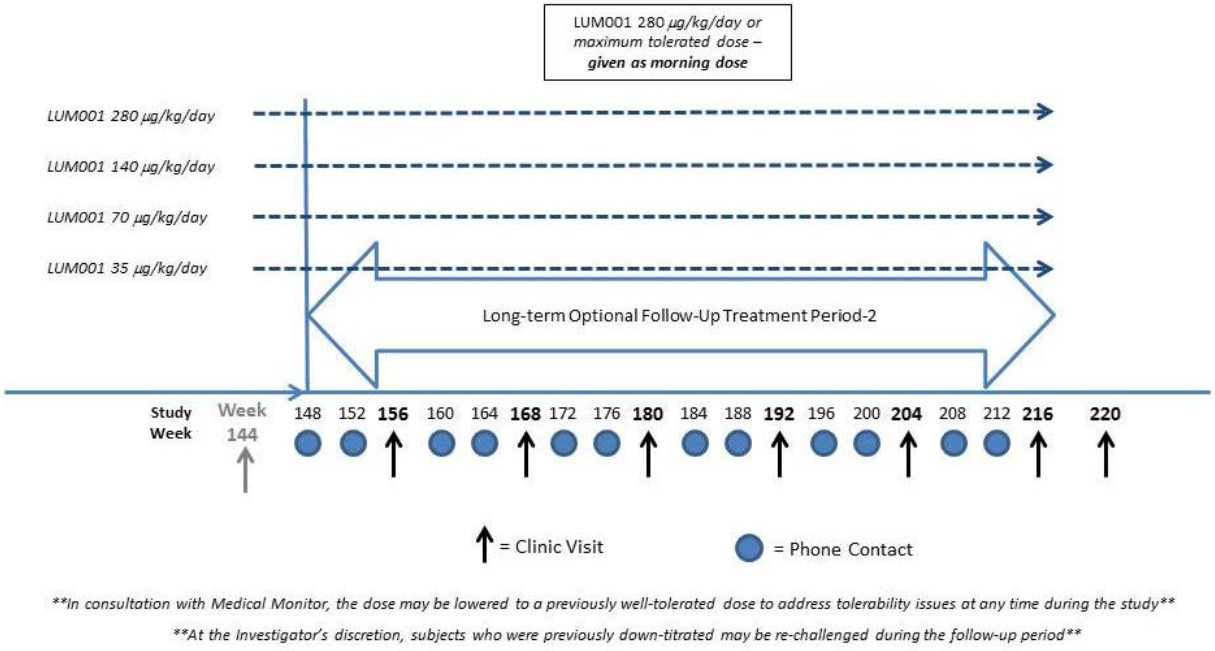


Figure 7: Long-term Optional Follow-up Treatment Period-2 (Week 144-Week 220)



5.5.1 Treatment

The Week 13 Visit from the LUM001-301 protocol will also serve as the Baseline Visit for the extension protocol. Eligible subjects will be enrolled in the extension study at the Baseline Visit (Day 0). Dosing with study drug will begin on Day 1, following the Baseline Visit on (Day 0).

Study drug will be prepared by a central pharmacy based on the subject's weight. During the study, weight will be monitored at each visit. A change from Baseline in a subject's weight that is greater than 10% will require a dose adjustment. Each subsequent 10% increase in weight will be considered the new baseline for determination of future dose adjustments. The central pharmacy will make weight-based dose adjustments at the time of the subject's next LUM001 preparation.

Diluent will be added by the central pharmacy pharmacist prior to shipping study drug to the site. Study drug will be dispensed to subjects/caregivers at the study site. The appropriate amount of study drug will be dispensed at the Study Day 0 visit and daily dosing will begin on Study Day 1. Subjects who weigh 10 kg or more will receive a 1.0 mL grape-flavored solution containing LUM001. Subjects who weigh less than 10 kg will receive a 0.5 mL grape-flavored solution containing LUM001. The volume administered will not change during the course of the study. Dosing will occur up to 216 weeks of treatment. Each daily dose will be administered in the morning at least 30 minutes before breakfast (qAM, ac). Study drug should be administered approximately at the same time every day.

5.5.1.1 Dose Escalation Period

For subjects randomized to placebo in the LUM001-301 protocol, or those who complete the core study more than 7 days prior enrollment into this study, the LUM001 dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose). For subjects who were randomized to receive active drug in the LUM001-301 protocol LUM001 doses will remain the same as the dose being taken at Week 13 of the core study. Study treatment for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to a specified dose-escalation regimen. This regimen will represent a real dose escalation for subjects previously randomized to placebo and a mock dose escalation for subjects previously randomized to active study treatment.

The dosing regimen for each treatment group during the dose escalation period is summarized in Table 4.

Table 4: Dose Escalation Regimens

LUM001-301 Protocol	**Extension Study Protocol LUM001-305**			
	Dose Escalation Period			
Week 13 (µg/kg/day)	**Week 1 Days 1 - 7 (µg/kg/day)**	**Week 2 Days 8 - 14 (µg/kg/day)**	**Week 3 Days 15 - 21 (µg/kg/day)**	**Week 4 Days 22 - 28 (µg/kg/day)**
Placebo [1]	14	35	70	140
35 [2]	35	35	35	35
70 [3]	70	70	70	70
140 [4]	140	140	140	140
280 [5]	280	280	280	280

[1] For subjects randomized to placebo in the LUM001-301 protocol, or those who complete the core study more than 7 days prior enrollment into this study, the LUM001 dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose).

[2] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 35 µg/kg/day will remain stable at 35 µg/kg/day, or to a maximum daily dose of 2.5 mg/day.

[3] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 70 µg/kg/day will remain stable at 70 µg/kg/day, or to a maximum daily dose of 5 mg/day.

[4] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 140 µg/kg/day will remain stable at 140 µg/kg/day, or to a maximum daily dose of 10 mg/day.

[5] LUM001 doses for subjects whose stable dose upon completion of the LUM001-301 protocol was 280 µg/kg/day will remain stable at 280 µg/kg/day, or to a maximum daily dose of 20 mg/day.

The primary anticipated adverse reaction or intolerance is gastrointestinal in nature (eg, diarrhea, abdominal pain, cramping, etc.). In the absence of GI intolerance, escalation to the next dose level for an individual subject may occur at the investigator's discretion, following a scheduled phone call or visit (see Schedule of Procedures, Section 16.1).

If a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the ChiLDReN protocol chair and Medical Monitor, may lower the dose to a previously tolerated dose for the remainder of the study. In these circumstances, an unscheduled visit will occur and the appropriate replacement study medication will be provided to the subject/caregiver.

5.5.1.2 Dose Optimization Period

Following the dose escalation period, the LUM001 dose for each subject may be increased or decreased by the investigator as clinically indicated with the objective of achieving control of pruritus at a dose level that is tolerated by the subject. Dose optimization will occur in a blinded, titrated manner with four dose levels available as treatment options: 35, 70, 140 or 280 µg/kg/day. Adjustments may occur at weekly intervals. Once an optimal LUM001 dose is achieved, the dose will be fixed for the duration of the study.

The maximum daily dose of LUM001 in this study is 280 µg/kg/day, up to a maximum daily dose of 20 mg. Blinded investigators may request dose adjustment for any subject based on an assessment of tolerability and effect on pruritus. Caregivers and age-appropriate subjects will be asked whether they wish to take a higher dose of the study medication to achieve greater relief of itching. If so, the dose may be adjusted upward, within the permitted dose range. However, the patient, caregiver, physician investigator, or the Medical Monitor may recommend against further escalation if there are safety or tolerability concerns. Doses of LUM001 will not be increased above 280 µg/kg/day or 20 mg per day at any time.

5.5.1.3 Stable Dosing and Safety Monitoring Periods

At the end of the Dose Optimization Period, subjects will continue dosing to complete the stable dosing and safety monitoring periods for up to 96 weeks of cumulative LUM001 exposure in this study.

Subjects who completed the 48-week study prior to the implementation of Protocol Amendment #4 may be re-contacted and re-consented for participation in the safety monitoring period of the study.

If, at any time during the study, a subject experiences intolerance due to gastrointestinal symptoms, the physician investigator may lower the dose to a previously tolerated dose.

To ensure the safety of subjects participating in this study, a Data Monitoring Board (DMB) will review SAE data, other key subject safety and study data at specified intervals for the duration of the study.

5.5.1.4 Long-term, Optional Follow-up Treatment Period

At Week 96, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll over into the long-term, optional follow-up treatment period. Following the

completion of the Week 96 study visit, subjects who choose to participate in the long-term, optional follow-up treatment period will be maintained at the same Week 96 dose level. Subjects with dose interruptions >7 consecutive days prior to implementation of Protocol Amendment 5 will be rescreened and require dose escalation upon resumption of study drug. The dose of LUM001 will be increased at weekly intervals up to the subject's previously tolerated dose under Protocol Amendment 4. Subjects who do not wish to enter the long term, optional follow-up treatment period will be contacted via telephone by the study site approximately 30 days after the last dose of the study drug.

Subjects who either completed the 96-week study prior to the implementation of Protocol Amendment 5, or have received permission from the ChiLDReN protocol chair and the Medical monitor, may be recontacted and reconsented for participation in the long-term optional follow-up treatment period of the study.

Study drug administration under Protocol Amendment 5 will not change from Protocol Amendment 4.

5.5.1.5 Long-term, Optional Follow-up Treatment Period-2

At Week 144, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll over into the long-term, optional follow-up treatment period-2. Following the completion of the Week 144 study visit, subjects who choose to participate in the long-term, optional follow-up treatment period-2 will be maintained at the same Week 144 dose level. Subjects who do not wish to enter the long term optional follow up treatment period-2 should complete the in-clinic Week 148 Visit 30 days after the last dose of study drug.

Subjects who either completed the 144-week study prior to the implementation of Protocol Amendment 6, or have received permission from the ChiLDReN protocol chair and the Medical Monitor, may be recontacted and reconsented for participation in the long-term, optional follow-up treatment period-2 of the study.

Study Drug Administration under Protocol Amendment 6 will not change from Protocol Amendment 5.

5.5.2 Dosing Interruptions

5.5.2.1 Dose Escalation Following Dose Interruption

Subjects with interruptions in LUM001 dosing of more than 7 consecutive days during the stable dosing, safety monitoring, and long-term, optional follow-up treatment periods will require dose escalation upon re-initiation of the study drug. The dose of LUM001 will be increased at weekly intervals up to the subject's previously achieved highest tolerated dose. Study drug for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen (Table 5).

Table 5: Dose Escalation Regimen for Re-initiation of LUM001 Dosing When Dosing Interruption is Greater than 7 Consecutive Days

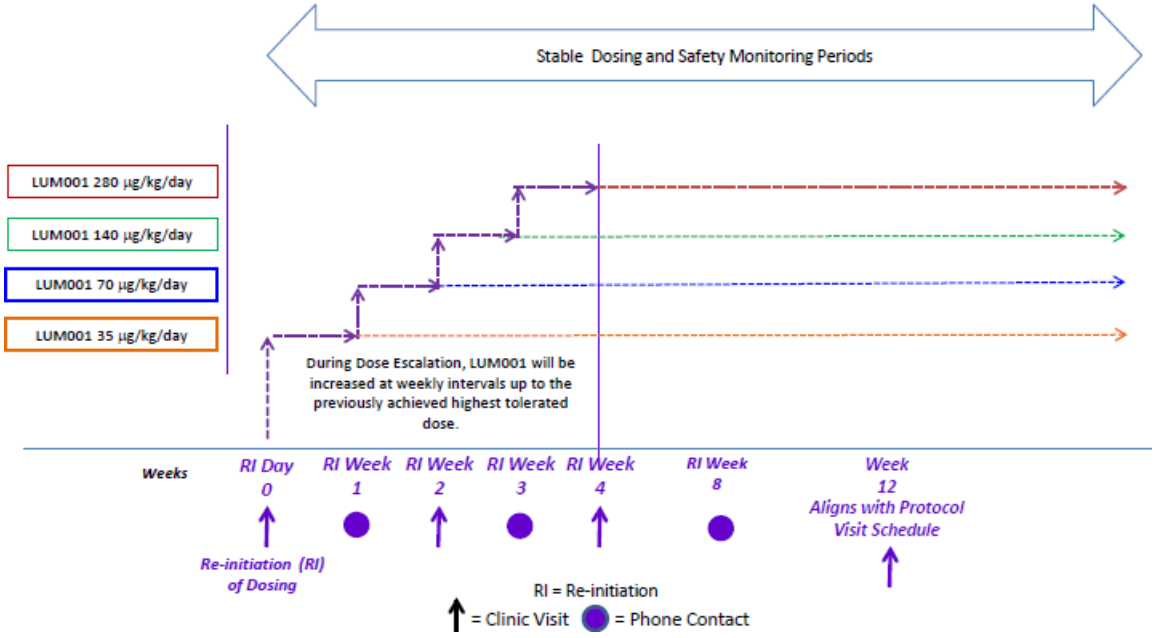
	Study Week			
	Week 1 (µg/kg/day)	Week 2 (µg/kg/day)	Week 3 (µg/kg/day)	Week 4 (µg/kg/day)
LUM001 Dose	35	70 [1]	140 [1]	280 [1]

[1] Weekly dose escalations will end once the highest tolerated dose achieved prior to the subject's LUM001 dosing interruption is reached.

5.5.2.2 Visit Schedule Following Dose Interruption for Stable Dosing and Safety Monitoring Periods

Upon re-initiation of study drug, subjects who undergo a dosing interruption of greater than 7 consecutive days will follow the same visit schedule and procedures that are specified for the Baseline Day 0 Visit (Section 8.1.1) and during Dose Escalation Treatment Period (Section 8.1.2). Completion of the ItchRO electronic diary, however, will not be required during this time. The visit schedule upon re-initiation of LUM001 dosing is shown in Figure 8.

Figure 8: Visit Schedule for Re-initiation of LUM001 when Dosing Interruption is Greater than 7 Consecutive Days



Subjects with dosing interruptions of greater than 7 consecutive days will require reintegration in the study to ensure that 1) their resumed visit schedule aligns with the protocol, and 2) their total LUM001 exposure during the study does not exceed 216 weeks.

If the decision to interrupt dosing occurred at the time of a Clinic Visit, the first visit upon dose re-initiation ("RI Day 0" in Figure 8) should be assigned to that same Clinic Visit. If the decision

to interrupt dosing occurred between Clinic Visits, the first visit upon dose re-initiation ("RI Day 0") should be assigned to the next Clinic Visit. Table 6 provides the assignment of the first study visit upon dose re-initiation based on when the dosing interruption occurred.

Table 6: Dosing Interruptions: Reintegration to Study Visit Schedule

Dosing Interruption	Assignment of First Dose Re-initiation Study Visit
Between Weeks 13 - 24	Week 24
Between Weeks 25 - 36	Week 36
Between Weeks 37 - 48	Week 48
Between Weeks 49 - 60	Week 60
Between Weeks 61 - 72	Week 72
Between Weeks 73 - 84	Week 84
After Week 84	To be managed on a case-by-case basis in consultation with the Medical Monitor and ChiLDReN Protocol Chair

5.5.2.3 Visit Schedule Following Dose Interruption for Long-term, Optional Follow-up Treatment Period

Upon re-initiation of study drug into the long-term optional follow-up treatment periods, subjects who undergo a dosing interruption of greater than 7 consecutive days will follow the re-entry dose escalation schedule as outlined in Figure 6 and in Study Schedule of Procedures E after receiving permission from the Sponsor and ChiLDReN protocol chair.

Dose interruptions greater than 7 consecutive days that occur between Week 104 and Week 216, should also be discussed with the ChiLDReN protocol chair and the Medical Monitor to determine how to reintegrate the subject into Study Schedule of Procedures D

5.5.3 Follow-up

A safety follow-up phone call will be made by the study site 30 days after the last dose of study drug for subjects participating in all versions of the protocol up through Protocol Amendment 4. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and any AEs noted during this phone call will be recorded. For subjects who participate in the long-term, optional follow-up treatment period, this phone call will be replaced by the Week 148 end of study (EOS) clinic visit. For subjects who participate in the long-term, optional follow-up treatment period-2, this phone call will be replaced by the Week 220 (EOS) clinic visit.

5.6 Study Termination

A subject is considered to have completed the study period(s) based on the version of the protocol they participated under. For subjects who consent to the long-term, optional follow-up treatment period or the long-term, optional follow-up treatment period-2, the subject is

considered to have completed the study if they participated in the Week 144 end of treatment (EOT) or Week 216 (EOT) visit, respectively.

The end of study for the purposes of regulatory reporting and EDC entry is the point of last contact with the last subject during the protocol-specified scheduled follow-up period or the EOS visit as specified in Schedule of Procedures F .

6. SUBJECT ENROLLMENT

6.1 Enrollment

Before subjects may be enrolled to participate in the study, the Sponsor, or designee, requires a copy of the appropriate written Independent Ethic Committee (IEC) or Institutional Review Board (IRB) approval of the protocol, informed consent/assent form(s) (ICF), and all other applicable subject information.

Following informed consent/assent, the subject will be considered enrolled into the study. The unique 6-digit subject identification number assigned to the subject upon screening in the LUM001-301 protocol will be used to identify the subject in the LUM001-305 extension study. This number will be used to identify the subject throughout the study. The subject's identification number must remain constant and must be used on all study documentation related to that subject.

Subjects will be enrolled in the long-term, optional follow-up treatment period based on the investigator's determination of meeting eligibility criteria outlined in Section 7. A subject will be considered enrolled in either the long-term, optional follow-up period under Protocol Amendment 5 or the long-term, optional follow-up period-2 under Protocol Amendment 6, respectively, after the subject consents and the investigator has determined the subject meets study entry eligibility criteria per Protocol Amendment 5 or 6, as appropriate . However, any subject who consents to Protocol Amendment 5 or 6 and does not meet criteria per the investigator is considered a screen failure for the long-term, optional follow-up period under Protocol Amendment 5 or 6, as appropriate. Final consent and eligibility determined for subjects rescreened will be collected in the case report form (CRF).

6.2 Replacement of Subjects

There will be no replacement of subjects who withdraw from the study.

6.3 Unblinding of Treatment Assignment

All subjects, investigators, and study center personnel, except for the central pharmacist who prepares the study drug and the pharmacy monitor who monitors the pharmacy records and procedures, will remain blinded to all subjects' treatment assignments until after the study database for Mirum's LUM001-305 protocol has been locked. Sponsor personnel and CRO personnel will remain blinded to all subjects' dose levels until after the study databases for the LUM001-301 protocol have been locked. Once the treatment assignments for these core studies have been unblinded, access to the unblinded treatment assignments for subjects participating in LUM001-305 will be provided to Sponsor and CRO personnel on a need-to-know basis only, with such access being restricted to the maximum extent feasible, consistent with their performing a comprehensive and timely analysis of the data from the LUM001-301 study.

If in the event of an emergency situation when knowledge of the treatment assignment will impact the clinical management of the subject, the investigator will have the ability to unblind the treatment assignment for that subject at any time by contacting the study's central pharmacy. If a subject is unblinded by the investigator, the Sponsor must be informed of the unblinding within 24 hrs. If the blinding is prematurely broken, it is the responsibility of the investigator to promptly document and explain any unblinding to the Sponsor.

Breaking of the blind should not occur except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or when causality must be determined prior to submitting a regulatory safety report for a SAE (as defined in Section 11.2.3).

Any unblinding event carried out in connection with submission of a regulatory safety report will be conducted by the Sponsor (see Section 11.1).

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Schedule of Procedures, Section 16.1) prior to unblinding, as knowledge of the treatment arm could influence subject assessment.

7. SUBJECT ELIGIBILITY

To be eligible to participate in this study, candidates must meet the following eligibility criteria before being dispensed study drug treatment.

Original Inclusion and Exclusion Criteria (through Protocol Amendment 4)

7.1 Inclusion Criteria

To participate in this study, subjects must meet all of the following criteria:

1. Male or female, 12 months to 18 years of age.
2. Competent to provide informed consent and assent (per IRB/EC), as appropriate.
3. Completed participation in the LUM001-301 protocol.
4. Females of childbearing potential must have a negative urine pregnancy test [β human chorionic gonadotropin (β-hCG)] at the Baseline Visit.
5. Sexually active females must be prepared to use an effective method (≤ 1% failure rate) of contraception during the trial. Effective methods of contraception are considered to be:
6. Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
7. Barrier method, eg, (a) condom with spermicide, or (b) diaphragm, with spermicide; or
8. Intrauterine device (IUD).
9. Subjects above the age of assent and caregivers and children must be able to read and understand English or Spanish.
10. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site.
11. Caregivers (and age appropriate subjects) must be willing and able to complete a daily electronic diary (ItchRO) during the first consecutive 12 weeks of the study and then for 4 consecutive weeks following the Week 24 and Week 44 visits.
12. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the ItchRO electronic diary software at the outset of the study.
13. Eligible subjects must be able to adhere to local Ethics Committee or Institutional Review Board (IRB) blood volume limits for laboratory testing.

Protocol Amendment 5 Inclusion Criteria: Eligible subjects for the long-term optional follow-up treatment period

Subjects will be considered eligible for the long-term optional follow-up treatment period if they meet the following criteria:

1. The subject has completed the protocol either through Week 96, or the ET visit, or has received permission from the sponsor and the ChiLDReN protocol chair to re-enter the study in the long-term, optional follow-up treatment period.

2. Females of child-bearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) at the time of entry into the long-term optional follow-up treatment period.
3. Male and female subjects of child-bearing potential who are sexually active, or are not currently sexually active, but become sexually active during the study or for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study.
4. Informed consent and assent (per IRB/EC) as appropriate.
5. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site.
6. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study.

Protocol Amendment 6 Inclusion Criteria: Eligible subjects for the long-term optional follow-up treatment period-2

1. The subject has completed the protocol through either Week 144, or the ET visit, or has received permission from the sponsor and the ChiLDReN protocol chair to re-enter the study in the long-term optional follow-up period-2.
2. Females of child-bearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) at the time of entry into the long-term optional follow-up treatment period-2.
3. Males and females of child-bearing potential who are sexually active, or are not currently sexually active, but become sexually active during the study or for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study.
4. Informed consent and assent (per IRB/EC) as appropriate.
5. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site.
6. Caregivers (and age appropriate subjects) must be willing to follow the rules of eDiary completion (see Section 8.4.1).

7.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Experienced an AE or SAE related to the study drug during the LUM001-301 protocol that led to the discontinuation of the subject from the core study.
2. Any conditions or abnormalities (including laboratory abnormalities) which, in the opinion of the Investigator, Medical Monitor or ChiLDReN Protocol Chair, may compromise the safety of the subject, or interfere with the subject participating in or completing the study.
3. History or known presence of gallstones or kidney stones.

4. History of non-adherence during the subject's participation in the LUM001-301 protocol. Non-adherence is defined by dosing compliance[1] of less than 80% in the LUM001-301 protocol.
5. Unlikely to comply with the study protocol, or unsuitable for any other reason, as judged by the investigator.

Protocol Amendment 5 Exclusion Criteria: Eligible subjects for the long-term optional follow-up treatment period

All exclusion criteria for the original LUM001-305 study apply upon re-entry into the long-term, optional follow-up treatment period.

Protocol Amendment 6 Exclusion Criteria: Eligible subjects for the long-term optional follow-up treatment period-2

All exclusion criteria for the original LUM001-305 study apply upon re-entry into the long-term optional follow-up treatment period-2.

1. Dosing compliance is calculated by [the total number of doses that were actually taken by the subject] divided by [the total number of doses that should have been taken by the subject] multiplied by 100.

8. STUDY PROCEDURES

8.1 Study Schedule

The schedule of assessments for this study is provided in the Schedule of Procedures, Section 16.1. Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs should be recorded in the appropriate source documents and CRFs.

8.1.1 Baseline (Day 0)

Evaluations and procedures completed for the Week 13 Visit of the LUM001-301 study will also serve as the evaluations for the Baseline Visit for the extension study. Informed consent (and/or assent when appropriate) for participation in the extension study must be obtained for all participating subjects and their parents or legal guardians, as appropriate. At the Baseline visit (Week 0), subjects will be assessed to confirm continued study eligibility including a review of medical history and will undergo a physical examination including body weight, height, and vital signs. Blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of bile acids and other cholestasis biochemical markers as well as for PK analysis (plasma levels of LUM001). The clinician scratch scale will be administered, as will the PedsQL. Female subjects of childbearing potential will have a urine pregnancy test and concomitant medications and any AEs will be recorded. The degree and severity of xanthomatosis will be evaluated for all subjects by the clinician xanthoma scale. Study drug for Weeks 1, and 2 will be supplied at the Baseline visit to eligible subjects.

8.1.2 Dose Escalation Treatment Period (Week 0 to Week 4)

Double-blind dosing in the dose escalation period will be initiated on the morning after the Baseline Visit. Caregivers and age appropriate subjects will be instructed to complete their ItchRO electronic diary (eDiary) twice daily (morning and evening). Subjects will return to the clinic at Weeks 2, and 4, and will receive follow-up phone calls at Weeks 1 and 3. On clinic visit days, vital signs (including height and weight measurements) will be collected and blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers. The clinician scratch scale will be administered, adherence to study drug will be assessed and additional dosing instructions will be supplied. Study diary compliance will be assessed and concomitant medications and any AEs will be recorded at clinic visits and at scheduled telephone contacts. Additional study drug will be supplied at Week 2 and Week 4.

Clinic visits and follow-up phone calls during the dose escalation period are allowed a ±2 day scheduling window.

8.1.3 Dose Optimization Period (Week 5 to Week 12)

During the dose optimization period, the dose for each subject may be increased or decreased at the investigator's discretion in a double-blind manner. The purpose of the dose optimization period is to allow the investigator to adjust the subject's LUM001 dose to a level that is both tolerable to the subject and maximizes the potential effect of LUM001 on pruritus. Once an optimal dose is achieved, the dose will be fixed for the duration of the study.

Electronic diaries will be completed twice daily by age-appropriate subjects and caregivers through Week 12 and then collected. Subjects will return to the clinic at Weeks 8 and 12 and will receive follow-up telephone calls at Weeks 6 and 10. At the clinic visits, vital signs (including height and weight measurements) will be collected and blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers. The clinician scratch scale will be administered and a review of study diary and medication compliance will be completed. Concomitant medications and any AEs will be assessed and recorded at each visit and at scheduled telephone contacts. Additional study drug will be supplied at Weeks 8 and 12.

Clinic visits and follow-up phone calls during the dose optimization period are allowed a ±5 day scheduling window.

8.1.4 Stable Dosing Period (Week 13 to Week 48)

Subjects will continue to receive study drug during the stable dosing treatment period according to the dose achieved during the dose optimization period. However, if a subject experiences intolerance due to gastrointestinal symptoms the investigator, in consultation with the ChiLDReN protocol chair and Medical Monitor, may lower the dose to a previously tolerated dose for the remainder of the study.

During the stable dosing period, subjects will return to the clinic at Weeks 24, 36, 44 and 48. Subjects who undergo a dose change at the Week 12 visit will also return to the clinic at Week 16 (see below). With the exception of Week 44, safety and clinical laboratory evaluations, blood sampling for study drug determination, and a physical exam (including collection of vital signs, height and weight measurements) will be completed at each clinic visit. In addition, the clinician scratch scale and clinician xanthoma scale will be administered and study drug compliance will be assessed. The PedsQL will be completed at Weeks 24 and 48 and the Caregiver Impression of Change (CIC) will be completed at Week 48. Subjects/caregivers will receive follow-up phone calls at Weeks 16, 20, 28, 32 and 40. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.

Subjects who undergo a dose change at the Week 12 visit will complete an on-site clinic visit at Week 16. Subjects who do not undergo a dose change at Week 12 will receive a follow-up phone call at Week 16. The study activities that will be conducted at the Week 16 clinic visit are described in the Schedule of Procedures (Section 16.1).

Electronic diaries will be completed by age-appropriate subjects and caregivers following the Week 24 and Week 44 visits. The diaries will be redistributed at Week 24 and completed twice daily for 4 weeks before being collected at Week 28. The diaries will then be redistributed at Week 44 and completed twice daily until the end of the study (Week 48). Re-training on the use of the diary will occur as appropriate at the Week 24 and Week 44 visits.

At the physician investigator's discretion, tapering or withdrawal of concomitant medications used for the treatment of pruritus may occur during the stable dosing period.

With the exception of Week 44, additional study drug will be supplied at each clinic visit during the stable dosing period.

Clinic visits and follow-up phone calls during the stable dosing period are allowed a ±14 day scheduling window.

8.1.5 Safety Monitoring Period (Week 49 to Week 96)

During the safety monitoring period, subjects will return to the clinic every 3 months, at Weeks 60, 72, 84, and 96.

Safety and clinical laboratory evaluations and a physical exam (including collection of vital signs, height, and weight measurements) will be completed at each clinic visit. The clinician scratch scale will also be completed at each clinic visit and study drug compliance will be assessed. The PedsQL, CIC, and the Clinician Xanthoma scale will also be administered at Weeks 60, 72, 84, and 96. Subjects/caregivers will receive follow-up phone calls at Weeks 52, 56, 64, 68, 76, 80, 88, and 92. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.

Twice daily completion of the ItchRO electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, 84, and 96 clinic visits. Review of electronic diary data and assessment of compliance will occur during scheduled telephone contacts at Week 64, 76, and 88 and during the Week 96 clinic visit. Electronic diaries will be provided to subjects and caregivers at these visits and re-training on the use of the diary will occur, as appropriate.

At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the safety monitoring period.

Additional study drug will be supplied at each clinic visit during the follow-up treatment period.

8.1.6 Week 96

Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the long-term, optional follow-up treatment period. This will include a formal re-assessment of the Protocol Amendment 5 inclusion and exclusion criteria and consenting of the subject at

Week 96 per Schedule C. Eligible subjects must have documented consents in order to continue in the long-term, optional follow-up treatment period. A physical exam (including collection of vital signs, height and weight measurements) will be performed. Blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers as well as for PK analysis (plasma levels of LUM001). The clinician scratch scale and PedsQL will be administered and the degree and severity of xanthomatosis will be evaluated using the clinician xanthoma scale. Review of the ItchRO electronic diary data and assessment of compliance will occur during the Week 96 clinic visit. The electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Twice daily completion of the diary will be required during the 2 weeks following the Week 96 clinic visit. Female subjects of childbearing potential will have a urine pregnancy test and concomitant medications and any AEs will be recorded.

Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected. Study drug will be discontinued at this visit if the subject chooses not to participate in the long-term optional follow-up treatment period. Subjects will be encouraged to complete all study activities and visits. Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week 96 visit, with the exception of the ItchRO assessment. For safety reasons, efforts must be made to follow subjects for at least 30 days following their last dose of study drug.

8.1.7 Follow-up Phone Call (30 days after Last Dose)

For subjects who do not roll over into the long-term, optional follow-up treatment period, a safety follow-up phone call will be made 30 days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and any AEs noted during this phone call will be recorded. For subjects who participate in the long-term optional follow-up treatment period, this phone call will be replaced by the Week 148 (EOS) clinic visit.

8.1.8 Long-term, Optional Follow-up Treatment Period (Week 96-148)

Once Protocol Amendment 5 is implemented at the site, subjects who are eligible and consent for entry into the long-term, optional follow-up treatment period will continue to receive study drug until the first of the following occurs:

i. The subjects complete 48 weeks of additional treatment after Week 96 (safety monitoring period)

ii. The subjects are eligible and consent to enter another LUM001 study

Subjects with no LUM001 dosing interruptions or interruptions ≤7 days will continue to receive the same LUM001 dose they last received during LUM001-305 (Week 96 dose) (refer to Figure 5). Study activities will proceed as outlined in Schedule of Procedures D .

Subjects with LUM001 dosing interruptions >7 days will be rescreened and require dose escalation upon resumption of study drug. The dose of LUM001 will be increased at weekly intervals up to 280 µg/kg/day or the subject's previously tolerated dose under Protocol Amendment 4 (refer to Figure 6). Study activities will proceed as outlined below and in Schedule of Procedures E .

- Protocol Amendment (PA) 5 Re-initiating (RI) Day -2 Clinic Visit: Consent (and/or assent as applicable) are obtained; eligibility criteria are confirmed. Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Concomitant medications and AEs will be recorded.
- PA5 RI Day 0 Clinic Visit: Eligibility criteria are confirmed. Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Clinician scratch scale, clinician xanthoma scale, and PedsQL are completed. Concomitant medications and AEs will be recorded. Study drug is dispensed and subject begins dosing at 35 µg/kg/day dose level.
- PA5 RI Week 1 Telephone Contact: Concomitant medications and AEs will be recorded. Subject escalates to 70 µg/kg/day dose level or previous maximum tolerated dose as established under Protocol Amendment 4.
- PA5 RI Week 2 Clinic Visit: Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Clinician scratch scale, clinician xanthoma scale, and PedsQL are completed. Concomitant medications and AEs will be recorded. Study drug is dispensed and subject escalates to 140 µg/kg/day dose or previous maximum tolerated dose as established under Protocol Amendment 4.
- PA5 RI Week 3 Telephone Contact: Concomitant medications and AEs will be recorded. Subject escalates to 280 µg/kg/day dose level or previous maximum tolerated dose as established under Protocol Amendment 4.
- PA5 RI Week 4 Clinic Visit: Physical examination (body weight, height, vital signs) is performed; blood and urine samples collected for clinical laboratory testing. Female subjects of childbearing potential will have a serum pregnancy test. Clinician scratch scale, clinician xanthoma scale, and PedsQL are completed. The ItchRO electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Twice daily completion of the electronic diary will be required during the 2 weeks following this visit. Concomitant medications and AEs will be recorded. Study drug is dispensed and subject continues dosing at 280 µg/kg/day dose level or previous maximum tolerated dose as established under Protocol Amendment 4.
- PA5 Schedule D Week 104 Telephone Contact (4 weeks after PA5 RI Week 4 Clinic Visit): Concomitant medications and AEs will be recorded. Subjects will then follow study activities as outlined in Schedule of Procedures D , Week 104.

Per Schedule of Procedures D , subjects will return to the clinic every 12 weeks at Weeks 108, 120, 132, 144 (EOT/ET visit) and at Week 148 (EOS visit). During the clinic visits, physical exam, body weight and height, vital signs, urine samples, and blood samples for clinical laboratory testing including fasting lipid panel and fat soluble vitamins, bile acids, and other cholestasis biochemical markers will be collected. ItchRO compliance will be assessed, the electronic diary will be issued, and the clinician scratch scale and clinician xanthoma scale will be assessed at every clinic visit. The PedsQL questionnaire and the CIC will be administered at Weeks 108, 144 and 148. Review of the ItchRO electronic diary data and assessment of compliance will occur during the Week 112, 124, and 136 telephone contacts. The ItchRO electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Twice daily completion of the electronic diary will be required during the 2 weeks following the Week 96, 108, 120, and 132 clinic visits and during the 4 weeks following the Week 144 visit. Subjects rolling over into the long-term optional follow-up treatment period-2 will complete the electronic diary for 2 weeks following the Week 144 visit. Female subjects of childbearing potential will have a urine pregnancy test at each clinic visit prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and AEs will be collected.

Telephone Contact will occur at Weeks 100, 104, 112, 116, 124, 128, 136, and 140 where collection of concomitant medications and any AEs will be recorded.

8.1.9 Week 144

Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the long-term, optional follow-up treatment period-2. This will include a formal reassessment of the Protocol Amendment 6 inclusion and exclusion criteria and consenting of the subject at Week 144, per Schedule of Procedures D . Eligible subjects must have documented consents in order to continue in the long-term, optional follow-up treatment period-2. Subjects who withdraw from the study prior to completion of the long-term, optional follow-up treatment period, should also undergo the procedures specified for the EOT/ET visit (Week 144). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis plasma levels of LUM001). In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL and the clinician xanthoma scale. The CIC assessment will be completed. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded. Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected. Study drug will be discontinued at this visit if the subject chooses not to participate in the long-term, optional treatment period-2. Review of the ItchRO electronic diary data and assessment of compliance will occur during the Week 144 clinic visit. The electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as appropriate. Twice daily completion of the diary will be

required for 2 weeks following the Week 144 clinic visit for subjects rolling over into the long-term, optional follow-up treatment period-2. Subjects not rolling over into long-term, optional follow-up treatment period-2 will be asked to complete the diary for 4 weeks following Week 144.

8.1.10 Week 148

Subjects who either elect not to participate in, or who are not eligible to participate in the long-term, optional, follow-up treatment period-2 will return to the study site 30 days after the last dose of study drug and undergo the procedures specified for the EOS visit (Week 148). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis plasma levels of LUM001). In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL, the clinician xanthoma scale, and the CIC. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded.

8.1.11 Long-term, Optional Follow-up Treatment Period-2 (Week 144-220)

Once Protocol Amendment 6 is implemented at the site, subjects who are eligible and consent for entry into the long-term, optional follow-up treatment period-2 will continue to receive study drug until the first of the following occurs:

i. The subjects complete 72 weeks of additional treatment after Week 144 (long-term, optional follow-up treatment period
ii. The subjects are eligible and consent to enter another LUM001 (SHP625) study

Subjects rolling over into the long-term optional follow-up treatment period-2 will continue to receive the same LUM001 dose they last received during LUM001-305 (Week 144 dose) (refer to Figure 7). Study activities will proceed as outlined in Schedule of Procedures F . Subjects with dose interruptions after Week 48 and prior to Week 96, or who early terminated, may re-enter the study with the permission from the sponsor and the ChiLDReN protocol chair. These subjects will initiate dose escalation at visit PA5 RI -2 (per Schedule of Procedures E) and then will follow study activities beginning at Week 104 (per Schedule of Procedures D).

Per Schedule of Procedures F , subjects will return to the clinic every 12 weeks at Weeks 156, 168, 180, 192, 204, 216 (EOT/ET visit) and at Week 220 (EOS visit). During the clinic visits, physical exam, body weight and height, vital signs, urine samples, and blood samples for clinical laboratory testing including fasting lipid panel and fat soluble vitamins, bile acids, and other cholestasis biochemical markers will be collected. The clinician scratch scale and clinician xanthoma scale will be assessed at every clinic visit. The PedsQL questionnaire and the CIC will be administered at Weeks 156, 216 and 220 clinic visits. The ItchRO electronic diaries will be provided to subjects and caregivers and retraining on the use of the diary will occur, as

appropriate. Caregivers are not required to complete the eDiary (ItchRO[Obs]) if the subject is living separately from the ItchRO observer; however, subjects ≥9 years of age will be required to complete ItchRO(Pt). Twice daily completion of the electronic diary will be required during the 2 weeks following the Week 144, 156, 168, 180, 192, and 204 clinic visits and during the 4 weeks following the Week 216 (EOT/ET) visit. Review of the ItchRO electronic diary data and assessment of compliance will occur during scheduled telephone contacts at Week 148, 160, 172, 184, 196, 208 and during the Week 220 clinic visit. Female subjects of childbearing potential will have a urine pregnancy test at each clinic visit prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and AEs will be collected.

Telephone Contact will occur at Weeks 148, 152, 160, 164, 172, 176, 184, 188, 196, 200, 208 and 212 where collection of concomitant medications and any AEs will be recorded.

8.1.12 Week 216 (EOT or ET)

Subjects who either complete the long-term, optional follow-up treatment period-2 or who withdraw from the study prior to completion should undergo the procedures specified for the EOT/early termination (ET) visit (Week 216). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis plasma levels of LUM001). In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL, the clinician xanthoma scale, and the CIC. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded. Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected. Study drug will be discontinued at this visit.

8.1.13 Week 220 (EOS)

All subjects will return to the study site 30 days after the last dose of study drug and undergo the procedures specified for the EOS visit (Week 220). These procedures include a physical exam (including collection of vital signs, height and weight measurements), blood and urine sampling for safety and clinical laboratory evaluations (including a fasting lipid panel, determination of fat-soluble vitamins, bile acids and other cholestasis biochemical markers, as well as for PK analysis plasma levels of LUM001). In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL, the clinician xanthoma scale, and the CIC. Female subjects of childbearing potential will have a urine pregnancy test. Concomitant medications and any AEs will be recorded.

8.2 Physical Examination, Weight and Height, Vital Signs

A physician Investigator will conduct a physical examination on each subject at Baseline, at Weeks 24, 36, and 48, and at Week 16 on subjects who undergo a change in dose at their

Week 12 visit. A physical examination will also be conducted for any subject who terminates from the study early at the Early Termination Visit. For subjects who enter into the safety monitoring period, physical examinations will be conducted at Weeks 60, 72, 84, and 96. For subjects who enter into the long-term, optional follow-up treatment period, physical examinations will be conducted at Weeks 108, 120, 132, 144 (EOT/ET) and Week 148 (EOS). For subjects who enter into the long-term, optional follow-up treatment period-2, physical examinations will be conducted at Weeks 156, 168, 180, 192, 204, 216 (EOT/ET) and Week 220 (EOS).

Body weight, height, and vital signs, including body temperature, blood pressure (BP), respiration and pulse, will be determined at every study clinic visit. A change in weight greater than 10% of the weight used to calculate the subject's current LUM001 dose will result in a dose adjustment. Each subsequent 10% increase in weight will be considered the new baseline for determination of future dose adjustments. This dose adjustment will be made by the central pharmacy when they make the subject's next LUM001 preparation.

8.3 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of planned tests is compiled in Section 16.2.

The Investigator is responsible for reviewing and signing all laboratory reports. The clinical significance of each value outside of the reference range will be assessed and documented as either not clinically significant (NCS) or clinically significant (CS). See Section 11.4.1 regarding laboratory abnormalities.

8.4 Pruritus and Quality of Life Assessments

8.4.1 Itch Reported Outcome (ItchRO™)

Pruritus will be assessed using a newly developed Itch caregiver/patient reported outcome measure (ItchRO^{TM}) administered as a twice daily electronic diary as described in Section 16.3. Caregivers for all subjects will complete the Observer instrument: ItchRO(Obs)™. Children ≥9 years of age will complete the patient instrument: ItchRO(Pt)™. Children between the ages of 5 and 8 years of age will complete the patient instrument with the assistance of their caregiver: ItchRO (Pt). Subjects and caregivers will be trained on the use of the electronic diary during their participation in LUM001-301 protocol.

During the dose escalation and dose optimization periods (Week 0 - Week 12), subjects/caregivers will be required to submit twice daily assessments using the electronic diary.

During the stable dosing period, daily completion of the diary will be required by subjects and caregivers only during the 4 consecutive weeks that follow the Week 24 and Week 44 clinic visits. At Week 24 and Week 44, subjects/caregivers will be provided with the electronic diary

and re-trained on its use, as needed. At the Week 24 visit, subjects/caregivers will also be provided with prepaid/pre-labeled mailing supplies that should be used to return the electronic diary to the study center immediately after they have completed the 4 weeks of diary entries. At the Week 44 visit, subjects/caregivers will be instructed to bring their electronic diary with them when they return for the Week 48 clinic visit.

During the safety monitoring periods, twice daily completion of the diary will be required by subjects and caregivers only during the 2 consecutive weeks that follow the Week 60, Week 72, and Week 84 clinic visits. During the long-term, optional follow-up treatment period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 96, Week 108, Week 120, and 132 clinic visits. Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) will also be asked to complete the ItchRO during the 4 weeks that follow the Week 144 (EOT) visit. During the long-term, optional follow-up treatment period-2, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 144, Week 156, Week 168, Week 180, Week 192, and Week 204 clinic visits and during the 4 weeks that follow the Week 216 (EOT) visit. At these visits, subjects/caregivers will be provided with the electronic diary and re-trained on its use, as needed. In cases where an ItchRO observer can no longer observe the subject (eg, no longer living with the subject), the ItchRO(Obs) will not need to be completed; however, ItchRO(Pt) will need to be completed by subjects aged ≥9 years of age. Subjects/caregivers will be instructed to bring their electronic diary with them when they return for their next clinic visit. The electronic diary will be collected at Week 148 for subjects who do not participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6), and at Week 220 for subjects who do participate in the long-term, optional follow-up treatment period-2.

8.4.2 Clinician Scratch Scale

A clinician's assessment of pruritus will be made by the principal investigator or sub-investigator using the clinician scratch scale (Section 16.4). This assessment will be completed at Baseline (Day 0) and at all clinic visits thereafter (Weeks 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96). For subjects who enter into the long-term, optional follow-up treatment period, the clinician scratch scale will be administered at Weeks 108, 120, 132, 144 (EOT/ET). Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) will also have the clinician scratch scale administered at Week 148 (EOS). For subjects who enter into the long-term, optional follow-up treatment period-2, the clinician scratch scale will be administered at Weeks 156, 168, 180, 192, 204, 216 (EOT/ET) and Week 220 (EOS).

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, hemorrhage and scarring. Whenever possible, the same individual should make the assessments for a subject visits.

8.4.3 Clinician Xanthoma Scale

A clinician's assessment of xanthomatosis will be made by the principal investigator or appropriate designee using the clinician xanthoma scale (Section 16.5). This assessment will be completed at Baseline (Day 0) and at Weeks 24, 36, 48, 60, 72, 84, and 96. For subjects who enter into the long-term, optional follow-up treatment period, the clinician's assessment of xanthomatosis will be administered at Weeks 108, 120, 132, 144 (EOT/ET). Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) will also have the clinician's assessment of xanthomatosis administered at Week 148 (EOS). For subjects who enter into the long-term, optional follow-up treatment period-2, the clinician's assessment of xanthomatosis will be administered at Weeks 156, 168, 180, 192, 204, 216 (EOT/ET) and Week 220 (EOS).

The clinician's assessment of the subject's xanthomatosis is focused on the number of lesions present and the degree to which the subject's lesions interfere or limit his or her activities. The clinician xanthoma scale uses a 5-point scale, in which 0 represents no evidence of xanthomatosis, 1 represents fewer than 20 scattered individual lesions, 2 represents more than 20 lesions that do not interfere with or limit activities, 3 represents large numbers of lesions that by their large numbers or size cause distortion of the face or extremities, and 4 represents xanthomas that interfere with function (such as hand use or ability to walk) because of excess size or number (Emerick and Whitington, 2002).

8.4.4 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL™ is a one-page questionnaire that will be administered to subjects and or caregivers at the Baseline (Day 0) and Week 24 and Week 48 clinical visits using the age-appropriate PedsQL module (Section 16.6). For subjects who enter into the long-term, optional follow-up treatment period, the PedsQL will be administered at Weeks 108, 144 (EOT/ET). Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) will also have the PedsQL administered at Week 148 (EOS). For subjects who enter into the long-term, optional follow-up treatment period-2, the PedsQL will be administered at Weeks 156, 216 (EOT/ET) and Week 220 (EOS). The PedsQL is a validated, modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescents (Varni et al., 2001).

In addition to the core generic PedsQL module, the multidimensional fatigue and family impact questionnaires will also be administered at the Baseline (Day 0) and Weeks 24, 48, 60, 72, 84, and 96 clinical visits using the age-appropriate module, see Section 16.6. For subjects who enter into the long-term, optional follow-up treatment period, the multidimensional fatigue and family impact questionnaires will be administered at Weeks 108 and 144 (EOT/ET). Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) will also have the multidimensional fatigue and family impact questionnaires administered at Week 148 (EOS). For subjects who enter into the long-term, optional follow-up treatment period-2, the multidimensional fatigue and family impact questionnaires will be

administered at Weeks 156, 216 (EOT/ET) and Week 220 (EOS). Age at the LUM001-301 baseline visit will be used as the age for the determination of the appropriate questionnaire to be used for the study. This same module will be used for the duration of the study regardless of subsequent birthdays throughout the study.

8.4.5 Caregiver Impression of Change

The Caregiver Impression of Change (CIC) is designed to assess the caregiver's perception of the subject's xanthoma severity at the end of study drug treatment compared to his/her xanthoma severity prior to the start of treatment with study drug. The CIC will be completed by all caregivers at the Weeks 48, 60, 72, 84, and 96 visits, see Section 16.1. For subjects who enter into the long-term, optional follow-up treatment period, the CIC will be administered at Weeks 108, 144 (EOT/ET). Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) will also have the CIC administered at Week 148 (EOS). For subjects who enter into the long-term, optional follow-up treatment period-2, the CIC will be administered at Weeks 156, 168, 180, 192, 204, 216 (EOT/ET) and Week 220 (EOS).

8.5 Restriction on the Lifestyle of Subjects

8.5.1 Contraception Requirements

Sexually active female subjects of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, from the time of enrollment until the end of the study. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized.

8.5.2 Fasting Requirements

On study days in which blood samples are collected for the lipid panel and/or cholestasis biomarkers, all subjects will be required to fast for at least 4 hours (only water is permitted) before blood sample collection. On these visit days study drug should be administered as usual (1 mL or 0.5 mL qAM, ac), in the morning 30 minutes before breakfast. After breakfast only water should be consumed until the scheduled clinic visit.

All subjects will have fat soluble vitamin levels monitored; blood samples for the analysis of fat soluble vitamins should be obtained before the daily dose of vitamins is administered, and approximately 4 hours after any food or formula.

9. STUDY DRUG

9.1 Study Drug Description

9.1.1 LUM001

LUM001 is a powder that is to be dissolved with an appropriate diluent in order to administer the study drug as an oral solution. The composition of LUM001 study drug oral solution is described in Table 7. The composition of LUM001 study drug 0.5 mL oral solution is described in Table 8.

Table 7: Composition of LUM001 1.0 mL Oral Solution

Component	Function	Quantity per 1.0 mL
LUM001	Active Ingredient	0.02 to 20 mg
Propylene Glycol	Co-solvent	250 mg
Sucralose	Sweetener	7.5 mg
Grape Flavoring Agent	Taste Masking Agent	5 mg
Water, q.s. to	Vehicle	1.0 mL

Table 8: Composition of LUM001 0.5 mL Oral Solution

Component	Function	Quantity per 0.5 mL
LUM001	Active Ingredient	0.02 to 20 mg
Propylene Glycol	Co-solvent	125 mg
Sucralose	Sweetener	3.75 mg
Grape Flavoring Agent	Taste Masking Agent	2.5 mg
Water	Vehicle	q.s. to 0.5 mL

9.2 Packaging and Labeling

The Sponsor will provide the central pharmacy with packaged study drug labeled in accordance with specific country regulatory requirements. Standard syringes will be provided by the sponsor for administration of study drug.

9.3 Drug Accountability

The central pharmacy and all study staff are required to document the receipt, dispensing and return/destruction of study drug supplies provided by the Sponsor.

At the conclusion of the study, any unused drugs, as well as original containers (even if empty), will be returned to the Sponsor or handled according to written instructions from the Sponsor, following approval by the Sponsor.

10. TREATMENT OF SUBJECTS

10.1 Study Drug Administration

The dose of study drug in this study is based on weight. During the study, the subject's weight will be monitored at each visit. A change in weight greater than 10% of the weight used to calculate the subject's current LUM001 dose will result in a dose adjustment. Each subsequent 10% increase in weight will be considered the new baseline for determination of future dose adjustments. This dose adjustment will be made by the central pharmacy when they make the subject's next LUM001 preparation.

Study drug (LUM001 with diluent) will be prepared by a central pharmacy based on the subject's last recorded weight from the LUM001-301 study. Diluent will be added by the central pharmacy pharmacist prior to shipping study drug to the site. Study drug will be dispensed to subjects/caregivers at the study site.

Each subject dose for subjects who weigh 10 kg or more will be administered orally as a 1.0 mL solution containing study drug (LUM001) using the syringe provided. Each subject dose for subjects who weigh less than 10 kg will be administered orally as a 0.5 mL solution containing study drug (LUM001)using the syringe provided. Study drug should be taken at least 30 minutes prior to the first meal of the day (qAM, ac) and should be administered approximately at the same time each day for the duration of the treatment period. See Sections 5.5.1.1, 5.5.1.2, and 5.5.1.3 for information regarding dosing during the dose escalation and stable dosing periods, respectively.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for study drug preparation, administration and storage.

10.2 Treatment Compliance

Compliance with treatment dosing will be monitored and recorded by the study site staff. Subjects and/or guardians will be asked to complete a paper diary indicating when they took their study medication and when they ate breakfast.

10.3 Concomitant Medications

A concomitant medication is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered during participation in the study (from baseline/Day 0 until the 30-day post-treatment follow-up visit). Concomitant medications should not be recorded prior to informed consent, or during gap periods when the subject is not participating in the study.

All medications (other than study drug) taken by subjects during the course of the study will be recorded and reviewed by the Principal Investigator (PI)/Investigator's designee. Concomitant

medication will be coded using the World Health Organization (WHO) Drug Dictionary (release date 01 September 2008, or more recent version if available). AEs related to administration of these medications must also be documented.

At the physician investigator's discretion, tapering or withdrawal of concomitant medications used for the treatment of pruritus may occur during stable dosing period. With the exception of vitamin supplementation and anti-pruritic medications, the dosage and dosing regimen of other concomitant medications should not change during the course of the study except for dose adjustments due to weight increase. All modifications to concomitant medications must be carefully documented in the relevant CRFs.

Concomitant use of bile acid or lipid binding resins or any investigational drug product other than LUM001 is not allowed during the study.

10.4 Other Protocol-required Drugs

There are no other protocol required drugs. Subjects are expected to maintain a stable dose and administration schedule for all permitted concomitant medications throughout the course of the study.

10.5 Safety Monitoring Rules

10.5.1 General Monitoring Rules

In the evaluation of AEs and the potential relationship to study drug it is important to note that due to their liver disease many subjects with Alagille syndrome will have abnormal liver enzyme levels (eg, ALT, ALP) total bilirubin, cholesterol and serum bile acids prior to their exposure to study drug in the lead-in study. If an individual subject exhibits a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 treatment emergent laboratory abnormality, with the exception of the specific rules outlined below (Sections 10.5) dosing can be suspended or continued as per the investigator's judgement and following discussion with the ChiLDReN protocol chair and the medical monitor. If suspended, the investigator, the ChiLDReN protocol chair, and the medical monitor will evaluate the subject's safety data and make a decision to either restart dosing at the same level, restart dosing at a lower dose level, or discontinue dosing.

10.5.2 Safety Monitoring Rules

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study, the initial clinical laboratory results exceeding the safety monitoring criteria presented below **must be confirmed** by performing measurements (in the central laboratory that performed the initial measurement) on new specimens. Of note: the INR retest should be conducted by the central laboratory but may also be

conducted at a local laboratory if needed. All new specimen collection for retesting should take place within 48-72 hours of the initial report. The results from the retest **must be available** prior to the next scheduled clinic visit or phone follow-up.

Stopping Rule Guidance: If any of the stopping criteria described below (refer to Section 10.5.1) are confirmed, the physician investigator in consultation with the ChiLDReN protocol chair and the medical monitor or appropriately qualified designee(s), will permanently discontinue the subject from further treatment with study drug. The subject will be evaluated as outlined below and will be encouraged to complete the early termination study procedures. Subjects who do not meet the stopping rules based on retest may continue dosing and the Investigator, the ChiLDReN protocol chair, and the medical monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. The investigator should also assess the need to capture an AE, its severity according to the CTCAE directives and potential causality. These assessments should also include an evaluation of whether criteria for an SAE are fulfilled (see Section 11.2.3).

10.5.2.1 Safety Monitoring for Liver Chemistry Tests

Safety monitoring criteria take into consideration the subject's historical baseline ALT and total bilirubin levels. Historical baseline levels will be defined as the values reported for each subject at their baseline visit for the LUM001-301 protocol.

If at any time in the study an ALT or total bilirubin result exceeds the criteria shown in the table below, in relation to the subject's historical baseline level, the initial measurement(s) should be confirmed within 48 to 72 hours of the initial report.

Historical Baseline[1] ALT	ALT
≤ ULN	> 5 x ULN
> ULN	> 3 x historical baseline and > 5 x ULN

Historical Baseline[1] Total Bilirubin	Total Bilirubin
Total Bilirubin 1-10 mg/dL (17.10 – 171.04 µmol/L)	3 mg increase over historical baseline level
Total Bilirubin >10 mg/dL (>171.04 µmol/L)	5 mg increase over historical baseline level

[1] Historical baseline values are those reported at baseline of the LUM001-301 protocol.

Frequency of Repeat Measurements: Subjects with a confirmed ALT or total bilirubin level that is continuing to rise should have their liver chemistry tests (ALT, ALP, INR and total bilirubin) retested as clinically indicated, until levels stabilize or begin to recover.

Further Investigation into Liver Chemistry Elevations: Based on the inclusion/exclusion criteria for this study, the population to be enrolled, will have pre-existing baseline liver disease and will be closely monitored by the investigators with experience in the management of pediatric hepatic

diseases. For subjects with a confirmed elevation in ALT or total bilirubin level, as described above, the following evaluations should be performed as clinically indicated:

- Close and frequent monitoring of liver enzyme and serum bilirubin tests as clinically indicated. Frequency of retesting can decrease if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. If the appropriate frequency of monitoring is not feasible study drug administration will be suspended.
- Obtain a detailed history of symptoms and prior and concurrent diseases.
- Obtain comprehensive history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Obtain a history for exposure to environmental chemical agents and travel
- Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel).
- Serology for autoimmune hepatitis (eg, antinuclear antibody [ANA]).

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the ChiLDReN protocol chair and the Medical monitor.

10.5.2.2 Stopping Rules for Liver Chemistry Elevations

In the event of confirmed laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the ChiLDReN protocol chair**, **and medical monitor,** discontinuation of dosing of a subject with study drug will be considered if:

Historical Baseline Tests	Change Observed
ALT (any level)	ALT ≥ 20 x ULN
Total Bilirubin 1-10 mg/dL (17.10 – 171.04 μmol/L)	5 mg increased **and** a 2 x increase over historical baseline level
Total Bilirubin >10 mg/dL (>171.04 μmol/L)	2 x increase over historical baseline level

[1] Historical Baseline values are those reported at baseline of the LUM001-301 protocol.

10.5.2.3 Safety Monitoring for Triglycerides

In the event of a confirmed laboratory result for fasting total triglyceride >500 mg/dL (>5.65 mmol/L), the Investigator, the ChiLDReN protocol chair, and the medical monitor may consider a temporary interruption of study drug. Dosing may resume when the triglyceride level returns to <300 mg/dL (3.39 mmol/L) or to the subject's baseline level.

10.5.2.4 Safety Monitoring for Fat Soluble Vitamins

Vitamin status will be assessed per the schedule of procedures (see Section 16.1), blood samples will be obtained at the study visits before the daily dose of vitamins is administered. In the event of a confirmed laboratory result that falls either below or above the normal range for a vitamin (25-hydroxy vitamin D, retinol, retinol binding protein, tocopherol (α), total lipids), or for an elevated INR (as a proxy for vitamin K status), the investigator should make the appropriate modification to the subject's vitamin supplementation regimen.

The response to the change in regimen will be assessed by relevant follow-up blood work one month later. Changes will continue to be made until the levels are in the desired range. Adjustments may be discontinued outside of the desired range if there is agreement between the Investigator, the ChiLDReN protocol chair, and medical monitor that vitamin sufficiency cannot be reasonably expected.

10.5.2.5 Monitoring/Stopping Rules for Coagulation Panel Results

In the event of a confirmed laboratory result for INR >1.5 (unresponsive to vitamin K therapy), the Investigator, the ChiLDReN protocol chair, and the medical monitor may consider a temporary interruption of study drug. Dosing may resume when the INR falls below 1.5 or returns to the subject's baseline level.

10.6 Adjustment of Dose

Gastrointestinal intolerance, as evidenced by diarrhea/loose stools, abdominal pain/cramping and nausea, is expected to be the most frequent manifestation of a lack of tolerability to study drug. If an individual subject exhibits a treatment emergent CTCAE Grade 2 or greater drug-related GI toxicity, study drug dose may be lowered to a previously well tolerated dose. This decision should be made in consultation with the ChiLDReN protocol chair and medical monitor. A requirement for intravenous fluids as treatment for diarrhea (without an alternative explanation) will lead to discontinuation of study drug.

If a subject experiences an acute illness requiring temporary discontinuation of study drug, they may continue their participation in the study and resume study treatment as long as the period of discontinuation does not exceed 7 days.

10.7 Withdrawal of Subjects from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. Any subject who withdraws consent to participate in the study will be removed from further treatment and/or study observation immediately upon the date of the request.

Any investigator decision to withdraw a subject from the study must first be discussed with the medical monitor prior to withdrawal. The Investigator will provide the reason for withdrawal on the appropriate eCRF.

For any subject who requests to stop study treatment or has withdrawn from study treatment at the request of the legal guardian, Investigator or Sponsor before completion of the protocol-specified treatment period, and has received >1 dose of study drug, every effort should be made to complete the assessments scheduled for the Early Termination visit (see Schedule of Procedures, Section 16.1), provided the subject has not withdrawn full consent. The Early Termination visit should be scheduled within 7 days of the last study drug dose. The electronic diary must also be retrieved.

For safety reasons, efforts must be made to follow subjects for at least 30 days following their last dose of study drug. If a subject withdraws due to an AE, the Investigator should arrange for the subject to have follow-up visit(s) until the AE has resolved or stabilized.

Subjects must be withdrawn from the study for any of the following reasons:

- Withdrawal of consent/assent by the subject or legal guardian.
- Pregnancy.
- An AE (including disease progression) that leads the Investigator to decide that the subject should be withdrawn. If a subject suffers an AE that, in the judgment of the Investigator or the Sponsor, presents an unacceptable consequence or risk to the subject, the subject must be discontinued from the study.
- Significant protocol deviation (eg, medication or treatment that is prohibited by the protocol).
- At the discretion of the Investigator if deemed not medically acceptable to continue study treatment.
- Noncompliance, including failure to adhere to the study requirements as stated in the study protocol.
- Administrative decision by the Investigator or Sponsor.

11. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

All AEs, whether observed by the Investigator, reported by the subject, the subject's caregiver, from laboratory findings, or other means, will be recorded on the AE eCRF and medical record.

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee throughout the conduct of the study.

11.1 Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of SAEs including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

The Investigator should immediately report all SAEs to the Sponsor or designee. It is essential to report SAEs in a timely manner to the Sponsor, or designee, along with completed documentation of AEs to allow the Sponsor, or designee, to identify potential study-related, study drug- or dose-related AEs.

The Sponsor is responsible for reporting any suspected adverse reaction that is both serious and unexpected to the applicable regulatory authorities. The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that the study drug caused the AE and, therefore, meets the definition of a SUSAR.

Additionally, Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) will be notified of any SAE according to applicable regulations. The Data Monitoring Board (DMB) will be notified of any SAE as specified in the DMB charter.

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purposes of regulatory reporting. The Sponsor or designee will submit SUSARs to regulatory agencies in blinded or unblinded fashion according to local law. The Sponsor or designee will submit SUSARs to Investigators in a blinded fashion.

11.2 Definitions

11.2.1 Adverse Event

An AE is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

An AE <u>does not</u> include the following:

- Continuous persistent disease/symptom present before the start of study drug, which does not unexpectedly progress, or change in severity following drug administration.
- Disease being studied and/or signs and symptoms associated with the disease, such as jaundice or itching, or abnormalities in liver enzymes already present at the baseline visit.
- Treatment failure or lack of efficacy.

11.2.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any AE caused by the study drug.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

11.2.3 Serious Adverse Event (SAE)

A serious AE is any AE that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death.
- Is life threatening: that is, poses an immediate risk of death at the time of the event.
- An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE.
- Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization. Admission to the hospital is the criterion that defines "serious", not the duration of hospital stay.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).

- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.3 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (ie, before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. In addition, AEs that occur while the subject is not enrolled in the study during a gap period (ie, prior to enrollment in Protocol Amendment 5), will be collected as medical history unless the AE started within 30 days of last dose. The Investigator should always group signs and symptoms into a single term that constitutes a single unifying diagnosis if possible.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. Following questioning and evaluation, all AEs, whether believed by the Investigator to be related or unrelated to the study drug, must be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice, and on the AE eCRF. Each AE is to be evaluated for seriousness, causal relationship to the study drug, intensity, action taken, any treatment given, outcome, and duration. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

11.3.1 Serious Adverse Events

In the interest of subject safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to study drug) should be reported to the Sponsor or designee within 24 hours of the study center's first knowledge of the event. The collection of SAEs will begin after the subject signs the informed consent form and stop 30 days after the last dose of study drug.

When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An initial report of the SAE should be completed and a copy should be transmitted to the Sponsor or designee.

Detailed information should be actively sought and provided to the Sponsor or designee as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

11.3.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the subject signs the ICF and will stop 30 days after the last dose of study drug. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

11.3.3 Evaluation of Adverse Events (Serious and Non-Serious)

The following should be documented on the Adverse Event Case Report Form.

11.3.3.1 Relationship to the Study Drug

The Investigator will document his/her opinion of the relationship of the AE to treatment with study drug using the following criteria:

- Related: There is clear evidence that the event is related to the use of study drug (eg, confirmation by positive re-challenge test).
- Possible: The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and study drug administration.
- Unlikely/Remote: An event for which an alternative explanation is more likely (eg, concomitant medications or ongoing medical conditions) or the temporal relationship to study drug administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related).
- Not Related: The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and study drug.

11.3.3.2 Severity

The CTCAE grade of the event should be reported according to CTCAE Version 4.0 (Section 16.8). If the CTCAE does not have a grading for a particular AE, the severity of the event should be reported based on the following:

- Mild (Grade 1): The event is easily tolerated by the subject and does not affect the subject's usual daily activities.
- Moderate (Grade 2): The event causes the subject more discomfort and interrupts the subject's usual daily activities.
- Severe (Grade 3): The event is incapacitating and causes considerable interference with the subject's usual daily activities.

Specific definitions will be provided for designated GI events expected to occur in this study, in order to aid Investigators with determination of event severity.

Please also refer to Section 10.5.2 regarding specific safety monitoring for liver chemistry tests given that subjects with ALGS may have abnormal liver enzymes at baseline.

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 11.2.3).

11.3.3.3 Action Taken with Study Drug

Action taken with study drug due to the event is characterized by one of the following:

- None: No changes were made to study drug administration and dose.
- Permanently Discontinued: Study drug was discontinued and not restarted.
- Temporarily Interrupted, restarted – same dose: Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose.
- Reduced dose: Dosing was reduced, temporarily interrupted or delayed due to the AE and restarted at the next lower dose.

11.3.3.4 Treatment Given for Adverse Event

Any treatment (eg, medications or procedures) given for the AE should be recorded on the AE eCRF (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

11.3.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by one of the following:

- AE Persists: Subject terminates from the trial and the AE continues.
- Recovered: Subject recovered completely from the AE.
- Became Serious: The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE).
- Change in Severity (if applicable): AE severity changed.

If the event is a SAE then the event's outcome is characterized by one of the following:

- Ongoing: SAE continuing.
- Recovered: Subject recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date).
- Fatal: Subject died (the date of death should be entered as the SAE resolution date).

11.4 Procedures for Handling Special Situations

The following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours.

- SAE (see Section 11.3.1).
- Pregnancy.
- Dosing errors.
- Treatment unblinding for any reason (see Section 6.3).

11.4.1 Pregnancy Reporting

If a subject becomes pregnant or a pregnancy is suspected in either a subject or in the partner of a male study participant during the study, the study center staff must be informed immediately. The Sponsor or designee should be notified within 24 hours of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination should be reported within 24 hours.

If pregnancy is suspected during the study (including follow-up), a pregnancy test will be performed. The subject with a confirmed pregnancy will be immediately withdrawn from treatment with study drug. However, the subject will be encouraged to complete the Early Termination procedures to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the subject in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the study center and Sponsor may require access to the mother and infant's medical records for an additional follow-up after birth.

Payment for all aspects of obstetrical care, child or related care will be the subject's responsibility.

11.4.2 Dosing Errors

Study drug dosing errors should be documented as protocol deviations. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the appropriate eCRF and paper subject diaries. If the subject takes a dose of study drug that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 11.3.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

11.4.3 Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment (eg, bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia). Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator, the ChiLDReN protocol chair, and the medical monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents.

12. STATISTICAL CONSIDERATIONS

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of the analyses to be performed. The SAP will be written prior to database lock.

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

Safety

All safety analyses will be performed on the Safety Population, defined as all subjects who received at least one dose of the study drug during the extension study.

Adverse Events will be examined over the entire treatment period, and for the dose escalation and optimization periods. Adverse events for each study period will be summarized overall by treatment group based on the treatment group at enrollment in the extension study at baseline (Study Day 0). Adverse events for the stable dosing period will also be summarized overall and by treatment group based on the stable dosing group.

Other safety measures including clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation and range will be given for the values themselves and by their mean changes from pre-defined reference points (see below) at each visit. Qualitative variables will be summarized using counts and percentages by baseline treatment group at each study visit.

Drug Level Analysis

Descriptive statistics analysis of LUM001 concentrations will be carried out on the plasma concentration data.

Efficacy

All efficacy analyses will also be performed on the Safety Population, defined as all subjects who received at least one dose of the study drug during the extension study.

Secondary efficacy measures will be analyzed similarly as above. Details of the analysis methods will be outlined in the SAP.

All data will be included in data listings.

12.1 Sample Size Considerations

Approximately 36 subjects meeting the study's inclusion and exclusion criteria may be enrolled in the study. Because this is an extension study for subjects who participated in the LUM001-301 protocol, the sample size is not based on statistical considerations.

12.2 Population

12.2.1 Safety Population

Because of the design of the study, there will be only one analysis population for the study. The Safety Population is defined as all subjects who were enrolled and received at least one dose of the study drug. The Safety Population will be used for all safety analyses. Subjects will be analyzed by treatment received.

12.2.2 Siblings

At the start of the LUM001-301 study, siblings enrolled in the study will be assigned in a blinded manner to the same treatment arm. The data from all enrolled participants (including siblings) will be used for the safety analysis. For the efficacy analysis, data from only one of the siblings will be used. The choice of which subject's data to use in the efficacy analysis will be done in a random fashion before the LUM001-301 study is unblinded. Additionally, a sensitivity analysis will be conducted using the data from the siblings that were not randomly chosen in order to assess the potential impact on the results. Additional methodological detail will be included in the protocol's SAP.

12.2.3 Demographic and Baseline Characteristics

12.2.3.1 Subject Disposition

Subject disposition will be summarized descriptively. The number and percentage of subjects enrolled, completed, and withdrawn, along with reasons for withdrawal, will be tabulated overall, and by treatment group assigned at LUM001-305 study entry.

The number and percentage of subjects receiving study drug following the protocol specified dose escalation procedure, stable dosing, safety monitoring, and long-term optional follow-up dosing regimens will be tabulated overall and by treatment group assigned in the core study (LUM001-301). Line listings will be prepared for all subjects not following the planned dosing schedule, showing all doses and dose changes occurring.

Other disposition and study conduct information, including major protocol violations will be listed. In addition, for subjects who had dose gaps or re-initiated to all protocol amendments, the number of days of the off-drug period will be summarized. Duration of the follow-up period will be tabulated.

12.2.3.2 Baseline Data

The following baseline data will be used to describe the study population:

- Demographic variables, including age, gender and race/ethnicity.
- Medical history.
- Baseline disease characteristics (eg, pruritus scores, liver biochemistries).
- Prior medications of interest (eg, ursodiol [UDCA], rifampicin) and concomitant medications.

Demographic and baseline characteristics will be summarized overall and descriptively by treatment group assigned in the core study (LUM001-301).

Baseline for this study will be considered Day 0 in the study.

Medical history information will be presented in listings.

12.2.4 Efficacy Analyses

12.2.4.1 Efficacy Variables

The primary evaluation will be the mean change from baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 baseline to Week 48 in:

- Fasting serum bile acid level.

Secondary evaluations will be the mean change from baseline (Day 0) of LUM001 301 and baseline (Day 0) of LUM001-305 through Week 216/EOT in:

- Biochemical markers of cholestasis and liver disease (eg, ALT, ALP, GGT and bilirubin [total and direct]).
- Pruritus as measured by the ItchRO instruments (ItchRO(Obs)™, caregiver instrument/ItchRO(Pt) ™ patient instrument).
    - During the first 12 weeks of the study, the electronic diary (ItchRO) will be completed twice daily (AM & PM). During the stable dosing period (Weeks 13-48), twice daily completion of the electronic diary (ItchRO) for 4 consecutive weeks will be required following the Week 24 and Week 44 clinic visits. For subjects who continue in the safety monitoring period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 60, 72, and 84 clinic visits. For subjects who continue in the long-term, optional follow-up treatment period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 96, 108, 120, and 132 clinic visits, and for 4 weeks following the Week 144 visit. For subjects who continue in the long-term optional follow-up treatment period-

2, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 144, 156, 168, 180, 192, 204 clinic visits, and for 4 weeks following the Week 216 visit.

- Xanthomas as measured by clinician xanthoma scale.
- Clinician scratch scale
- Fasting serum bile acid level

The exploratory evaluation will be the mean change in weight z-score from baseline Day 0 of LUM001-301 and baseline (Day 0) of LUM001-305 through Week 216 (EOT/ET).

Exploratory evaluations will include the mean change from baseline in ItchRO, fasting sBA, and biochemical markers of cholestasis and liver disease at Week 144, Week 216, (EOT/ET) and at Week 220 (EOS). The exploratory evaluation will be the mean change in weight z-score from baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 through Week 216 (EOT/ET).

Additional exploratory evaluations will be specified in the SAP and may include analyses between Week 144 (EOT/ET) and Week 148 (EOS) for subjects who complete Protocol Amendment 5 and between Week 216 (EOT/ET) and Week 220 (EOS) for subjects who complete Protocol Amendment 6.

12.2.4.2 Primary Efficacy Analysis

The change from baseline to Week 48 in the serum bile acid will be tabulated overall and by treatment group assigned in the core study (LUM001-301), using summary statistics including the number of observations, the mean, median, standard deviation, minimum and maximum. Differences from baseline will be calculated and summarized as above, with a 95% confidence interval for the mean.

12.2.4.3 Secondary, Exploratory and Other Efficacy Analyses

Secondary Analyses

Secondary efficacy variables that are continuous measures will be analyzed similarly to the primary efficacy analyses.

Change from baseline in Xanthoma scale will be categorized as improved, stable or worsened.

Exploratory Analyses

Exploratory efficacy variables that are continuous measures will be analyzed similarly to the primary efficacy analyses.

Additional exploratory analyses may be performed and will be defined in the SAP.

Other Analyses

Analyses of PedsQL and the CIC will be performed and will be defined in the SAP.

12.2.5 Safety Analyses

Safety analyses will be performed on the Safety Population.

12.2.5.1 Safety Assessments

The following assessments will be used to monitor safety:

- AEs and SAEs.
- Clinical laboratory results.
- Vital signs.
- Physical exam findings, including body weight and height.
- Concomitant medication usage.

12.2.6 Safety Analysis

Safety analyses will be performed on the Safety Population.

Safety data, including AEs, clinical laboratory tests, vital signs, physical examinations, and concomitant medication usage will be summarized descriptively overall for the safety population. Individual subject listings will be prepared for all safety data.

12.2.6.1 Adverse Events

Frequencies (number and percentage) of subjects with one or more treatment emergent AEs will be summarized overall, and by treatment group assigned in the core study (LUM001-301), by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA™) terminology. All treatment emergent AEs, all treatment emergent AEs potentially related to study drug, all treatment emergent SAEs and all treatment emergent SAEs potentially related to study drug will be summarized. Specific AEs of special interest, particularly GI related AEs, will be outlined in the SAP and summarized. AEs will be summarized overall and then separately for the dose escalation/optimization, stable dose, safety monitoring and long-term, optional follow-up treatment periods of the study.

The incidence of AEs, and their severity, as well as the incidence of subjects who withdraw due to an AE will be tabulated. A subject listing of all treatment emergent AEs, and AEs causing study discontinuation will be presented.

12.2.6.2 Laboratory Tests

Clinical laboratory (chemistry panel, complete blood count (CBC) with differential, coagulation, lipid panel, cholestasis biomarkers, fat soluble vitamins, and urinalysis parameters) test parameters will be listed for individual subjects and summarized overall, and by treatment group assigned in the core study (LUM001-301) for each study visit. Change from baseline will also be presented over time, as appropriate. Percent change from baseline will be added for laboratory values as outlined in the SAP.

A separate listing will present laboratory values of all subjects who change from normal to abnormal or from abnormal to normal during the course of the study. Changes within a treatment group for selected safety measures will be assessed at Weeks 8, 12, 24, 36, 48, 96, and at additional time points during the long-term, optional follow-up treatment periods.

The effect of LUM001 on fat soluble vitamin levels will be assessed. These laboratory values will be summarized as above and listed for individual subjects. A separate listing will present laboratory values of all subjects who change from sufficient to insufficient or from insufficient to sufficient during the course of the study.

12.2.6.3 Physical Exams, Vital Signs and Weight/Height Measurements

Changes in physical exam findings after baseline will be listed for individual subjects.

Vital signs, weight and height (both weight and height are to be measured as an absolute number and as a z-score for age and gender) will be listed for individual subjects and summarized overall, and by treatment group assigned in the core study (LUM001-301) for each study visit. Changes from baseline for all visits after the baseline visit will be included in the summary table. Baseline for vital signs will be defined as the last evaluation before dosing with study drug. This will include the LUM001-301 baseline visit (Day 0) and the LUM001-305 baseline (Day 0) visit.

12.2.6.4 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized descriptively by Anatomic Therapeutic Chemical (ATC) class, using counts and percentages.

12.2.6.5 Study Drug Exposure

Due to poor absorption of LUM001, very low systemic exposure and plasma drug levels are expected. The key measurement will be the pharmacodynamic effect on serum bile acid levels. However, exposure to study drug will be measured at specified study visits approximately 4 hours post dose and data will be summarized and listed across the treatment period by treatment group. Average daily dose, total drug exposure, and total subject days of exposure to study medication will be summarized descriptively by treatment group.

12.2.7 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 and the blind is broken. Thus all such analyses will be interpreted cautiously and not used for formal inference, although inferential statistics may be used as part of the data summary.

13. INVESTIGATOR'S REGULATORY OBLIGATIONS

13.1 Informed Consent

The written informed consent/assent document(s) should be prepared in the language(s) of the potential patient population, on an English version provided by the Sponsor or designee.

The Investigator is responsible for obtaining written informed consent/assent from the subject and/or their legally acceptable representative(s). Before any tests or assessments are performed, an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study will be provided to the subject and/or legally acceptable representative. The subject and/or legally acceptable representative must be given sufficient time to consider whether to participate in the study and be assured that withdrawal from the study may be requested at any time without jeopardizing medical care related to or required as a result of study participation.

Subjects and/or their legally acceptable representative(s) will be required to read, sign, and date an IEC approved informed consent/ascent form (ICF/IAF) summarizing the discussion prior to enrollment. Since this is a pediatric study, in addition to the written informed consent, the assent of the child must also be obtained, as required by each study center's governing IRB. The person who conducted the informed consent discussion (not necessarily an Investigator) should also sign and date the ICF/IAF. The original signed ICF/IAF should be retained in accordance with institutional policy. Subjects and/or their legally acceptable representative(s) will be given a copy of their ICF, and IAF.

The subject's and/or legal representative's agreement and the acquisition of informed consent should be documented in the subject's medical record. When the study is completed and the CRF has been monitored, the ICF will be kept in the Investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the performance of the study.

Over the course of the study, the ICF/IAF may be modified, as appropriate (eg, due to protocol amendment or significant new safety information). The resulting IEC-approved ICF/IAF will be used for all subjects subsequently entering the study or those already enrolled and still actively participating in the trial.

13.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2008, the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

13.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent/assent forms, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent/assents form(s) must be received by the Sponsor or designee before recruitment of subjects into the study and shipment of study drug. A copy of the written approval of any other items/materials that must be approved by the study center or IEC/IRB must also be received by the Sponsor or designee before recruitment of subjects into the study and shipment of study drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent/assent documents. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious AEs occurring at the study center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

13.4 Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the CRFs or other documents submitted to the Sponsor or designee, subjects should be identified by unique initials and a subject study number only. Documents that are not for submission to the Sponsor or designee (eg, signed informed consent/assent forms) should be kept in strict confidence by the Investigator.

In compliance with federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, regulatory agency(ies), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of Mirum Pharmaceuticals, Inc.; it shall not be disclosed to others without written consent of Mirum Pharmaceuticals, Inc.; and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only Mirum Pharmaceuticals, Inc., as they deem necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal regulations, the Investigator is obliged to furnish Mirum Pharmaceuticals, Inc., with the complete test results and all data compiled in this study.

14. ADMINISTRATIVE AND LEGAL OBLIGATIONS

14.1 Study Personnel

Prior to the start of this study, the Investigator must supply the Sponsor or designee with a list of the names of the Investigator(s) for the study and other possible participants, their professional background (eg, Investigator, coordinator, technician) and their role in the study. The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

14.2 Pre-study Documentation Required

The Investigator must provide the Sponsor or designee with the following documents (copies should be kept by the Investigator in the clinical site's regulatory document binder):

- Signed and dated Protocol Signature Page.
- Completed and signed statement of Investigator (Form FDA 1572/financial disclosure form) (where applicable).
- Curriculum vitae (CV) of the Investigator and sub-investigators (where applicable, all persons listed on Form FDA 1572).
- Letter of approval from the IEC/IRB for both protocol and consent/assent forms.
- Copy of the IEC/IRB-approved written informed consent/assent forms, and any other written information and/or advertisement to be used.
- IEC/IRB membership list or compliance certification letter.
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, including a copy of the laboratory certificate (where applicable).
- In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided. The Sponsor's monitor must be notified if the laboratory is changed.
- List of normal laboratory values (where applicable).

In addition, in advance of enrolment of subjects, study staff is required to complete all required training.

14.3 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent/assent documents. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The Investigator must send a copy of the approval letter

from the IEC/IRB to the Sponsor or designee. Amendments to the protocol will not be implemented until written IEC/IRB approval has been received.

14.4 Study Termination

Both the Sponsor or designee and the Investigator reserve the right to terminate the study the Investigator's site, according to the terms of the study contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

The Sponsor or designee reserves the right to terminate the study overall.

14.5 Study Documentation and Storage

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. All original source documents supporting entries in the CRFs must be maintained and be readily available.

The Investigator and the study center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. The clinical site's regulatory document binder essential elements should include:

- Subject files containing completed CRFs (eCRFs), informed consents/assents, and supporting copies of source documentation.
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee.
- If drug supplies are maintained at the study center, documentation for proof of receipt, study drug accountability records, return of study drug for destruction, final study drug product reconciliation statement, and all drug-related correspondence.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

14.5.1 Parent Report for Teenagers (ages 13-18 years)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

14.6 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (eg, CRFs and other pertinent data) provided that subject confidentiality is respected. Quality control audits may be performed at the Sponsor's discretion.

Throughout the course of the study, a study monitor will make frequent contacts with the Investigator and/or study staff. This will include telephone calls and on-site visits. During the on-site visits, the CRFs will be reviewed for completeness and adherence to the protocol, accuracy, consistency of the data, and adherence to local regulations on the conduct of clinical research. The monitor will need access to subject medical records and other study-related records needed to verify the entries on the CRFs. The study monitor will also perform drug accountability checks and review the clinical site's regulatory document binder to assure completeness of documentation in all respects of clinical study conduct. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

The Investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

14.7 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

14.8 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Subjects will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Informed Consent document.

15. REFERENCES

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16. APPENDICES

16.1 Schedule of Procedures

Schedule of Procedures A: Baseline – Week 12

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

Schedule of Procedures A: Baseline – Week 12

Study Period	Baseline	Treatment Period							
		Dose Escalation[c]				Dose Optimization			
Study Week		1	2	3	4	6	8	10	12
Study Day	Day 0[1]	7	14	21	28	42	56	70	84
Window (in days)		(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)

[1] Evaluations and procedures completed for the Week 13 Visit of the LUM001-301 protocol will also serve as the evaluations for the Baseline Visit for this extension study.
[2] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[3] See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[4] Subjects are required to fast at least 4 hrs. (only water permitted prior to collection).
[5] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[6] Subjects must be available to receive a phone call from study staff.
[a] At the indicated visits, oxalate will be part of the urinalysis.
[b] During the first 12 weeks of the study, the eDiary (ItchRO) will be completed twice daily (AM & PM). Compliance will be assessed at each visit/phone contact.
[c] Subjects should be dosed for at least 7 days at each dose level.
[d] At Weeks 2, 8, 12, 24, 36 and 48, blood will be drawn approximately 4 hours post dosing for drug level analysis. At Week 4, blood will be drawn approximately 2 hours post-dosing for drug level analysis.

Schedule of Procedures B - Stable Dosing: Week 16 – Week 48

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

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

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

Schedule of Procedures B - Stable Dosing: Week 16 – Week 48

Study Period	Treatment Period (cont'd)								
	Stable Dosing								
Study Week	16[6]	20	24	28	32	36	40	44	Week 48
Study Day	112	140	168	196	224	252	280	308	336
Window (in days)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)

	Clinic Visit
	Phone Contact

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

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

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

Study Period	Treatment Period (cont'd) Safety Monitoring Period											Study Termination	Follow-Up
Study Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**Week 96 (or Early Term[7])**	**30 days after final dose[8]**
Study Day	364	392	420	448	476	504	532	560	588	616	644	672	
Window (in days)	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**	**(±5)**
Phone Contact[6]	X	X		X	X		X	X		X	X		X

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

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

	Clinic Visit
	Phone Contact

Schedule of Procedures D – Long-term, Optional Treatment Period: Week 96 – Week 148
for those subjects with ≤7 days from the last dose of LUM001 applicable as follows:

- **If another study becomes available for subjects prior to completion of Protocol Amendment 5, the subject will complete EOT assessments as outlined for Week 144.**
- **Subjects who complete 48 weeks of additional treatment and who are not eligible for another study will complete EOS assessments as outlined for Week 148.**

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

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

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

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

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

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

	Clinic Visit
	Phone Contact

Schedule of Procedures E – Re-Entry into Long-term Optional Treatment Period/Long-term Optional Treatment Period-2: applicable as follows:

- **Subjects either previously completed the follow-up period up to Week 96, or has received permission from the sponsor and the ChiLDReN protocol chair to re-enter the study.**

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

Study Period	**Dose Escalation Treatment Period**						
PA5 DE Study Week	**PA5 RI -2[h]**	**PA5 RI Day 0**	**PA5 RI Week 1**	**PA5 RI Week 2**	**PA5 RI Week 3**	**PA5 RI Week 4**	**PA5 Schedule D - Week 104**
Scheduling Considerations		**0**					
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**
Informed Consent/Assent	X						
Assess Eligibility for study re-entry	X	X					
Physical Exam	X	X		X		X	
Body Weight & Height	X	X		X		X	
Vital Signs[a]	X	X		X		X	
CBC with Differential[b]	X	X		X		X	
Coagulation[b]	X	X		X		X	
Chemistry Panel[b]	X	X		X		X	
Lipid Panel[b,c]		X		X		X	
Cholestasis Biomarkers[b,c]		X		X		X	
Fat Soluble Vitamins[b,c,d]		X		X		X	
Urinalysis[b]		X		X		X	
Serum Pregnancy Test (if indicated)[e]	X	X		X		X	
Clinician Scratch Scale		X		X		X	
Clinician Xanthoma Scale		X		X		X	

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

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

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.
[h] Subjects with dose interruptions prior to Week 96 or who early terminated may re-enter the study under Protocol Amendment 6. These subjects will initiate dose escalation at visit PA5 RI -2.

Clinic Visit
Phone Contact

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

- **If another study becomes available for subjects prior to completion of Protocol Amendment 6, the subject will complete EOT assessments as outlined for Week 216.**
- **Subjects who complete 72 weeks of additional treatment and who are not eligible for another study will complete EOS assessments as outlined for Week 220.**

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

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

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

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

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

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

	Clinic Visit

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

Study Period	Long-term, Optional Follow-up Treatment Period-2																	EOT/ET Visit	EOS Visit
Study Week	148	152	156	160	164	168	172	176	180	184	188	192	196	200	204	208	212	Week 216[7]	Week 220
Study Day																			
Window (in days)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±5)

[7] Subjects who withdraw early during the follow-up treatment period-2 should complete all evaluations at this visit.

Phone Contact

16.2 List of Laboratory Analytes

CBC with Differential

Red blood cells
Hemoglobin
Hematocrit
MCV, MCH, MCHC
Platelets
White blood cells
WBC Differential (% and absolute)
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Coagulation

Activated partial thromboplastin time (aPTT) (sec)
Prothrombin time (PT) (sec)
INR

Clinical Chemistry

Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Phosphate
Glucose
Blood urea nitrogen (BUN)
Creatinine
Uric Acid
Total bilirubin
Direct bilirubin (conjugated)
Indirect bilirubin (unconjugated)
Alkaline phosphatase (ALP)
AST (SGOT)
ALT (SGPT)
GGT

Lipid Panel[1]

Total cholesterol
LDL-C (direct)
HDL-C
Triglycerides (TG)

Cholestasis Biomarkers[1]

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

Fat Soluble Vitamins[1]

25-hydroxy vitamin D
Retinol
Retinol binding protein
Tocopherol (α)
Total lipids

Urinalysis

pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Occult blood and cells
Nitrite
Urobilinogen
Leukocyte esterase
Microscopic examination[2]
Oxalate[3]

LUM001 Drug Levels

LUM001 in plasma

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

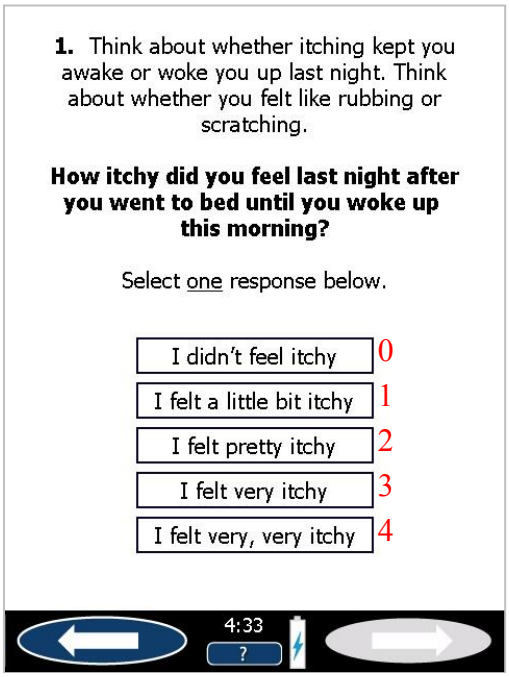
16.3 Itch Reported Outcome Instrument (ItchRO™)

Many of the ALGS subjects in this study are expected to be between the ages of 12 months and 10 years, necessitating reliance upon an observer-reported outcome instrument (ObsRO) to evaluate a pruritus endpoint.

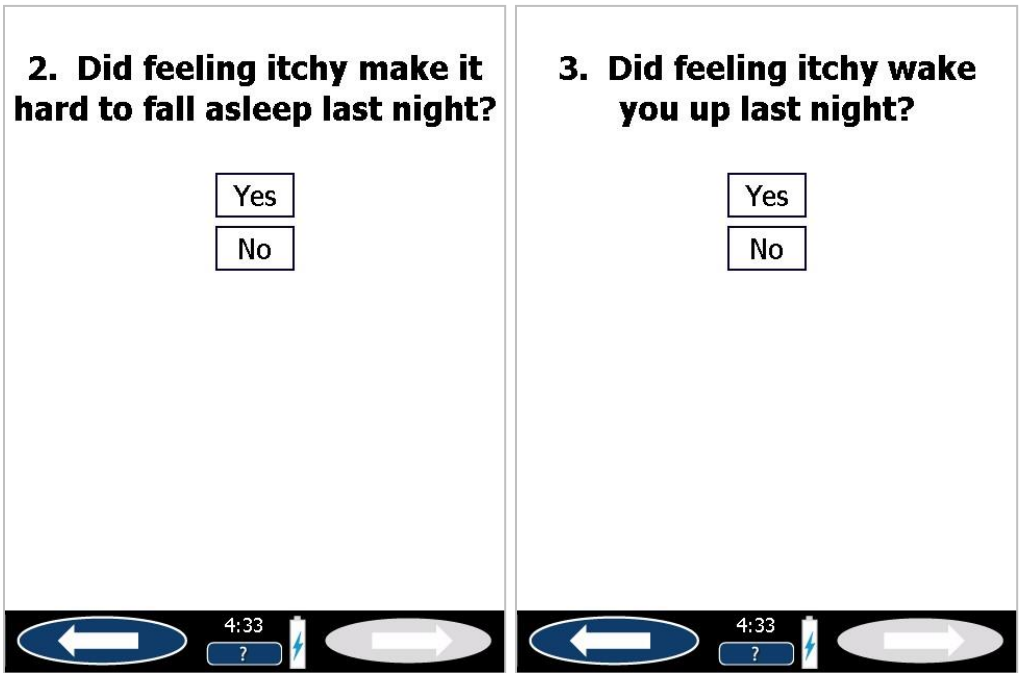
The ItchRO instrument is being developed both as a patient reported outcome measure (PROM) for pediatric subjects (9 years of age and older) and an ObsRO for caregivers/parents. The ItchRO will be completed using an electronic diary (eDiary) twice daily (morning and evening) for both the PROM and ObsRO.

16.3.1 Patient Itch Reported Outcome Instrument, ItchRO(Pt)™

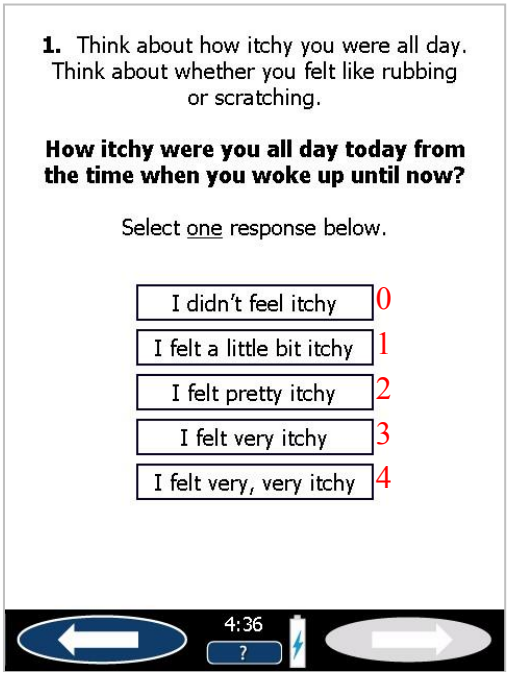
A screen shot from the ItchRO(Pt) **morning report** is show below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Pt) morning report score is 0 and the maximum score is 4.



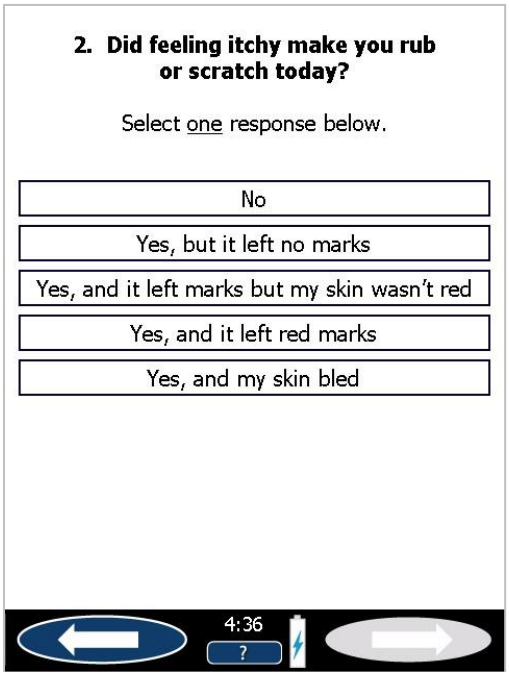
If the patient selects "I didn't feel itchy at all" the morning diary is complete, if not the following screens will be shown on the eDiary:



A screen shot from the ItchRO(Pt) **evening report** is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Pt) evening report score is 0 and the maximum score is 4.

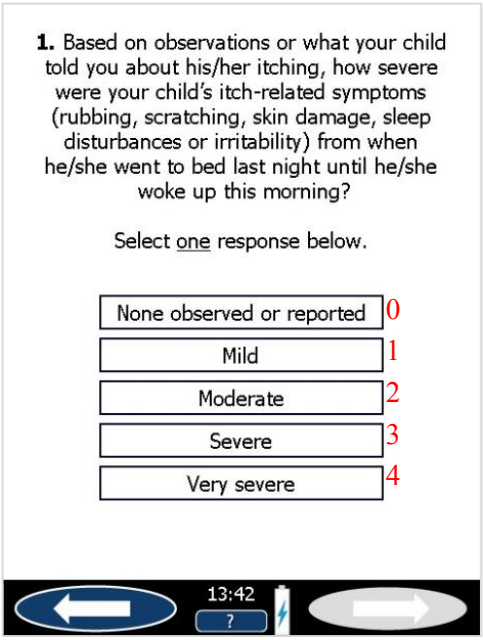


If the patient selects "I didn't feel itchy" the evening diary is complete, if not the following screen will be shown on the eDiary:

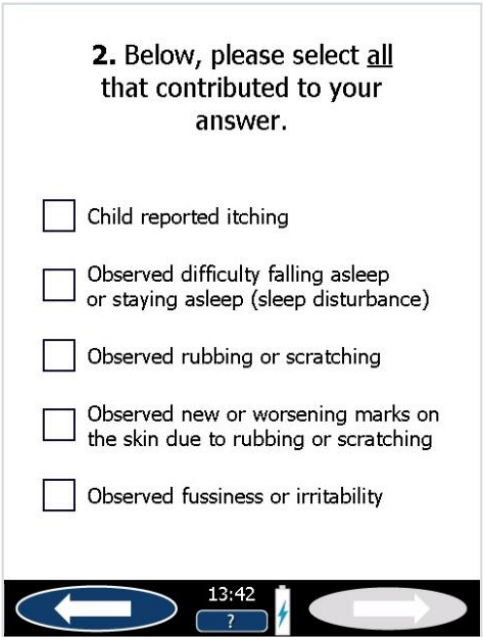


16.3.2 Observer Itch Reported Outcome Instrument, ItchRO(Obs)™

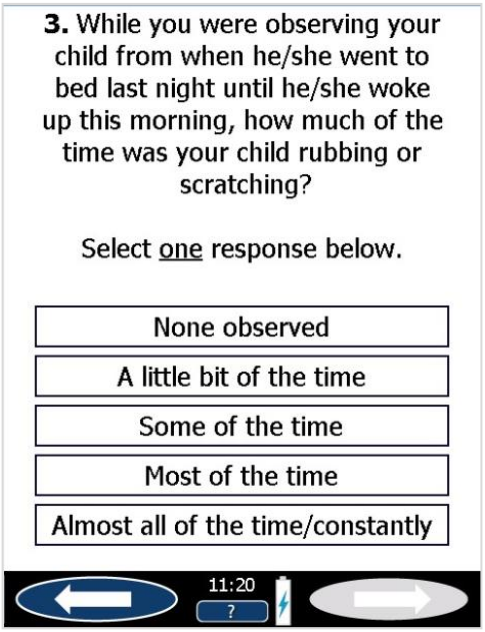
A screen shot from the ItchRO(Obs) **morning report** is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) morning report score is 0 and the maximum score is 4.



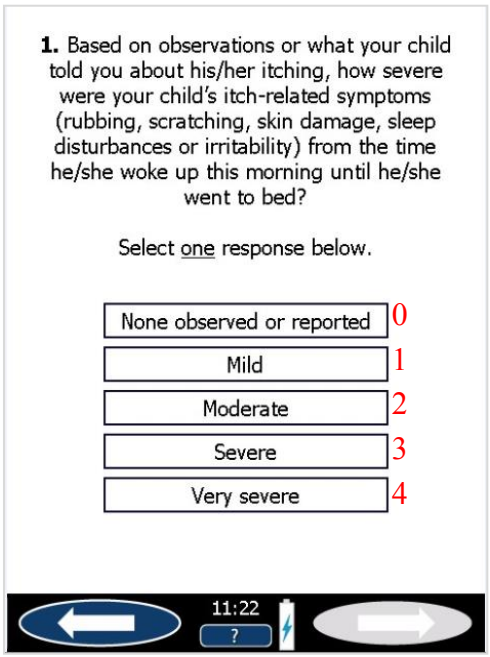
If the caregiver selects "None observed or reported" the morning diary is complete, if not the following screen will be shown on the eDiary:



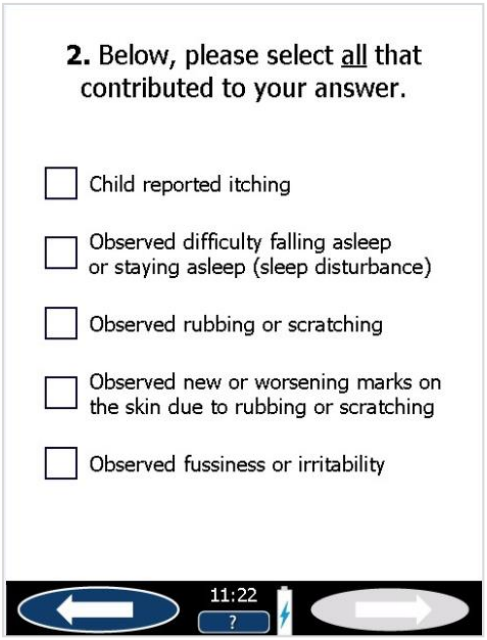
All caregivers will also be required to answer the following question on the ItchRO(Obs) **morning report**:



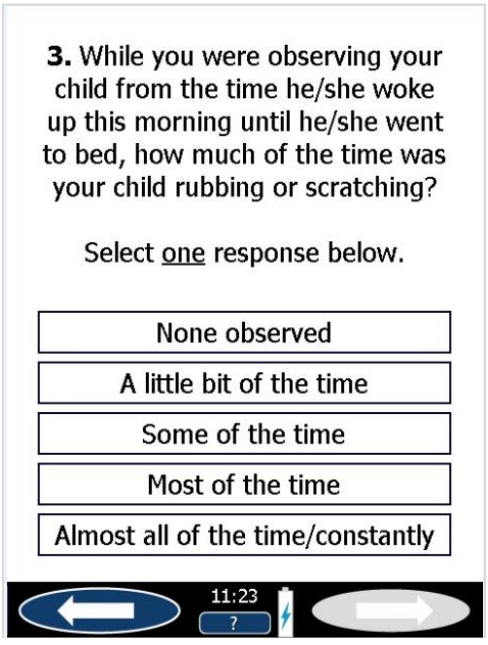
A screen shot from the ItchRO(Obs) **evening report** is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) evening report score is 0 and the maximum score is 4.



If the caregiver selects "None observed or reported" the evening diary is complete, if not the following screen will be shown on the eDiary:



All caregivers will also answer the following question on the ItchRO(Obs) **evening report**:



16.4 Clinician Scratch Scale

This scoring scale was originally developed to assess pruritus before and after surgical intervention in children with ALGS and PFIC (Whitington and Whitington, 1988).

The clinician will rate the subject's pruritus, as evidenced by scratching, according to the following scale:

Score	Description
0	None
1	Rubbing or mild scratching when undistracted
2	Active scratching without evident skin abrasions
3	Abrasion evident
4	Cutaneous mutilation, hemorrhage and scarring evident

16.5 Clinician Xanthoma Scale

The Clinician Xanthoma scoring scale was originally developed to assess xanthomas before and after surgical intervention in children with ALGS (Emerick and Whitington, 2002)

The clinician will rate the subject's degree of xanthomatosis according to the following scale:

Score	Description
0	None
1	Minimal
2	Moderate
3	Disfiguring
4	Disabling

In the study in which this scale was used to assess xanthomas before and after surgical intervention in children with ALGS, "minimal" xanthomas represented fewer than 20 scattered individual lesions, "moderate" represented more than 20 lesions that did not interfere with or limit activities, "disfiguring" represented large numbers of lesions that by their large numbers or size caused distortion of the face or extremities, and "disabling" represented xanthomas that interfered with function (such as hand use or ability to walk) because of excess size or number.

16.6 Pediatric Quality of Life Inventory (PedsQL™)

The PedsQL Generic Cores Scale is composed of 23 items to assess pediatric HRQoL measurements across 4 domains: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). Each item consists of a 5-level Likert item survey (0-4). Each PedsQL™ age-appropriate form should take less than four minutes to complete.

Pediatric HRQoL measurement instruments must be sensitive to cognitive development and must include both child self-report and parent proxy-report. Accordingly, the PedsQL consists of developmentally appropriate forms for 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.

Quality of life will be assessed using the appropriate PedsQL™ module(s) provided below.

16.6.1 Parent Report for Infants (ages 1-12 months)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 1-12 months)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Low energy level	0	1	2	3	4
2. Difficulty participating in active play	0	1	2	3	4
3. Having hurts or aches	0	1	2	3	4
4. Feeling tired	0	1	2	3	4
5. Being lethargic	0	1	2	3	4
6. Resting a lot	0	1	2	3	4

PHYSICAL SYMPTOMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Having gas	0	1	2	3	4
2. Spitting up after eating	0	1	2	3	4
3. Difficulty breathing	0	1	2	3	4
4. Being sick to his/her stomach	0	1	2	3	4
5. Difficulty swallowing	0	1	2	3	4
6. Being constipated	0	1	2	3	4
7. Having a rash	0	1	2	3	4
8. Having diarrhea	0	1	2	3	4
9. Wheezing	0	1	2	3	4
10. Vomiting	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling angry	0	1	2	3	4
3. Crying or fussing when left alone	0	1	2	3	4
4. Difficulty soothing himself/herself when upset	0	1	2	3	4
5. Difficulty falling asleep	0	1	2	3	4
6. Crying or fussing while being cuddled	0	1	2	3	4
7. Feeling sad	0	1	2	3	4
8. Difficulty being soothed when picked up or held	0	1	2	3	4
9. Difficulty sleeping mostly through the night	0	1	2	3	4
10. Crying a lot	0	1	2	3	4
11. Feeling cranky	0	1	2	3	4
12. Difficulty taking naps during the day	0	1	2	3	4

PedsQL 3

*In the past **ONE month**, how much of a **problem** has your child had with …*

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Not smiling at others	0	1	2	3	4
2. Not laughing when tickled	0	1	2	3	4
3. Not making eye contact with a caregiver	0	1	2	3	4
4. Not laughing when cuddled	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Not imitating caregivers' actions	0	1	2	3	4
2. Not imitating caregivers' facial expressions	0	1	2	3	4
3. Not imitating caregivers' sounds	0	1	2	3	4
4. Not able to fix his/her attention on objects	0	1	2	3	4

16.6.2 Parent Report for Infants (ages 13 to 24 months)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 13-24 months)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Low energy level	0	1	2	3	4
2. Difficulty participating in active play	0	1	2	3	4
3. Having hurts or aches	0	1	2	3	4
4. Feeling tired	0	1	2	3	4
5. Being lethargic	0	1	2	3	4
6. Resting a lot	0	1	2	3	4
7. Feeling too tired to play	0	1	2	3	4
8. Difficulty walking	0	1	2	3	4
9. Difficulty running a short distance without falling	0	1	2	3	4

PHYSICAL SYMPTOMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Having gas	0	1	2	3	4
2. Spitting up after eating	0	1	2	3	4
3. Difficulty breathing	0	1	2	3	4
4. Being sick to his/her stomach	0	1	2	3	4
5. Difficulty swallowing	0	1	2	3	4
6. Being constipated	0	1	2	3	4
7. Having a rash	0	1	2	3	4
8. Having diarrhea	0	1	2	3	4
9. Wheezing	0	1	2	3	4
10. Vomiting	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling angry	0	1	2	3	4
3. Crying or fussing when left alone	0	1	2	3	4
4. Difficulty soothing himself/herself when upset	0	1	2	3	4
5. Difficulty falling asleep	0	1	2	3	4
6. Crying or fussing while being cuddled	0	1	2	3	4
7. Feeling sad	0	1	2	3	4
8. Difficulty being soothed when picked up or held	0	1	2	3	4
9. Difficulty sleeping mostly through the night	0	1	2	3	4
10. Crying a lot	0	1	2	3	4
11. Feeling cranky	0	1	2	3	4
12. Difficulty taking naps during the day	0	1	2	3	4

PedsQL 3

*In the past **ONE month**, how much of a **problem** has your child had with …*

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Not smiling at others	0	1	2	3	4
2. Not laughing when tickled	0	1	2	3	4
3. Not making eye contact with a caregiver	0	1	2	3	4
4. Not laughing when cuddled	0	1	2	3	4
5. Being uncomfortable around other children	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Not imitating caregivers' actions	0	1	2	3	4
2. Not imitating caregivers' facial expressions	0	1	2	3	4
3. Not imitating caregivers' sounds	0	1	2	3	4
4. Not able to fix his/her attention on objects	0	1	2	3	4
5. Not imitating caregivers' speech	0	1	2	3	4
6. Difficulty pointing to his/her body parts when asked	0	1	2	3	4
7. Difficulty naming familiar objects	0	1	2	3	4
8. Difficulty repeating words	0	1	2	3	4
9. Difficulty keeping his/her attention on things	0	1	2	3	4

16.6.3 Parent Report for Toddlers (ages 2-4 years)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

PARENT REPORT for TODDLERS (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

16.6.4 Parent Report for Young Children (ages 5-7 years)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

PedsQL-4.0-Core PYC- United States/English
PedsQL-4.0-Core-PYC_AU4.0_eng-USori.doc

16.6.5 Parent Report for Children (ages 8-12 years)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

16.6.6 Pediatric Quality of Life Inventory v 4.0 for Young Children (ages 5-7 years)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

YOUNG CHILD REPORT (ages **5-7**)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (***Where?_____***)	0	2	4
8. Do you ever feel too tired to play	0	2	4

Remember, tell me how much of a problem this has been for you for the last few weeks.

EMOTIONAL FUNCTIONING ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling good	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

PedsQL 3

How much of a problem is this for you?

Not at all 

Sometimes 

A lot 

16.6.7 Pediatric Quality of Life Inventory for Children (ages 8-12 years)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

16.6.8 Pediatric Quality of Life Inventory for Teenagers (ages 13-18 years)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

16.6.9 Multidimensional Fatigue Scale Parent Report for Toddlers (ages 2-4 years)

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

16.6.10 Multidimensional Fatigue Scale Parent Report for Young Children (ages 5-7 years)

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

16.6.11 Multidimensional Fatigue Scale Parent Report for Children (ages 8-12 years)

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

. On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

16.6.12 Multidimensional Fatigue Scale Parent Report for Teenagers (ages 13-18 years)

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

16.6.13 Multidimensional Fatigue Scale Young Child Report (ages 5-7 years)

ID# _____

Date: _____

PedsQL™
Multidimensional Fatigue Scale

Standard Version

YOUNG CHILD REPORT (ages **5-7**)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the past few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

General Fatigue *(PROBLEMS WITH…)*	NOT AT ALL	SOME-TIMES	A LOT
1. Do you feel tired	0	2	4
2. Do you feel physically weak (not strong)	0	2	4
3. Do you feel too tired to do things that you like to do	0	2	4
4. Do you feel too tired to spend time with your friends	0	2	4
5. Do you have trouble finishing things	0	2	4
6. Do you have trouble starting things	0	2	4

Remember, tell me how much of a problem this has been for you for the last few weeks.

Sleep/Rest Fatigue *(PROBLEMS WITH…)*	NOT AT ALL	SOME-TIMES	A LOT
1. Do you sleep a lot	0	2	4
2. Is it hard for you to sleep through the night	0	2	4
3. Do you feel tired when you wake up in the morning	0	2	4
4. Do you rest a lot	0	2	4
5. Do you take a lot of naps	0	2	4
6. Do you spend a lot of time in bed	0	2	4

Cognitive Fatigue *(PROBLEMS WITH…)*	NOT AT ALL	SOME-TIMES	A LOT
1. Is it hard for you to keep your attention on things	0	2	4
2. Is it hard for you to remember what people tell you	0	2	4
3. Is it hard for you to remember what you just heard	0	2	4
4. Is it hard for you to think quickly	0	2	4
5. Do you have trouble remembering what you were just thinking	0	2	4
6. Do you have trouble remembering more than one thing at a time	0	2	4

PedsQL 3

How much of a problem is this for you?

Not at all

Sometimes

A lot

PedsQL (5-7) Fatigue
05/01
PedsQL TM Multidimensional Fatigue Scale - Young child (5-7) - United States/English
PedsQoL-Fatigue-YC-AU4.0eng-USorig

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16.6.14 Multidimensional Fatigue Scale Child Report (ages 8-12 years)

ID# _____

Date: _____

PedsQL™
Multidimensional Fatigue Scale

Standard Version

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for you …*

GENERAL FATIGUE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel tired	0	1	2	3	4
2. I feel physically weak (not strong)	0	1	2	3	4
3. I feel too tired to do things that I like to do	0	1	2	3	4
4. I feel too tired to spend time with my friends	0	1	2	3	4
5. I have trouble finishing things	0	1	2	3	4
6. I have trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I sleep a lot	0	1	2	3	4
2. It is hard for me to sleep through the night	0	1	2	3	4
3. I feel tired when I wake up in the morning	0	1	2	3	4
4. I rest a lot	0	1	2	3	4
5. I take a lot of naps	0	1	2	3	4
6. I spend a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4
6. I have trouble remembering more than one thing at a time	0	1	2	3	4

16.6.15 Multidimensional Fatigue Scale Teen Report (ages 13-18 years)

ID# _____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for you …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired	0	1	2	3	4
2. I feel physically weak (not strong)	0	1	2	3	4
3. I feel too tired to do things that I like to do	0	1	2	3	4
4. I feel too tired to spend time with my friends	0	1	2	3	4
5. I have trouble finishing things	0	1	2	3	4
6. I have trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I sleep a lot	0	1	2	3	4
2. It is hard for me to sleep through the night	0	1	2	3	4
3. I feel tired when I wake up in the morning	0	1	2	3	4
4. I rest a lot	0	1	2	3	4
5. I take a lot of naps	0	1	2	3	4
6. I spend a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4
6. I have trouble remembering more than one thing at a time	0	1	2	3	4

16.6.16 Family Impact Module v 2.0

ID#_____

Date:_____

PedsQL™

Family Impact Module

Version 2.0

PARENT REPORT

DIRECTIONS

Families of children sometimes have special concerns or difficulties because of the child's health. On the following page is a list of things that might be a problem for **you**. Please tell us **how much of a problem** each one has been for **you** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with…*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired during the day	0	1	2	3	4
2. I feel tired when I wake up in the morning	0	1	2	3	4
3. I feel too tired to do the things I like to do	0	1	2	3	4
4. I get headaches	0	1	2	3	4
5. I feel physically weak	0	1	2	3	4
6. I feel sick to my stomach	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel anxious	0	1	2	3	4
2. I feel sad	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I feel frustrated	0	1	2	3	4
5. I feel helpless or hopeless	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel isolated from others	0	1	2	3	4
2. I have trouble getting support from others	0	1	2	3	4
3. It is hard to find time for social activities	0	1	2	3	4
4. I do not have enough energy for social activities	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4

COMMUNICATION *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel that others do not understand my family's situation	0	1	2	3	4
2. It is hard for me to talk about my child's health with others	0	1	2	3	4
3. It is hard for me to tell doctors and nurses how I feel	0	1	2	3	4

PedsQL 3

*In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with…*

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I worry about whether or not my child's medical treatments are working	0	1	2	3	4
2. I worry about the side effects of my child's medications/medical treatments	0	1	2	3	4
3. I worry about how others will react to my child's condition	0	1	2	3	4
4. I worry about how my child's illness is affecting other family members	0	1	2	3	4
5. I worry about my child's future	0	1	2	3	4

DIRECTIONS

Below is a list of things that might be a problem for **your family**. Please tell us **how much of a problem** each one has been for **your family** during the **past ONE month.**

*In the past **ONE month**, as a result of your child's health, how much of a problem has **your family** had with…*

DAILY ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Family activities taking more time and effort	0	1	2	3	4
2. Difficulty finding time to finish household tasks	0	1	2	3	4
3. Feeling too tired to finish household tasks	0	1	2	3	4

FAMILY RELATIONSHIPS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Lack of communication between family members	0	1	2	3	4
2. Conflicts between family members	0	1	2	3	4
3. Difficulty making decisions together as a family	0	1	2	3	4
4. Difficulty solving family problems together	0	1	2	3	4
5. Stress or tension between family members	0	1	2	3	4

16.7 Caregiver Impression of Change (CIC)

The Caregiver Impression of Change (CIC) is designed to assess the caregiver's perception of the subject's xanthoma severity at the end of study drug treatment compared to his/her xanthoma severity prior to the start of treatment with study drug. The CIC will be completed by all caregivers at the Week 48, 60, 72, 84, and 96 visits. For subjects who enter into the long-term, optional follow-up treatment period, the CIC will be administered at Weeks 108, 144. Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) will also have the CIC administered at Week 148 (EOS). For subjects who enter into the long-term, optional follow-up treatment period-2, the CIC will be administered at Weeks 156, 168, 180, 192, 204, 216 (EOT/ET) and Week 220 (EOS).

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.

CIC

How would you rate the change in your child's xanthoma severity since the start of the study?

- ☐ Much better (1)
- ☐ Better (2)
- ☐ A little better (3)
- ☐ No change (4)
- ☐ A little worse (5)
- ☐ Worse (6)
- ☐ Much worse (7)

16.8 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Adverse events should be graded by severity based using CTCAE Version 4.0 (Published: May 28, 2009 [v4.03: June 14, 2010]).

16.9 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	14 Apr 2014	
Amendment 1	29 Jan 2015	Global
Amendment 2	12 Feb 2015	Global
Amendment 3 *Note: no summary of changes included for Protocol Amendment 3 as this protocol version was never operationalized.*	27 Apr 2016	Global
Amendment 4	27 Apr 2016	Global
Amendment 5	13 Nov 2017	Global
Amendment 6	25 Jun 2018	Global
Amendment 6.1	08 Feb 2019	Global

16.9.1 Protocol Amendment 6.1 Summary of Changes

Protocol Number: LUM001-305

Protocol Title: A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Amendment: **6.1**

Date: **08 February 2019**

The LUM001-305 protocol is being amended to reflect the change of sponsorship from Lumena Pharmaceuticals LLC (Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc) to Mirum Pharmaceuticals, Inc.

The following changes have been made to the Protocol Amendment 6 (25 Jun 2018). Note that correction of typos and grammatical errors are not captured in the below table.

New text indicated in bold; deleted text indicated in strikethrough.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Section(s) Affected by Change	**Description of Change**	**Rationale**
Cover page, Sponsor; Title Page, Sponsor; Sponsor Signature Page, Sponsor; Protocol Signature page, Sponsor	Replaced Shire's address with the new sponsor's address.	To provide new Sponsor's (Mirum) address
Title Page, Medical Lead and Premier Medical Monitor; Protocol Signature page, Sponsor (Mirum) Approval	Updated the Medical Lead and add Premier medical monitor information.	To provide updated and correct information.
Product Quality Complaints	Replaced Shire's contact with the new sponsor's contact.	To provide new Sponsor's contact information.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Schedule D	Footnote added to eligibility assessment at Week 144	To clarify subjects that completed PA5 rolling over from PA5 to PA6 will be assessed for eligibility. Subjects who did not consent to PA5 and re-enter into PA6 will not have eligibility re-assessed
	Added drug dispensation at Week 144	To claritfy for subjects entering PA6
Schedule E	Added Drug Compliance to be done at Weeks 2 and 4	To ensure compliance is assessed

16.9.2 Protocol Amendment 6 Summary of Changes

Protocol Number: LUM001-305

Protocol Title: A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Amendment: **6**

Date: **25 Jun 2018**

The LUM001-305 protocol is being amended to allow continued participation in the long-term optional follow-up treatment period-2, beyond what was previously described in Protocol Amendment 5. Study treatment in the long-term optional follow-up treatment period-2 will continue until the first of the following occurs: (i) the subjects complete 72 weeks of additional treatment (after Week 144 [long-term, optional follow-up treatment period]), or (ii) the subjects are eligible to enter another LUM001 study.

The following changes have been made to the Protocol Amendment 6 (25 Jun 2018). Note that correction of typos and grammatical errors are not captured in the below table.

New text indicated in bold; deleted text indicated in strikethrough.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	**Amendment Date** **25 Jun 2018**	**Global/Country/Site Specific** **Global**
Section(s) Affected by Change	**Description of Change**	**Rationale**
Title Page, Medical Lead	Updated phone number for Shire Medical Lead.	To provide updated contact information.
Emergency Contact Information, Premier Medical Monitor	Updated the Premier medical monitor information.	To provide updated and correct information.
Section 1, Study Design; Section 5.1, Study Design; Section 5.5, Overall Study Duration and Follow-up	Updated study design text to reflect addition of new long-term optional follow-up treatment period-2 of 72 weeks. Stated that eligible subjects will remain on treatment until either of the following occur: (i) subjects complete 72 weeks of additional treatment (after Week 144 [long-term optional follow-up	To extend the treatment period to allow continued participation in the study.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	**Amendment Date** **25 Jun 2018**	**Global/Country/Site Specific** **Global**
	treatment period]), or (ii) the subjects are eligible to enter another LUM001 study.	
Section 7.1, Inclusion Criteria	Moved inclusion criteria from Section 7.2 in Protocol Amendment 5 to Section 7.1 in Protocol Amendment 6.	To correct misplacement of Protocol Amendment 5 inclusion criteria as these were erroneously included in Section 7.2 in prior protocol version.
Section 1, Inclusion Criteria; Section 7.1, Inclusion Criteria	Updated inclusion criteria for Protocol Amendment 5 to clarify that eligible subjects either completed Week 96 or received permission from the sponsor and ChiLDReN protocol chair, not the Premier medical monitor.	To clarify that permission for re-entry into the study should come from the ChiLDReN protocol chair, not the Premier medical monitor.
Section 1, Inclusion Criteria; Section 7.1, Inclusion Criteria	Added inclusion criteria for Protocol Amendment 6: 1. The subject has completed the protocol through either Week 144, or the ET visit, or has received permission from the sponsor and the ChiLDReN protocol chair to re-enter the study in the long-term optional follow-up period-2. 2. Females of child-bearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) at the time of entry into the long-term optional follow-up treatment period-2. 3. Males and females of child-bearing potential who are sexually active, or are not currently sexually active, but become sexually active during the study or for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study. 4. Informed consent and assent (per IRB/EC) as appropriate. 5. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site. 6. Caregivers (and age appropriate subjects) must be willing to follow the rules of eDiary completion.	To specify inclusion criteria for Protocol Amendment 6.
Section 1, Exclusion Criteria; Section 7.2, Exclusion Criteria	<u>Exclusion Criteria:</u> All exclusion criteria for the original LUM001-305 study apply upon re-entry into the long-term optional follow-up treatment period-2.	To specify exclusion criteria for Protocol Amendment 6.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	**Amendment Date** **25 Jun 2018**	**Global/Country/Site Specific** **Global**
Section 1, Study Drug Dosage and Administration; Section 5.5.1, Treatment	Updated text to indicate that dosing will occur up to 216 weeks of treatment.	To reflect the addition of the long-term optional treatment period-2.
Section 1, Study Drug Dosage and Administration; Section 5.5.1.5, Long-term Optional Follow-up Treatment Period-2; Section 8.1.11, Long-term Optional Follow-up Treatment Period-2	Added text describing enrollment of subjects into the long-term optional follow-up treatment period-2. Added new sections 5.5.1.5 and 8.1.11, Long-term Optional Follow-up Treatment Period-2. Added text stating that subjects who choose to participate in the long-term optional follow-up treatment period-2 will be maintained at the same Week 144 dose level and that subjects who choose not to participate will be contacted by the study site 30 days after the last dose of study drug.	To reflect the addition of the long-term optional treatment period-2.
Section 1, Study Visit Schedule and Procedures; Section 5.5, Overall Study Duration and Follow-up	Updated text under schematic describing study procedures for Week 96 – Week 148 to indicate that subjects with dose interruptions >7 days between Week 96 and Week 100 should use this schedule to dose escalate.	To clarify for study sites that subjects with dose interruptions >7 days between Week 96 and Week 100 should re-enter the study at PA5 RI-2 and dose escalate.
Section 1, Study Visit Schedule and Procedures; Section 5.5, Overall Study Duration and Follow-up; Section 8.1.11, Long-term Optional Follow-up Treatment Period-2; Section 8.1.12, End of Treatment or Early Termination Visit; Section 8.1.13, End of Study Visit	Updated descriptions of study design text to reflect the addition of the long-term optional follow-up treatment period-2, including the addition of 2 new sections: 8.1.12, End of Treatment or Early Termination Visit; and Section 8.1.13, End of Study Visit. Added new text describing the study activities that will occur during the end of treatment (EOT)/early termination (ET), and end of study (EOS) visits. Added new study schematic showing study activities for subjects who roll over into the long-term, optional follow-up treatment period-2.	To reflect the addition of the long-term optional treatment period-2.
Section 1, Drug Level Evaluations	Plasma levels of LUM001 will be evaluated at Baseline and Weeks 2, 4, 8, 12, 24, 36, 48, 96, ~~144~~ **216** (EOT/ET) and ~~148~~ 220 (EOS).	To update the timing of PK sample collections, per the addition of the long-term optional treatment period-2.
Section 1, Safety and Tolerability Evaluations	Added text to indicate that SAEs would also be evaluated.	To clarify the scope of the safety analysis.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	**Amendment Date** **25 Jun 2018**	**Global/Country/Site Specific** **Global**
Section 1, Efficacy Evaluations; Section 12.2.4.1, Efficacy Variables	Updated text to indicate that secondary and exploratory endpoints would be evaluated from baseline to Week 216 (EOT). Added text updating the electronic diary (ItchRO) requirements to reflect the addition of the long-term optional treatment period-2. Added text indicating that additional exploratory evaluations will be specified in the SAP and may include evaluations between Week 144 (EOT/ET) and Week 148 (EOS) and between Week 216 (EOT/ET) and Week 220 (EOS) for subjects who complete Protocol Amendment 5 and 6, respectively.	To update the scope of the efficacy analysis.
Section 8.1.8; Long-term Optional Follow-up Treatment Period	Added text indicating that dose of LUM001 may be increased during the dose escalation period up to 280 µg/kg/day. Added text indicating that PA5 Schedule D Week 104 telephone contact would occur 4 weeks after PA5 RI Week 4 Clinic Visit. Added text stating that subjects rolling over into the long-term optional treatment period-2 will complete the electronic diary for additional 2 weeks following the Week 144 visit.	To clarify the maximum dose level of LUM001. To clarify timing of Week 104 telephone contact. To clarify requirement of electronic diary for subjects rolling over into Protocol Amendment 6.
Section 8.1.9; Week 144	Updated section title and added text to reflect the potential roll-over of subjects from Protocol Amendment 5 to Amendment 6 and the electronic diary completion requirements for all subjects.	To reflect extended treatment period under Protocol Amendment 6 and to clarify the electronic diary completion requirements.
Section 5.5.2.2, Visit Schedule Following Dose Interruption for Stable Dosing and Safety Monitoring Periods	Updated text to indicate that total LUM001 exposure should not exceed 216 weeks.	To reflect the addition of the long-term optional treatment period-2.
Section 5.5.2.3, Visit Schedule Following Dose Interruption for Long-term, Optional Follow-up Treatment Periods	Updated text to indicate that subjects with dose-interruptions greater than 7 consecutive days should receive permission from the Sponsor and ChiLDReN protocol chair when following the re-entry dose escalation schedule. Clarified timing of dosing interruptions.	To clarify that permission should be obtained from both the Sponsor and ChiLDReN protocol chair. To specify timing of permitted dose interruptions.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	**Amendment Date** **25 Jun 2018**	**Global/Country/Site Specific** **Global**
Section 5.5.3, Follow-up	Added text indicating that for subjects who participate in the long-term optional follow-up treatment period-2, the follow-up safety phone call will be replaced by the Week 220 (EOS) clinic visit.	To reflect the addition of the long-term optional treatment period-2.
Section 5.6, Study Termination	Updated text to indicate that subjects who participate in the long-term, optional, follow-up treatment period-2, will be considered completed if they participate in the Week 216 (EOT) visit.	To reflect the addition of the long-term optional treatment period-2.
Section 6.1, Enrollment	Added text describing the assessment of eligibility and enrollment process for subjects rolling over into the long-term optional follow-up treatment period-2.	To reflect the addition of the long-term optional treatment period-2.
Section 8.2, Physical Examination, Weight and Height, Vital Signs; Section 8.4.1, Itch Reported Outcome (ItchRO™); Section 8.4.2, Clinician Scratch Scale; Section 8.4.3, Clinician Xanthoma Scale; Section 8.4.4, Pediatric Quality of Life Inventory (PedsQL); Section 8.4.5, Caregiver Impression of Change	Edited text to reflect additional time points for these assessments that will occur during the long-term optional follow-up treatment period-2. In section 8.4.1, ItchRO, added text: **In cases where an observer can no longer observe the subject (eg, no longer living with the subject), the ItchRO(Obs) will not need to be completed; however, ItchRO(Pt) will need to be completed by subjects aged ≥9 years of age.**	To reflect the addition of the long-term optional treatment period-2. To update the ItchRO requirement to reflect the fact that some subjects may be living away from home (eg, at college); therefore, the daily completion of the ItchRO(Obs) may no longer be feasible.
Section 12.2.4.3, Secondary, Exploratory and Other Efficacy Analyses	Removed text: Change from baseline in Xanthoma scale will be categorized as improved, stable or worsened~~ and will be compared between treatment groups using the chi-square test.~~ ~~P-values from the secondary and exploratory efficacy analyses will be interpreted as hypothesis generating and not definitive.~~	To correct erroneous text; the chi square test is not relevant for this extension study.
Section 16.1, Schedule of Procedures C	Added a footnote to ItchRO assessment at Week 96 and at follow-up visit to indicate that the electronic diary should be completed for 2 weeks following the Week 96 visit.	To correct an oversight in the prior protocol amendment.
Section 16.1, Schedule of Procedures D	Added a new row for informed consent/eligibility assessment for Protocol Amendment 6 with the following footnote: **1. Subjects can consent to roll over into the long-term optional follow-up treatment period-2, per Schedule F.**	To reflect the addition of the long-term optional treatment period-2.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	**Amendment Date** **25 Jun 2018**	**Global/Country/Site Specific** **Global**
Section 16.1, Schedule of Procedures D	Added a footnote to the EOS visit: **9. Subjects who elect not to participate in the long-term, optional follow-up treatment period-2 (Protocol Amendment 6) should return to the study site 30 days after the last dose of study drug and complete all evaluations at this visit.**	To reflect the addition of the long-term optional treatment period-2.
Section 16.1, Schedule of Procedures E	Updated table title to clarify that subjects who either previously completed up to Week 96, or has received permission from the sponsor and the ChiLDReN protocol chair (not the Premier medical monitor) may re-enter the study using Scheduled E. Added a footnote to the PA5 RI -2 visit: **h. Subjects with dose interruptions prior to Week 96 or who early terminated may re-enter the study under Protocol Amendment 6. These subjects will initiate dose escalation at visit PA5 RI -2.**	To reflect the addition of the long-term optional treatment period-2. To clarify for study sites that subjects with dose interruptions >7 days prior to Week 96 or who early terminated should re-enter the study at PA5 RI -2 and dose escalate.
Section 16.1, Schedule of Procedures F	Added Schedule of Procedures F - Long-term, Optional Follow-up Treatment Period-2: Week 144 – Study Completion/Termination, applicable as follows: • If another study becomes available for subjects prior to completion of Protocol Amendment 6, the subject will complete EOT assessments as outlined for Week 216. • Subjects who complete 72 weeks of additional treatment and who are not eligible for another study will complete EOS assessments as outlined for Week 220.	To reflect the addition of the long-term optional treatment period-2.
Section 16.7; Caregiver Impression of Change (C)	Edited text to reflect additional time points for CIC assessments that will occur during the long-term optional follow-up treatment period-2.	To reflect the addition of the long-term optional treatment period-2.
Section 16.9, Protocol History; 16.9.1, Protocol Amendment 5 Summary of Changes	Updated protocol history to reflect sections to reflect Protocol Amendments 5 and 6. Moved Protocol Amendment 5 Summary of Changes from beginning of protocol to Section 16.9.1.	To reflect Protocol Amendments 5 and 6.

16.9.3 Protocol Amendment 5 Summary of Changes

Protocol Number: LUM001-305

Protocol Title: A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Amendment: **5**

Date: **13 Nov 2017***

*NIDDK DSMB Approval Date: 13 Nov 2017

The LUM001-305 protocol is being amended to allow continued participation in the long-term optional follow-up treatment period, beyond what was previously described in Protocol Amendment 4. Study treatment in the long-term optional follow-up treatment period will continue until the first of the following occurs: (i) the subjects complete 48 weeks of additional treatment (after Week 96 [safety monitoring period]), or (ii) the subjects are eligible to enter another LUM001 study.

The following changes have been made to the Protocol Amendment 5 (13 Nov 2017). Note that correction of typos and grammatical errors are not captured in the below table.

New text indicated in bold; deleted text indicated in strikethrough.

Section	Description of Change
Title Page, Medical Lead; Protocol Signature page, Sponsor (Shire) Approval	**Changed from:** **Medical Lead:** ~~Beatriz Caballero, MD~~ Shire~~ Human Genetic Therapies,Inc.~~ ~~Zahlerweg 10~~ ~~6300 Zug~~ ~~Switzerland~~ ~~Phone: +41(0) 41 288 42 30~~ ~~Email: bcaballero@shire.com~~ **To:** **Medical Lead:** **Nirav Desai, MD** Shire 300 Shire Way Lexington, MA 02451 **Phone: (781) 869-7756** **Email: nirav.desai@shire.com**
	Inserted new page containing emergency contact information for reporting of serious adverse events (SAEs) to be aligned with Shire protocol template.
Product Quality Complaints	Inserted new page containing product quality complaint information for reporting of investigational product quality complaints to be aligned with Shire protocol template.
Section 1, Objectives; Section 3, Study Objectives	Added new exploratory objective to evaluate the long-term effect of LUM001 on weight in pediatric subjects with ALGS.
Section 1, Study Design; Section 5.1, Study Design; Section 5.5, Overall Study Duration and Follow-up	Updated study design text to reflect addition of new long-term optional follow-up treatment period of 48 weeks. Stated that eligible subjects will remain on treatment until either of the following occur: (i) subjects complete 48 weeks of additional treatment (after Week 96 [safety monitoring period]), or (ii) the subjects are eligible to enter another LUM001 study.
Section 1, Inclusion Criteria; Section 7.2, Inclusion Criteria	**Inclusion Criteria:** **1. The subject has completed the protocol either through Week 96, or the ET visit, or has received permission from the sponsor and the Premier Medical monitor to re-enter the study in the long-term, optional follow-up treatment period.** **2. Female subjects of child-bearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) at the time of entry into the long-term optional follow-up treatment period.** **3. Male and female subjects of child-bearing potential who are sexually active, or are not currently sexually active, but become sexually active during the study or for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study.** **4. Informed consent and assent (per IRB/EC) as appropriate.** **5. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site.** **6. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study.** **Exclusion Criteria:**

Section	Description of Change
	1. **All exclusion criteria for the original LUM001-305 study apply upon re-entry into the long-term, optional follow-up treatment period.**
Section 1, Treatment Groups	Updated study design text to reflect addition of new long-term optional follow-up treatment period of 48 weeks.
Section 1, Study Drug Dosage and Administration; Section 5.5.1, Treatment; Section 8.2, Physical Examination, Weight and Height, Vital Signs; Section 10.1, Study Drug Administration	Updated text describing weight-based dosing adjustments to indicate that each subsequent 10% increase in weight will be considered the new baseline for determination of future dose adjustments Updated text to indicate that dosing will occur up to 144 weeks of treatment.
Section 1, Study Drug Dosage and Administration; Section 5.5.1.5, Long-term Optional Follow-up Treatment Period-2 Section 8.1.11, Long-term Optional Follow-up Treatment Period-2	Added text describing enrollment of subjects into the long-term optional follow-up treatment period-2. Added new sections 5.5.1.5 and 8.1.11, Long-term Optional Follow-up Treatment Period-2 describing study activities that will occur during this treatment period. Added text stating that subjects who choose to participate in the long-term optional follow-up treatment period-2 will be maintained at the same Week 144 dose level and that subjects who choose not to participate should complete the in-clinic Week 148 visit that will occur 30 days after the last dose of study drug.
Section 1, Study Visit Schedule and Procedures; Section 8.1.8, Long-term Optional Follow-up Treatment Period; Section 8.1.9, Week 144; Section 8.1.10, Week 148; Section 8.1.12, End of Treatment (EOT) or Early Termination (ET) visit; Section 8.1.13., End of Study Visit	Updated descriptions of study design text to reflect the addition of the long-term optional follow-up treatment period-2, including updates to study activities during the long-term optional treatment period, Week 144/ET visit, Week 148 visit (EOS). Added new text describing the study activities that will occur during the long-term optional follow-up treatment period, the end of treatment (EOT)/early termination (ET), and end of study (EOS) visits. Added new study schematics showing study activities for subjects who roll over into the long-term, optional follow-up treatment period-2. Added new sections 8.19, End of Treatment or Early Termination Visit and 8.1.10, End of Study Visit.
Section 1, Drug Level Evaluations	Plasma levels of LUM001 will be evaluated at Baseline and Weeks **2, 4, 8,** 12, 24, 36, 48, **96, 144 (EOT/ET) and 148 (EOS).**
Section 1, Efficacy Evaluations; Section 12.2.4.1, Efficacy Variables	The primary evaluation will be the mean change from **baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305** ~~baseline~~ to Week 48 in: • Fasting serum bile acid level. Secondary evaluations will be the mean change from **baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 through** ~~baseline to Weeks **12,** 48, 96 and~~ **Week 144/ET** in: • Biochemical markers of cholestasis and liver disease (**eg,** alanine aminotransferase [ALT], alkaline phosphate [ALP], gamma-glutamyltransferase [GGT] and bilirubin [total and direct]). • Pruritus as measured by the ItchRO instruments (ItchRO(Obs)™, caregiver instrument/ItchRO(Pt)™ patient instrument).

Section	Description of Change
	○ During the first 12 weeks of the study, the electronic diary (ItchRO) will be completed twice daily (AM & PM). During the stable dosing period (Weeks 13-48), twice daily completion of the electronic diary (ItchRO) for 4 consecutive weeks will be required following the Week 24 and Week 44 clinic visits. For subjects who continue in the safety monitoring period, twice daily completion of the ~~electronic diary (~~ItchRO~~)~~ **will be required** for 2 consecutive weeks ~~will be required~~ following the Week 60, 72, and 84 clinic visits. **For subjects who continue in the long-term optional follow-up treatment period, twice daily completion of the ItchRO will be required for 2 consecutive weeks following the Week 96, 108, 120, and 132 clinic visits and for 4 weeks following the 144/ET clinic visit.** • Xanthomas as measured by clinician xanthoma scale. • **Clinician scratch scale** • **Fasting serum bile acid levels** **The exploratory evaluation will be the mean change in weight z-score from Baseline (Day 0) of LUM001-301 and baseline (Day 0) of LUM001-305 through Week 144/ET.**
Section 1, Statistical Considerations; Section 12.2.6.1, Adverse Events	Updated safety analysis text to indicate that AEs will be summarized overall and by treatment group assigned in the core study (LUM001-301).
Section 4.4.2, Previous Clinical Experience	Added text describing safety and efficacy results for the completed Phase 2 randomized, double-blind, placebo-controlled study has been completed in pediatric subjects from 12 months to 18 years with ALGS (LUM001-302 – IMAGO).
Section 4.5, Rationale for Dose and Schedule of Administration	Added reference to completed Phase 2 study LUM001-301.
Section 5.5.2.3 Visit Schedule Following Dose Interruption for Long-term Optional Follow-up Treatment Period	Added new section 5.5.2.3, Visit Schedule Following Dose Interruption for Long-term, Optional Follow-up Treatment Period Added text and study schematic describing study procedures to be followed for subject with LUM001 dosing interruptions >7 consecutive days prior to entry into Protocol Amendment 5. Added "Dosing Interruptions: Reintegration to Study Visit Schedule during Protocol Amendment 5" table to show study visit assignments for subjects with LUM001 dosing interruptions >7 consecutive days.
Section 5.5.3, Follow-up	Added text indicating that the 30-day safety phone call will apply for subjects who participate in all version of the protocol up through Protocol Amendment 4. Added text indicating that for subjects who participate in the long-term optional follow-up treatment period, this phone call will be replaced by the Week 148 (EOS) clinic visit.
Section 5.6, Study Termination	Updated text to indicate that a subject will be considered to have completed the study based on the version of the protocol they participated under. For subjects who participate in the long-term, optional, follow-up treatment period, they will be considered completed if they participate in the Week 144 (EOT) visit.
Section 6.1, Enrollment	Added text describing the assessment of eligibility and enrollment process for subjects rolling over into the long-term optional follow-up treatment period.

Section	Description of Change
Section 8.2, Physical Examination, Weight and Height, Vital Signs; Section 8.4.1, Itch Reported Outcome (ItchRO™); Section8.4.2, Clinician Scratch Scale; Section 8.4.3, Clinician Xanthoma Scale; Section 8.4.4, Pediatric Quality of Life Inventory (PedsQL); Section 8.4.5, Caregiver Impression of Change	Edited text to reflect additional time points for these assessments that will occur during the long-term optional follow-up treatment period.
Section 10.3, Concomitant Medications	Added text indicating that concomitant medications should not be collected prior to informed consent or during gap periods when the subject is not participating in the study.
Section 10.5.1, General Monitoring Rules	If an individual subject exhibits a CTCAE Grade 3 treatment emergent ~~toxicity~~ **laboratory abnormality**, with the exception of the specific rules outlined below (Section 10.5) dosing ~~will~~ **can** be suspended~~. Continued dosing with study drug may be considered~~ **or continued as per the investigator's judgment and** following discussion with the **ChiLDReN protocol chair** and the ~~Sponsor Medical Monitor. The Investigator and Sponsor Medical Monitor~~ **sponsor medical monitor. If suspended, the investigator, the ChiLDReN protocol chair, and sponsor medical monitor** will evaluate the subject's safety data and make a decision to either restart dosing at the same level, restart dosing at a lower dose level, or discontinue dosing.
Section 10.5.2, Safety Monitoring Rules	**Of note: the INR retest should be conducted by the central laboratory, but may also be conducted at a local laboratory on an as needed basis.** **Subjects who do not meet the stopping rules based on retest may continue dosing and the Investigator, the ChiLDReN protocol chair**, and the sponsor medical monitor (or appropriately qualified designee) **should confer as to whether additional close monitoring of the subject is appropriate.** **The investigator should also assess the need to capture an AE, its severity according to the CTEAE directives and potential causality. These assessments should also include an evaluation of whether criteria for an SAE are fulfilled (see Section 11.2.3).**
Section 10.5.2.2, Stopping Rules for Liver Chemistry Elevations; Section 10.5.2.3, Safety Monitoring for Triglycerides; Section 10.5.2.4, Safety Monitoring for Fat Soluble Vitamins Section 10.5.2.5, Monitoring/Stopping Rules for Coagulation Panel Results	Added language indicating that all dose adjustments or drug interruptions would be conducted in coordination with the ChiLDReN protocol chair, in addition to the investigator and sponsor medical monitor.

Section	Description of Change
Section 11.3, Monitoring and Recording of Adverse Events	**In addition, AEs that occur while the subject is not enrolled in the study during a gap period (ie, prior to enrollment in Protocol Amendment 5) will be collected as medical history unless the AE started within 30 days of last dose.**
Section 11.3.1, Serious Adverse Events	Updated to indicate that collection of SAEs will begin after the subject signs the informed consent/assent form and stop 30 days after the last dose of study drug.
Section 11.3.2, Non-serious Adverse Events	Updated to indicate that collection of non-serious AEs will begin after the subject signs the informed consent/assent form and stop 30 days after the last dose of study drug.
Section 11.3.3.2, Severity	**Please also refer to Section 10.5.2 regarding specific safety monitoring for liver chemistry tests given that subjects with ALGS may have abnormal liver enzyme levels at baseline.**
Section11.4.1, Pregnancy Reporting	If a subject becomes pregnant or a pregnancy is suspected **in either a subject or in the partner of a male study participant** during the study…
Section 11.4.3; Abnormalities of Laboratory Tests	Added language indicating that all clinically significant abnormalities will be monitored by the investigator, sponsor medical monitor, and ChiLDReN protocol chair.
Section 12.2.3.1, Subject Disposition	The number and percentage of subjects enrolled, completed, and withdrawn, along with reasons for withdrawal, will be tabulated overall, and by treatment ~~group when entering the study as well as after the dose optimization period~~. **assigned at LUM001-305 study entry.** **In addition, for subjects who had dose gaps or re-initiated to all protocol amendments, the number of days of the off-drug period will be summarized.**
Section 12.2.6.2, Laboratory Tests	Changes within a treatment group for selected safety measures will be assessed at Weeks 8, 12, 24, 36 and ~~at the final study evaluation visit (Week 48) using methods to be specified in the SAP,~~ **48, 96, and at additional time points during the long-term optional follow-up treatment period.**
Section 16.1, Schedule of Procedures D-E	Added Schedule of Procedures D - Long-term, Optional Follow-up Treatment Period: Week 96 – Study Completion/Termination for those subjects with ≤7 days from the last dose of LUM001 applicable as follows: • If another study becomes available for subjects prior to completion of Protocol Amendment 5, the subject will complete EOT assessments as outlined for Week 144. • Subjects who complete 48 weeks of additional treatment and who are not eligible for another study will complete EOS assessments as outlined for Week 148. Added Schedule of Procedures E - Long-term, Optional Treatment Period: Subject Re-entry under Protocol Amendment 5, applicable as follows: • Subject either previously completed the follow-up period as defined under Protocol Amendment 4, or has received permission from the sponsor and the Premier medical monitor to re-enter the study under Protocol Amendment 5 and has subsequently experienced an interruption in LUM001 dosing >7days. • Subject is considered eligible for study re-entry under Protocol Amendment 5.

16.9.4 Protocol Amendment 4 Summary of Changes

Protocol Number: LUM001-305

Protocol Title: A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Amendment: **4***

Date: 27 April 2016*

*NIDDK DSMB Approval Date: 24 June 2016

Note: Original NIDDK DSMB approval for Amendment 3 was obtained on 21 March 2016. However, following this approval, additional edits were made to correct previously unidentified inconsistencies within the protocol. Shire then approved the corrected version of Amendment 3 on 27 April 2016. Because edits were made after the NIDDK DSMB approved Amendment 3, the revised protocol (version date 27 April 2016) was up-versioned to Amendment 4 (version date 27 April 2016). Amendment 4 was approved by the NIDDK DSMB on 24 June2016 and by Shire on 28 June 2016. Amendment 3 was never operationalized.

Protocol Amendment 2 (12 February 2015) was amended to extend the duration of the study to 100 weeks. Additional edits, as captured in the below table, were made to Protocol Amendment 2 and Amendment 3 to improve the clarity of the protocol and/or correct minor inconsistencies. Note that correction of typos and grammatical errors are not captured in the below table.

New text indicated in bold; deleted text indicated in strikethrough.

Section	Description of Change
Title page; Medical Lead	**Changed from:** **Sponsor Contact:** Ciara Kennedy, PhD Lumena Pharmaceuticals, Inc. Phone: +1-858-337-7922 Email: ckennedy@lumenapharma.com **To:** **Medical Lead:** **Beatriz Caballero, MD** **Shire, Inc.** **Zahlerweg 10** **6300 Zug** **Switzerland** **Phone: +41(0) 41 288 42 30** **Email: bcaballero@shire.com**
Cover page; Sponsor Title page; Sponsor Sponsor Signature page, Sponsor	**Changed from:** Lumena Pharmaceuticals LLC 12531 High Bluff Drive, Suite 110 San Diego, CA 92130 USA **To:** Lumena Pharmaceuticals LLC** **300 Shire Way** **Lexington, MA 02421** USA ****Lumena Pharmaceuticals, LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc**
Study Synopsis; Study Design Section 5.1; Study Design Section 8.1.4; Stable Dosing Period	The study is divided into ~~3~~ **4**parts: a dose escalation period, a dose optimization period, ~~and~~ a stable dosing period**, and a safety monitoring period**. Planned participation for each subject enrolled in the study is ~~48~~ **approximately 100** weeks **(inclusive of the safety follow-up contact approximately 30 days after the last dose of LUM001)**. <u>Stable Dosing ~~Period~~ **and Safety Monitoring Periods**</u> Following completion of the 8-week dose optimization period, all subjects will enter the stable dosing period lasting 36 weeks. ~~During the remainder of the study~~ **followed by a safety monitoring period lasting up to 48 weeks. During the stable dosing and safety monitoring periods**, subjects will be dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose. However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the **ChiLDReN protocol chair and** Sponsor Medical Monitor, may lower the dose to a previously tolerated dose for the rest of the study.

<table>
<tr><td>Study Synopsis; Exclusion Criteria
Section 7.2; Exclusion Criteria</td><td>2. Any conditions or abnormalities (including laboratory abnormalities) which, in the opinion of the Investigator or Medical Monitor or ChiLDReN Protocol Chair, may compromise the safety of the subject, or interfere with the subject participating in or completing the study.</td></tr>
<tr><td>Study Synopsis; Study Drug Dosage and Administration
Section 5.5.1; Treatment
Section 5.5.1.1; Dose Escalation Period
Section 5.5.1.3; Stable Dosing and Safety Monitoring Periods
Section 5.5.2; Dosing Interruptions (new section)
Section 10.6; Adjustment of Dose</td><td>Dosing will occur over a ~~48~~ 96-week treatment period.

If a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the ChiLDReN protocol chair and Sponsor Medical Monitor, may lower the dose to a previously tolerated dose for the rest of the study.

Stable Dosing ~~Period~~ and Safety Monitoring Periods
At the end of the Dose Optimization Period, subjects will continue dosing to complete ~~48~~ the stable dosing and safety monitoring periods for up to 96 weeks of cumulative LUM001 exposure in this study.

Subjects who completed the 48-week study prior to the implementation of Protocol Amendment #4 may be re-contacted and re-consented for participation in the safety monitoring period of the study.

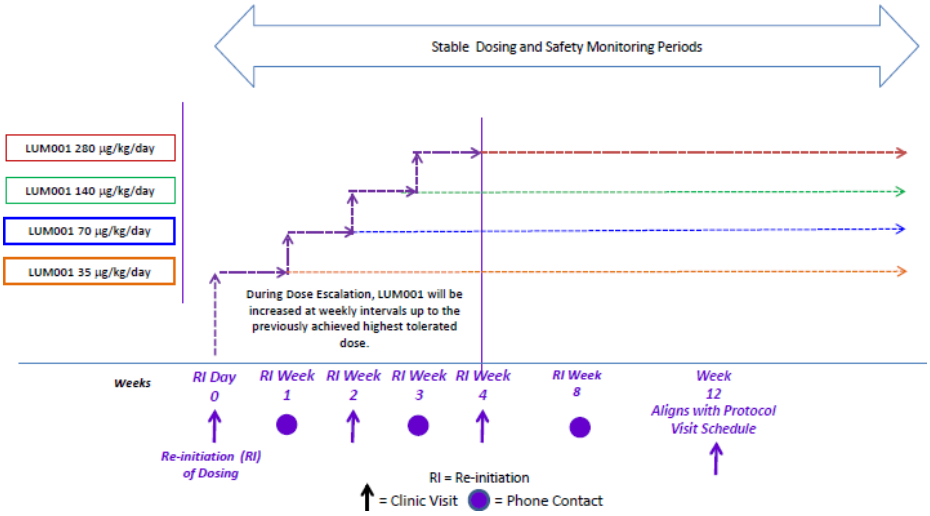
Dosing Interruptions

Dose Escalation Following Dose Interruption

Subjects with interruptions in LUM001 dosing of more than 7 consecutive days during the stable dosing or safety monitoring periods will require dose escalation upon re-initiation of the study drug. The dose of LUM001 will be increased at weekly intervals up to the subject's previously achieved highest tolerated dose. Study drug for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to the protocol's specified dose-escalation regimen (Table 5).

Table 5: Dose Escalation Regimen for Re-initiation of LUM001 when Dosing Interruption is Greater than 7 Consecutive Days
<table>
<tr><th></th><th colspan="4">Study Week</th></tr>
<tr><th></th><th>Week 1 (µg/kg/day)</th><th>Week 2 (µg/kg/day)</th><th>Week 3 (µg/kg/day)</th><th>Week 4 (µg/kg/day)</th></tr>
<tr><td>LUM001 Dose</td><td>35</td><td>70 [1]</td><td>140 [1]</td><td>280 [1]</td></tr>
<tr><td colspan="5">[1] Weekly dose escalations will end once the highest tolerated dose achieved prior to the subject's LUM001 dosing interruption is reached.</td></tr>
</table>
Visit Schedule Following Dose Interruption
Upon re-initiation of study drug, subjects who undergo a dosing interruption of greater than 7 consecutive days will follow the same visit schedule and procedures that are specified for the Baseline Day 0 Visit (Section 8.1.1) and during Dose Escalation Treatment Period (Section 8.1.2). Completion of the ItchRO electronic diary, however, will not be required during this time. The visit schedule upon re-initiation of LUM001 dosing is shown in Figure 4.</td></tr>
</table>

Figure 4: Visit Schedule for Re-initiation of LUM001 Dosing When Dosing Interruption is Greater than 7 Consecutive Days



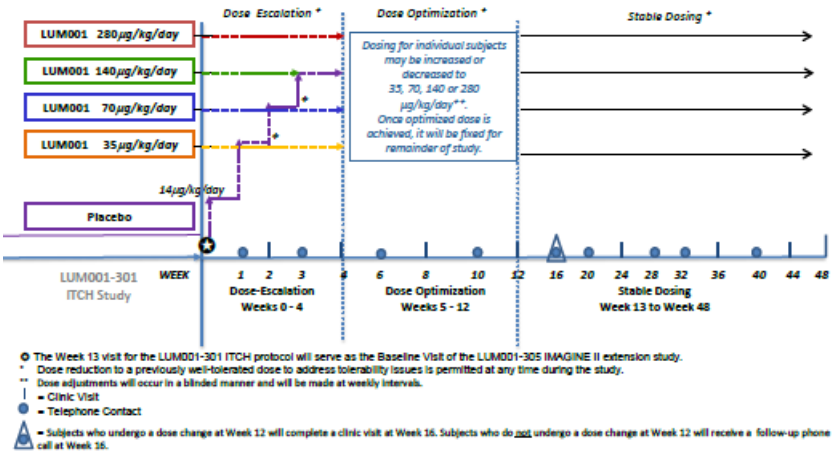
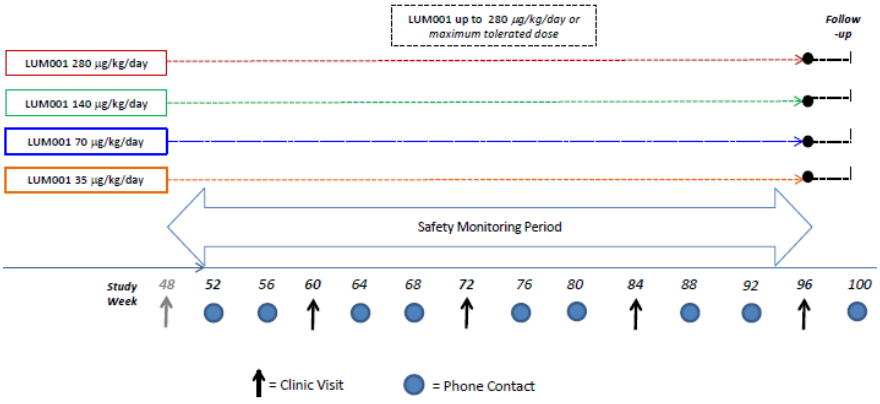
Subjects with dosing interruptions of greater than 7 consecutive days will require reintegration in the study to ensure that 1) their resumed visit schedule aligns with the protocol, and 2) their total LUM001 exposure during the study does not exceed 96 weeks.

If the decision to interrupt dosing occurred at the time of a Clinic Visit, the first visit upon dose re-initiation ("RI Day 0" in Figure 4) should be assigned to that same Clinic Visit. If the decision to interrupt dosing occurred between Clinic Visits, the first visit upon dose re-initiation ("RI Day 0") should be assigned to the next Clinic Visit. Table 6 provides the assignment of the first study visit upon dose re-initiation based on when the dosing interruption occurred.

Table 6: Dosing Interruptions: Reintegration to Study Visit Schedule

Dosing Interruption	Assignment of First Dose Re-initiation Study Visit
Between Weeks 13 - 24	Week 24
Between Weeks 25 - 36	Week 36
Between Weeks 37 - 48	Week 48
Between Weeks 49 - 60	Week 60
Between Weeks 61 - 72	Week 72
Between Weeks 73 - 84	Week 84
After Week 84	To be managed on a case-by-case basis in consultation with the Medical Monitor and ChiLDReN Protocol Chair

Study Synopsis; Rationale for Dose and Schedule Selection Section 4.5; Rationale for Dose and Schedule of Administration	**The dose may also be down-titrated, at the investigator's discretion and in consultation with the ChiLDReN protocol chair and the Sponsor Medical Monitor, for subjects experiencing intolerance to a given dose.**

Study Synopsis; Study Visit Schedule and Procedures Section 5.5; Overall Study Duration and Follow-up Section 8.1.4; Stable Dosing Period Section 8.1.5; Safety Monitoring Period (Week 49 to Week 96) Section 8.1.6; Week 96/Study Termination (End of Study) Section 8.1.8; Early Termination	**Changed:** For an individual subject, the study participation period will consist of a 4-week dose escalation period, followed by 8-weeks of dose optimization ~~and~~ a 36-week stable dosing **period, and a 48-week safety monitoring period**. Planned participation for each subject enrolled in the extension study is ~~48~~ **a maximum of 100** weeks, **inclusive of the safety follow-up contact approximately 30 days after the last dose of LUM001**. Study activities will be conducted as described in the Schedule of Procedures (Section 16.1). Study Scheme (as described below): Day 0 – Week 48  **<u>Week 49 – Week 100:</u>**  <u>Stable Dosing Treatment Period (Week 13 to Week 48)</u>: **…** However, if a subject experiences intolerance due to gastrointestinal symptoms the investigator, in consultation with the **ChiLDReN protocol chair and** Sponsor Medical Monitor…

	With the exception of the Week 44, ~~A~~ additional study drug will be supplied at each clinic visit **during the stable dosing period.** **<u>Safety Monitoring Period (Week 49 to Week 96)</u>: During the safety monitoring period, subjects will return to the clinic every 3 months, at Weeks 60, 72, 84, and 96.** **Safety and clinical laboratory evaluations and a physical exam (including collection of vital signs, height, and weight measurements) will be completed at each clinic visit. The clinician scratch scale will also be completed at each clinic visit and study drug compliance will be assessed. The PedsQL, Caregiver Impression of Change (CIC), and the Clinician Xanthoma scale will also be administered at Weeks 60, 72, 84, and 96. Subjects/caregivers will receive follow-up phone calls at Weeks 52, 56, 64, 68, 76, 80, 88, 92, and 100. Concomitant medications and any adverse events will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.** **Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, and 84 clinic visits. Review of electronic diary data and assessment of compliance will occur during scheduled telephone contacts at Week 64, 76, and 88 and during the Week 96 clinic visit. Electronic diaries will be provided to subjects and caregivers at these visits and re-training on the use of the diary will occur, as appropriate.** **At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the safety monitoring period.** **With the exception of the Week 96 visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period.** **Week 96** / Study Termination (End of Study): At the Week ~~48~~ **96/**Study Termination Visit, a physical exam (including collection of vital signs, height and weight measurements)… Early Termination: Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week ~~48~~ **96**/Study Termination Visit. ~~Subjects will be encouraged to complete all study activities and visits.~~ Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week ~~48~~ **96**/ Study Termination visit (Section 16.1).

Study Synopsis; Efficacy Evaluations Section 12.2.4.1; Efficacy Variables	The primary evaluation ~~for the durability of the therapeutic effect~~ will be the **mean** change from Baseline (Day 0) to Week 48 in: Secondary evaluations ~~for the durability of the therapeutic effect~~ will be the **mean** change from Baseline (Day 0) to ~~Week~~ **Weeks** 48 and **96 and** the change from Week 12 to ~~Week~~ **Weeks** 48 **and 96** in: **For subjects who continue in the safety monitoring period, twice daily completion of the electronic diary (ItchRO) for 2 consecutive weeks will be required following the Week 60, 72, and 84 clinic visits.** **Secondary evaluations will be the mean change from Baseline to Week 96 and the change from Week 12 to Weeks 48 and 96 in serum bile acid.** Additional exploration of evaluations ~~of safety and durability of therapeutic effect,~~ will be specified in the statistical analysis plan.
Study Synopsis; Statistical Considerations Section 12; Statistical Considerations	~~Special attention will be paid to change from baseline for those on placebo at baseline and to durability of effect during the first 12 weeks for those on active study drug at baseline and to durability during the stable dosing period for all subjects at all dose levels.~~
Section 8.4.1; Safety Monitoring Period	**During the safety monitoring periods, daily completion of the diary will be required by subjects and caregivers only during the 2 consecutive weeks that follow the Week 60, Week 72, and Week 84 clinic visits. At these visits, subjects/caregivers will be provided with the electronic diary and re-trained on its use, as needed. Subjects/caregivers will be instructed to bring their electronic diary with them when they return for their next clinic visit. The electronic diary will be collected at Week 96.**
Section 8.4.2; Clinician Scratch Scale	This assessment will be completed at Baseline (Day 0) and at all clinic visits thereafter (Weeks 2, 4, 8, 12, 24, 36, **48, 60, 72, 84, and** ~~48~~**96**).
Section 8.4.3; Clinician Xanthoma Scale	This assessment will be completed at Baseline (Day 0) and at Weeks 24, 36, 48, **60, 72, 84, and 96**).
Section 8.4.4; Pediatric Quality of Life Inventory (PedsQL)	In addition to the core generic PedsQL module, the multidimensional fatigue and family impact questionnaires will also be administered at the Baseline (Day 0) and ~~Week~~ **Weeks** 24, 48, **60, 72, 84,** and **96** clinical visits using the age-appropriate module…
Section 8.4.5; Caregiver Impression of Change Section 16.7, Caregiver Impression of Change (CIC)	The CIC will be completed by all caregivers at the ~~Week~~ **Weeks** 48, **60, 72, 84,** and **96** visits.
Section 10.5.2; Safety Monitoring Rules	Stopping Rule Guidance: If any of the stopping criteria described below (refer to Section 10.5.1) are confirmed, the physician investigator in consultation with the **ChiLDReN protocol chair and the** Sponsor Medical Monitor or appropriately qualified designee**(s)**, will permanently discontinue…
Section 10.5.2.1; Safety Monitoring for Liver Chemistry Tests	Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the **ChiLDReN protocol chair and the** Sponsor Medical Monitor.
Section 10.6; Adjustment of Dose	This decision should be made in consultation with the **ChiLDReN protocol chair and** Sponsor Medical Monitor.

Section 11.3.1; Serious Adverse Events	In the interest of subject safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to study drug) should be reported to the Sponsor or designee within 24 hours of the study center's first knowledge of the event. The collection of SAEs will begin after the subject signs the informed consent form and stop at the end of the subject's follow-up period which is defined as Week ~~52~~ **100** or 30 days after the last dose of study drug for those subjects that terminate the prior to the Week ~~48~~ **96** visit.
Section 11.3.2; Non-Serious Adverse Events	The recording of non-serious AEs will begin after the subject signs the informed consent form and will stop at the end of the subject's follow-up period, which is defined as Week ~~52~~ **100**. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.
Section 16.1; Schedule of Procedures	**Added:** Removed " / Study termination" from title and the "follow-up" column from the Schedule of Procedure for the Stable Dosing Period (Week 16-Week 48). Added new Schedule of Procedures for the Safety Monitoring Period (Week 52 – Week 96/Study Termination.
Overall	Throughout the protocol, reference to evaluating durability of effect of LUM001 was removed to better reflect the correspondence of analyses to study objectives which characterize the evaluation of long-term LUM001 effects on efficacy, and which do not characterize these effects as "durability of effect."

16.9.5 Protocol Amendment 2 Summary of Changes

Protocol Number: LUM001-305

Protocol Title: A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Amendment: **2**

Date: February 12, 2015

The following changes have been made to Protocol Amendment 1:

- The date of the document has been changed throughout to February 12, 2015.
- The logo on the protocol's cover page was updated to reflect the Childhood Liver Disease Research Network's (ChiLDReN) current design.

The following table provides a summary list of changes to the protocol:

Section	Description of Change
Header	Date changed to February 12, 2015
Cover Page	Date changed to February 12, 2015
Sponsor Signature Page	Date changed to February 12, 2015
Title Page	Date changed to February 12, 2015
Protocol Signature Page	Date changed to February 12, 2015

16.9.6 Protocol Amendment 1 Summary of Changes

Protocol Number: LUM001-305

Protocol Title: A MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND DURABILITY OF THE THERAPEUTIC EFFECT OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTI), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Amendment: **1**

Date: January 29, 2015

The following changes have been made to the original protocol:

The number of subjects enrolled in the study has been increased from 24 to approximately 36 to reflect current number of subjects planned in the LUM001-301 protocol.

An inclusion criterion has been added indicating that eligible subjects must be able to adhere to local Ethics Committee or Institutional Review Board (IRB) blood volume limits for laboratory testing.

The statistical section has been revised to address the statistical management of data generated from siblings enrolled in the study and to clarify the interpretation of p-values from secondary and exploratory analyses.

Minor changes have been made to the text to improve the clarity of the protocol and/or correct minor inconsistencies.

The following table provides a summary list of changes to the protocol:

Section	Description of Change
Number of Subjects (Synopsis, Section 5.4), Statistical Considerations (Section 12)	Changed number of subjects from 24 to approximately 36 to reflect current number of subjects planned in the LUM001-301 protocol
Inclusion Criteria (Synopsis, Section 7.1)	Added inclusion criterion requiring the ability of eligible subjects to adhere to local Ethics Committee or Institutional Review Board (IRB) blood volume limits for laboratory testing
Itch Reported Outcome (Section 8.4.4)	Clarified that age at the screening visit will be used as the age for the determination of the appropriate use of the electronic diary for the duration of the study, regardless of subsequent birthdays during the study.

Section	Description of Change
Study Schedule (Section 8.1)	Clarified that samples for the determination of fat soluble vitamins are not collected at Weeks 2 and 4. Note: Blood samples for the determination of fat-soluble vitamins are to be collected at the following: Baseline, Week 8, Week 12, Week 24, Week 36 and at Week 48
PedsQL (Section 8.4.4)	Clarified that the age at the LUM001-301 baseline visit will be used as the age for the determination of the appropriate questionnaire to be used for the study. This same module will be used for the duration of the study regardless of subsequent birthdays throughout the study.
LUM001 (Section 9.1.1)	Tables 5 and 6 have been updated to reflect quantity of LUM001 per 1.0 mL and 0.5 mL oral solutions
Synopsis, Statistical Considerations (Section 12.2.2)	Language was added to address the statistical management of data generated from siblings enrolled in the study.
Statistical Considerations (Section 12.2.4.3)	Clarified that the p-values from the secondary and exploratory analyses will be interpreted as hypothesis generating and not definitive.
Section 16.2	Removed Serum βhCG from list of analytes. Urine pregnancy tests, as indicated, are performed during this protocol.
All Sections, as appropriate	Reference to a 'core LUM001 treatment protocol' was changed to the 'LUM001-301 protocol'. Only subjects who completed participation in protocol LUM001-301 are eligible for participation in this study (LUM001-305).
All Sections, as appropriate	Sponsor name was changed from Lumena Pharmaceuticals, Inc. to Lumena Pharmaceuticals LLC
All Sections	Minor changes have been made to the text to improve the clarity of the protocol and/or correct minor inconsistencies and typographical errors.