CLINICAL PROTOCOL

PROTOCOL NUMBER: LUM001-303

IMAGINE STUDY

A MULT**I**CENTRE 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**

Protocol Amendment 5.1: 08 February 2019

Protocol History

Original Protocol:	13 Sep 2013
Protocol Amendment 1:	05 Nov 2013
Protocol Amendment 2:	28 Feb 2014
Protocol Amendment 3:	17 Sep 2014
Protocol Amendment 4:	04 Nov 2015
Protocol Amendment 5:	16 May 2017

EudraCT No: 2013-003832-54

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

SPONSOR SIGNATURE PAGE

LUM001-303

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Developed in Collaboration with ChiLDREN

Sponsor:
Mirum Pharmaceuticals, Inc.
70 Willow Road, Suite 200
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USA

TITLE PAGE

Study Drug:	LUM001
Protocol Number:	LUM001-303
Amendment Number:	5.1
Date:	08 February 2019
EudraCT No:	2013-003832-54
Study Phase:	Phase 2
Protocol Title:	A Multicentre 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: medmonitorLUM303@premier-research.com
Medical Lead:	Thomas Jaecklin, MD, MSc 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 Harmonisation (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:** 10.2.2019
Thomas Jaecklin, MD, MSc SVP Clinical Development	

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)
- European Union (EU) Directives and national laws (where applicable)

Clinical Study Title:

A MULTICENTRE 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 PAEDIATRIC SUBJECTS WITH ALAGILLE SYNDROME

Protocol Number:	LUM001-303
Amendment Number:	5.1
Date:	08 February 2019
EudraCT No:	2013-003832-54
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 e-mail the Premier Research Serious Adverse Event Form within 24 hours to the Premier Research Pharmacovigilance Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover) and below.

Premier Research SAE Reporting:

US and Canadian sites: fax 215-972-8765, or e-mail GlobalPV-US@premier-research.com

EU/ROW sites: fax +421 2 6820 3713 or e-mail PVDS-ROW@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 (US and Canada) sites:

Central phone number: +1 512 686 1256 (US)

European and ROW sites:

Central phone number: +44 118 936 4096 (United Kingdom)

For non-emergencies, the Premier Research Medical Monitor may be contacted by e-mail: medmonitorLUM303@premier-research.com

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Investigators are required to report investigational product quality complaints to Mirum within 24 hours. This includes any instances wherein the quality or performance of a Mirum product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 11.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	medinfo@mirumpharma.com
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 AMENDMENT 5.1 SUMMARY OF CHANGES

Protocol Number: LUM001-303

Protocol Title: A MULTICENTRE 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: **5.1**

Date: 08 February 2019

The LUM001-303 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 5 (16 May 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
Cover page, Sponsor; Title Page, Sponsor; Sponsor Signature Page, Sponsor; Protocol Signature page, Sponsor	**Changed from:** 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 **To:** **Mirum Pharmaceuticals, Inc.** **70 Willow Road, Suite 200** **Menlo Park, California 94025** **USA**
Title Page, Medical Lead and Premier Medical Monitor; Protocol Signature page, Sponsor (Mirum) Approval	**Changed from:** **Medical Lead:** Thomas Jaecklin, MD, MSc Shire Zahlerweg 10 6300 Zug Switzerland Phone: +41(0) 79 850 77 18 Email: thomas.jaecklin@shire.com **To:** **Medical Lead:** **Thomas Jaecklin, MD, MSc** **Mirum Pharmaceuticals AG** **Innere Margarethenstrasse 5** **4051 Basel** **Switzerland** **Phone: +41(0) 79 850 77 18** **Email: tjaecklin@mirumpharma.com** **Changed from:** **Sponsor Medical Monitor:** Susanne Schmidt, MD **To:** **Medical Monitor:** **Cagil Ozen, MD**
Emergency Contact Information	Changed the Premier Medical Monitor from Susanne Schmidt to Cagil Ozen.

<table>
<tr><th>Section</th><th>Description of Change</th></tr>
<tr><td>Product Quality Complaints</td><td>
Changed from:
<table>
<tr><td>Origin of Product Quality Complaint</td><td>E-mail Address</td></tr>
<tr><td>North and South America</td><td>PQC@shire.com</td></tr>
<tr><td>European Union and Rest of World</td><td>PQCROW@shire.com</td></tr>
</table>
Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
1-800-828-2088

To:
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<tr><td>North and South America</td><td>medinfo@mirumpharma.com</td></tr>
<tr><td>European Union and Rest of World</td><td>medinfo@mirumpharma.com</td></tr>
</table>
Telephone numbers (provided for reference if needed):

Mirum, Menlo Park, CA (USA)
1-650-667-4085
</td></tr>
<tr><td>Schedule E</td><td>Added Drug Compliance at Week 4</td></tr>
<tr><td>Schedule F</td><td>Added ADE Eligibility Assessment at Week 12 starting at RP2</td></tr>
<tr><td>Schedule H</td><td>Added Global Therapeutic Questionnaire T EOT/EOS</td></tr>
<tr><td>Section 16</td><td>Added Caregiver Global Therapeutic Benefit Questionnaire</td></tr>
</table>

1 STUDY SYNOPSIS

Sponsor	Mirum Pharmaceuticals, Inc.
Protocol Number	LUM001-303
Protocol Title	A Multicentre 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 (up to and including Week 72) is to: • Evaluate the long-term safety and tolerability of LUM001 in pediatric subjects with ALGS. Secondary objectives of the study (up to and including Week 72) 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. Objectives of the long-term optional follow-up treatment period for subjects who are eligible for Protocol Amendment 5: • To offer eligible subjects in the LUM001-303 study continued study treatment until the first of the following occur: (i) the subjects are eligible to enter another LUM001 study, or (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication. • To explore twice a day (BID) dosing regimen and higher daily dosing of LUM001. • To obtain safety and efficacy data in subjects treated long term on LUM001. • To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma. • To assess palatability of the LUM001 formulation.
Study Design	This is a multicentre, double-blind study of LUM001 in children ≥12 months of age diagnosed with ALGS who have completed participation in the LUM001-302 study. <u>All subjects will receive active drug (LUM001) in this study</u>. The study is divided into 5 parts: a dose escalation period, a dose optimization period, a stable dosing period, an optional 52-week follow-up period, and a long-term optional follow-up treatment period for eligible subjects who choose to stay on treatment with LUM001. <u>Dose Escalation Period</u> All subjects entering the extension study will participate in a 4-week double-blind dose escalation period during which: • Subjects who were randomized to receive placebo during the LUM001-302 study will receive weekly dose increases of LUM001 up to a target dose of 140 µg/kg/day.

	• Subjects who were randomized to receive active drug during the LUM001-302 study will continue to receive the dose of LUM001 that they were taking at Week 13 of the LUM001-302 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. <u>Dose Optimization Period</u> 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 level will be increased or decreased in a double-blind manner. Increases in dose will be based on effect on efficacy (sBA and ItchRO[Obs] score) and safety assessments. Reductions in dose will be based on tolerability. At the investigator's discretion, the doses for 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 Period</u> Following completion of the 8-week dose optimization period, all subjects will enter the stable dosing period lasting 60 weeks. During the remainder of the study, 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 medical monitor, may lower the dose to a previously tolerated dose. <u>Optional Follow-up Treatment Period:</u> At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the optional 52-week, follow-up treatment period to receive study drug at the dose they were receiving at Week 72. • For subjects who are eligible to roll over into the follow-up treatment period, those with <7 days since the last dose of LUM001, will be maintained at the same dose level. • For subjects who are eligible to roll over into the follow-up treatment period having ≥7 days since the last dose of LUM001, will be dose escalated up to 280 µg/kg/day or the highest tolerated dose following a 4 week dose escalation beginning at 35 µg/kg/day. • For subjects who do not wish to enter the follow-up treatment period, or are not eligible to enter the follow-up treatment period, a safety follow-up phone call will be made by the study site 30 days after the last dose of study drug. <u>Long-term optional Follow Up Treatment Period (Protocol Amendment 5):</u> The long-term optional follow up treatment period is for eligible subjects who choose to stay on treatment with LUM001. During this long-term optional follow-up treatment period, subjects may have their dose of LUM001 increased to a maximum of 560 µg/kg/day (280 µg/kg BID), based on efficacy (sBA and ItchRO score) and safety assessments. Subjects' participation in the long-term optional follow-up treatment period will continue until the first

	of the following occur: i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
Number of Subjects	Approximately 18 subjects who enrolled in the LUM001-302 study and who meet the study's inclusion and exclusion criteria will be enrolled in the study.
Study Population	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 study LUM001-302. 4. Females of childbearing potential must have a negative urine pregnancy test [β human chorionic gonadotropin (β-hCG)] at the Baseline Visit. 5. Males and females of childbearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study. 6. Subjects are expected to have consistent caregiver(s) for the duration of the study. 7. Caregivers (and age appropriate subjects) must be able to read and understand English. 8. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site. 9. 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. 10. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the ItchRO electronic diary software at the outset of the study. Exclusion Criteria Subjects will be excluded from the study if they meet any of the following criteria: 1. Experienced an adverse event or serious adverse event (SAE) related to the study drug during the LUM001-302 study that led to the discontinuation of the subject from the LUM001-302 study. 2. Any conditions or abnormalities (including laboratory abnormalities) which, in the opinion of the investigator or the medical monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study. 3. History or presence of gallstones or kidney stones. 4. History of non-adherence during the subject's participation in the LUM001-302 study, or earlier in the LUM001-303 study. Non-adherence is defined by dosing compliance of less than 80% in the LUM001-302 study or earlier in the LUM001-303 study. 5. Unlikely to comply with the study protocol, or unsuitable for any other reason, as judged by the investigator. Eligible subjects for the 52-week optional follow-up treatment period: Subjects will be considered eligible for the 52-week optional follow-up treatment period if they have completed the protocol through the Week 72 visit with no safety concerns. Subjects who were discontinued due to safety reasons can be re-challenged if blood tests are

	back to relatively normal values for this patient population and the subject does not meet any of the protocol's stopping rules; the decision will be made by the investigator in consultation with the medical monitor. Subjects who have undergone a surgical disruption of the enterohepatic circulation will not be eligible to enter into the follow-up treatment period. Subjects who were discontinued for other reasons will be considered on an individual basis. Inclusion Criteria: Subjects will be considered eligible for the long-term optional follow-up treatment period if they meet the following criteria: 1. The subject has either: a. Completed the protocol through either the Week 124 or the ET visit with no major safety concerns. OR b. Discontinued due to safety reasons judged unrelated to the study drug, and laboratory results have returned to levels acceptable for this patient population or individual and subject does not meet any of the protocol's stopping rules at the time of entry into the follow-up period. The decision will be made by the investigator in consultation with the medical monitor. Subjects who were discontinued for other reasons will be considered on an individual basis. 2. Females of childbearing 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. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug, must agree and use acceptable contraception during the study. 4. Informed consent and assent (per IRB/EC) as appropriate. 5. 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: All exclusion criteria mentioned for the original study LUM001-303 apply upon re-entry into the long-term optional follow-up treatment period.
Treatment Groups	Based on tolerability and effect on pruritus 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 After Week 124 and/or implementation of this amendment, whichever occurs first, subjects will be considered for a long-term optional follow-up treatment period, if eligible, receiving up to 560 µg/kg/day (given as twice daily doses of 280 µg/kg), or to a maximum possible daily dose of 50 mg/day.
Study Drug Dosage and Administration	Subjects will receive a grape-flavored solution containing LUM001, administered orally once a day (QD) or BID using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the doses should be taken approximately at the same time each day for the duration of the treatment period.

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 ≥10% will require a dose adjustment. 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.

Dose Escalation Period

For subjects randomized to placebo in the LUM001-302 study, or those who complete the LUM001-302 study more than 7 days prior to enrollment into this study, the LUM001 dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose)**.** For subjects who were randomized to receive active drug in the LUM001-302 study, LUM001 doses will remain the same as the dose taken at Week 13. 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.

LUM001-302 Study	**Extension StudyLUM001-303**			
	Dose Escalation Period			
Week 13 (µg/kg/day)	**Week 1 Days 1 - 7 (µg/kg/day)**	**Week 2 Days 8 - 14 (µg/kg/day)**	**Week 3 Days 15 - 21 (µg/kg/day)**	**Week 4 Days 22 - 28 (µg/kg/day)**
Placebo[1]	14	35	70	140
35[2]	35	35	35	35
70[3]	70	70	70	70
140[4]	140	140	140	140
280[5]	280	280	280	280

1. For subjects randomized to placebo in the LUM001-302 study, or those who complete the LUM001-302 study more than 7 days prior to enrollment into this study, the LUM001 dose during the first 4 weeks of the study will be increased at weekly intervals to 140 µg/kg/day, or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose)**.**
2. LUM001 doses for subjects whose stable dose upon completion of LUM001-302 Treatment Protocol study was 35 µg/kg/day will remain stable at 35 µg/kg/day, or to a maximum daily dose of 2.5 mg/day.
3. LUM001 doses for subjects whose stable dose upon completion of LUM001-302 Treatment 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 LUM001-302 Treatment 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 LUM001-302 Treatment Protocol was 280 µg/kg/day will remain stable at 280 µg/kg/day, or to a maximum daily dose of 20 mg/day.

If a subject experiences intolerance due to gastrointestinal symptoms (eg, diarrhea, abdominal pain, cramping) at any time during the study, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose.

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 subject, caregiver, physician investigator, or the sponsor 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 Period

At the end of the Dose Optimization Period, subjects will continue dosing to complete 72 weeks of cumulative LUM001 exposure in this study.

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

Optional Follow-up Treatment Period:

At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility for entry into the 52-week, follow-up treatment period. The three following possible scenarios may occur:

- Subjects who are eligible to roll over into the optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level.
- Subjects who are eligible to roll over into the optional follow-up treatment period with a LUM001 dose interruption of ≥7 days, will be dose escalated up to 280 µg/kg/day or a maximum tolerated dose following a 4-week dose escalation beginning at 35 µg/kg/day.
- Subjects who do not wish to enter the optional follow-up treatment period, will be contacted via telephone by the study site approximately 30 days after the last dose of study drug.

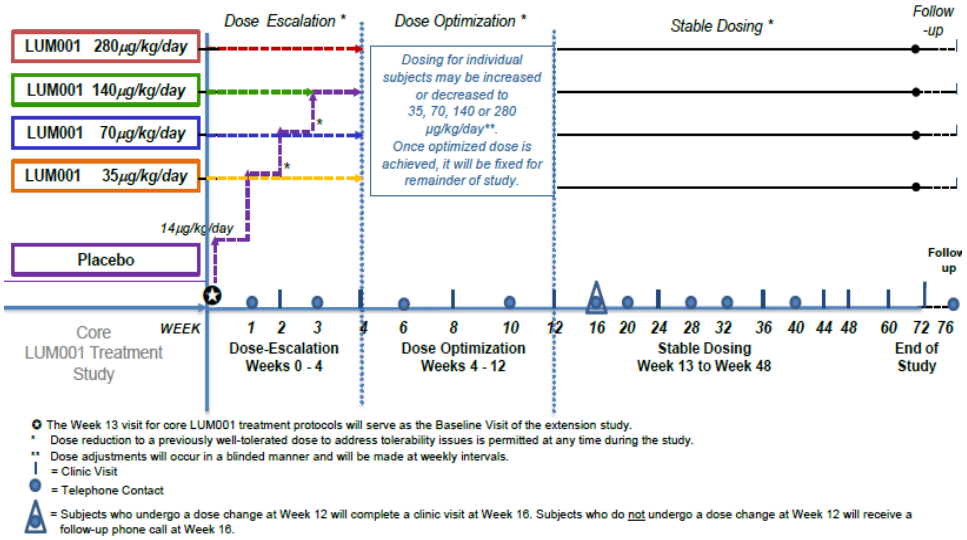
Long-term Optional Follow-up Treatment Period:

Upon completion of the 52-week optional follow-up treatment period and/or implementation of this amendment, whichever occurs first, subjects will be assessed by the investigator to determine their willingness and eligibility for entry into the long-term optional follow-up treatment period. All subjects will be re-initiated at the same LUM001 dose they last received during LUM001-303. The appropriate amount of study drug will be dispensed at the Protocol Amendment 5 Day 0/baseline visit, but daily dosing will not begin until the following day, Protocol Amendment 5, Study Day 1. Eligibility assessment for afternoon dose escalation will then occur in all subjects based on efficacy (ItchRO[Obs] and sBA) and safety assessments following approximately 12 weeks of dose re-initiation as follows:

- Subjects with normal sBA level AND ItchRO(Obs) score <1.5 will be maintained at the same dose level and will continue morning dosing only.
- Subjects with sBA level above normal AND/OR ItchRO(Obs) score ≥1.5 will start BID dosing (afternoon dose escalation) as follows:
    - The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the

	afternoon dose is initiated in order to limit the amount of propylene glycol in the diluent administered. o The afternoon dose will be initiated at half the dose level of the morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be doubled to match the morning dose. • Subjects with abnormal sBA level AND ItchRO(Obs) score ≥1.5 who had normal sBA level and ItchRO(Obs) score <1.5 prior to dose interruption will remain on the maximum tolerated morning dose (the dose they received last during LUM001-303) for an additional 2 weeks until their efficacy and safety assessments are repeated for eligibility assessment for afternoon dose escalation. • The sBA value used for determination of afternoon dose escalation eligibility will be the most recent available value collected within the prior 16 weeks. The ItchRO(Obs) score used for afternoon dose escalation eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 16 weeks. • The maximum daily dose will be 280 µg/kg BID, ie, 560 µg/kg/day (up to a maximum possible daily dose of 50 mg/day). • 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 study drug. **<u>Study Drug Administration under Protocol Amendment 5</u>** **QD Dosing Regimen** For QD dosing, the required dose will be delivered in 0.5 mL volume for subjects who weigh less than 10 kg and in 1.0 mL for subjects who weigh 10 kg or more. **BID Dosing Regimen** For BID dosing, the required dose is delivered in half the dosing volume: 0.25 mL BID for subjects who weigh less than 10 kg and 0.50 mL BID for subjects who weigh 10 kg or more. For subjects weighing less than 10 kg at study re-entry, once a weight of 10 kg is reached while in the study, the subject will be moved from 0.5 mL total daily dosing volume (0.25 mL BID) to 1.0 mL total daily dosing volume (0.50 mL BID).
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 study drug 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) adverse events (AEs). These signs and symptoms were believed to be related to increased bile acid excretion and a concomitant increases 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 and that LUM001 is likely to produce a correspondingly 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 study 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 14days in 40 hyperlipidemic pediatric patients (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 medical monitor, for subjects experiencing intolerance to a given dose. During the follow-up treatment period, the dose will be escalated for those subjects who had been off treatment for ≥7 days. The dose will be escalated over the first 4 weeks up to 280 µg/kg/day or to the maximum tolerated dose starting at 35 µg/kg/day. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001 and allows for subjects to reach 280 µg/kg/day or a maximum tolerated dose within a 4-week period. The study drug may be adjusted if there is a change of ≥10% in body weight since the screening visit or if there is a change of ≥10% in weight since the last weight based medication adjustment to maintain the target dose. Under Protocol Amendment 5, an afternoon dose is introduced for eligible subjects in the long-term optional follow-up treatment period. LUM001 doses will be escalated over a period of 4-8 weeks up to a maximum dose of 280 µg/kg BID (or maximum tolerated dose). The afternoon dose is only initiated and escalated in subjects with elevated sBA and/or ItchRO(Obs) ≥1.5 on the maximum (or maximum tolerated) morning dose. If a subject experiences intolerance (such as gastrointestinal symptoms like diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001. Twice daily dosing is used in this study based on the findings of a healthy volunteers study in adult males (Study SHP625-101), which demonstrated that bile acid levels in feces increase with escalating doses and twice-daily regimen of LUM001 (up to 100 mg QD and 50 mg BID). In this study, subjects who were randomized to LUM001 treatment, received 1 of 4 doses of LUM001 (10, 20, 50, 100 mg) during 7 days. No titration was used in this study. There was a dose-dependent increase in total fecal BA excretion. In addition, BID dosing (ie, 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (ie, 100 mg QD). It is therefore hypothesized that twice-daily dosing has the potential to allow for more complete target engagement throughout the day at the level of the distal ileum. The higher dosing level is also supported by favorable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (post-natal day [PND] 21 through PND63). As expected for a drug intentionally designed to be minimally absorbed, systemic LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies in adult rats. No adverse effects were observed on postnatal

	growth and development of offspring at the highest doses tested (200 mg/kg/day in males, 1000 mg/kg/day in females). This study was initiated in juvenile animals at PND21, which from a whole animal development perspective, is typically representative of a 2-year old child. However, given the fact that LUM001 is a minimally absorbed drug, of particular importance is the age at which the GI tract is considered functionally mature. In humans this is considered to have occurred by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs during the first 3 weeks of life. Therefore, results from this study can be used to support the dosing levels proposed here for children 12 months of age and older.
Study Visit Schedule and Procedures	Study activities will be conducted as described in the Schedule of Procedures. **Synopsis Figure 1: Study Design for LUM001-303 (Up to and including Week 72):**  Baseline (Day 0): Evaluations and procedures completed for the Week 13 Visit of the LUM001-302 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. 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. Blood will also be collected for PK analysis. The clinician scratch scale will be administered, as well as the PedsQL. Females who are of childbearing potential will have a urine pregnancy test and concomitant medications and any adverse events 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 adverse events 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 adverse events 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 72): 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 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, 48, 60 and 72. 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 will be administered and study drug compliance will be assessed. The PedsQL will be completed at Weeks 24, 48 and 72 the Caregiver Impression of Change (CIC) will be completed at Weeks 48 and 72. Subjects/caregivers will receive follow-up phone calls at Weeks 16, 20, 28, 32 and 40. Concomitant medications and any adverse events 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. 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 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. Additional study drug will be supplied at each clinic visit during the stable dosing period. Week 72: Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the optional 52-week treatment period. Eligible subjects must have documented consent in order to continue in the 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. Blood will also be collected for PK analysis. 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. Females who are of childbearing potential will have a urine pregnancy test and concomitant medications and any adverse events 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 optional follow-up treatment period.

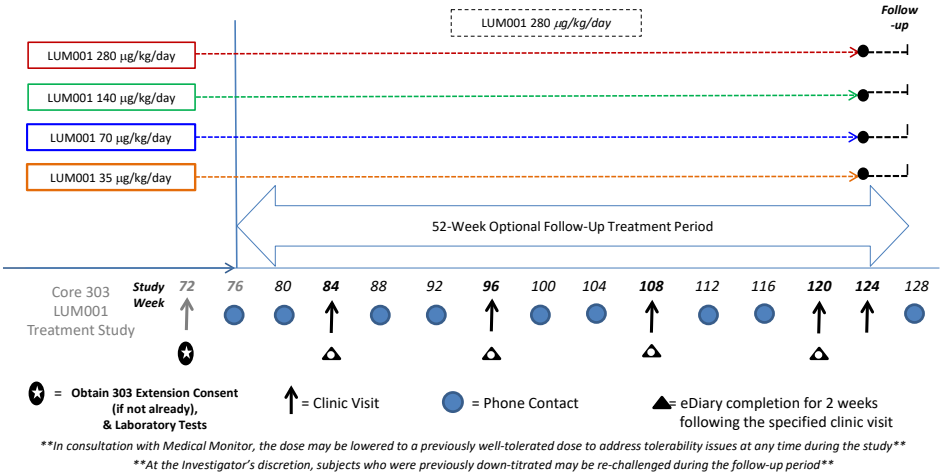
Subjects will be encouraged to complete all study activities and visits. Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week 72 visit. For safety reasons, efforts must be made to follow subjects for at least 30 days following their last dose of study drug.

Follow-up Period (post-Week 72): For subjects who do not roll over into the optional follow-up treatment period, a safety follow-up phone call will be made by the study site 30 days after the last dose of study drug. 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 adverse events noted during this phone call will be recorded.

Optional Follow-up Treatment Period (post Week 72 to Week 124):

Subjects who are eligible to roll over into the follow-up treatment period will continue to receive study drug at the dose they were receiving at Week 72 for up to 52 weeks or until a new study opens to enrollment, whichever occurs first (Synopsis Figure 2). During the follow-up treatment period, subjects will return to the clinic every 12 weeks, at Weeks 84, 96, 108, 120, and 124.

Synopsis Figure 2: Follow-up Treatment Scheme
(no interruption in LUM001 dosing, or interruption <7 days)

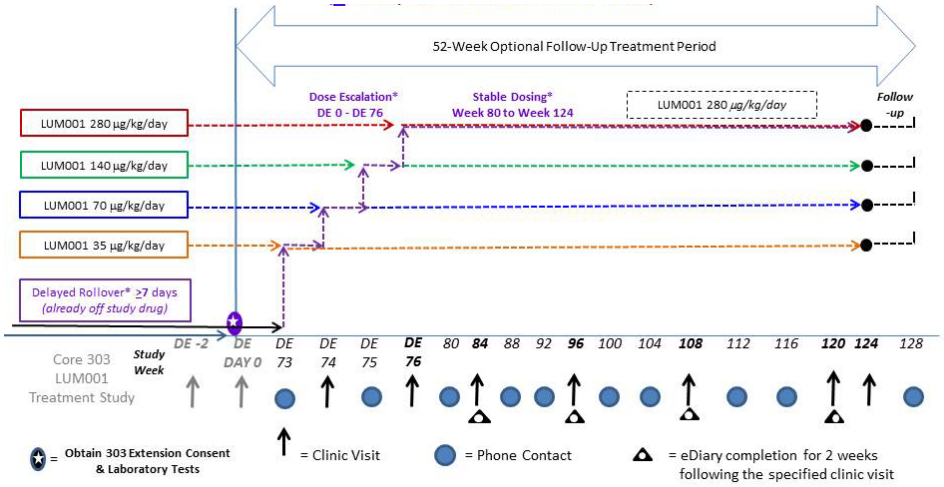


Subjects with ≥7 days since last dose of LUM001 will be dose escalated up to 280 µg/kg/day or to the highest tolerated dose starting at 35 µg/kg/day (Synopsis Figure 3). This escalation regimen is supported by the safety profile observed in completed and ongoing clinical

studies of LUM001 and allows for subjects to reach 280 µg/kg/day or a highest tolerated dose within a 4-week period. The dose escalation (DE) period will proceed as follows:

- DE Week -2 Clinic Visit: obtain consent, obtain weight, and draw labs.
- DE Day 0 Clinic Visit: investigator evaluates laboratory results, study drug is dispensed and subject begins at 35 µg/kg/day dose level.
- DE Week 73 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated.
- DE Week 74 Clinic Visit: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated.
- DE Week 75 Telephone Contact: subject escalates to 280 µg/kg/day dose, if prior dose level was tolerated.
- DE Week 76 Clinic Visit: subject continues in Follow-up Treatment Period at 280 µg/kg/day, or highest tolerated dose

Synopsis Figure 3: Follow-up Treatment Scheme
(interruption in LUM001 dosing ≥7 days):



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

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. In addition, the clinician scratch scale will be administered and study drug compliance will be assessed. The PedsQL will be administered at DE Day 0 (for subjects requiring dose escalation) and at Weeks 84, 96, 108, 120, and 124 or ET visit. The Caregiver Impression of Change (CIC) assessment will be completed at Weeks 108, 120, and 124 or ET visit. Subjects/caregivers will receive follow-up phone calls at Weeks 76, 80, 88, 92, 100, 104, 112, 116, and at 30 days following the last dose of study drug. Concomitant medications and any AEs 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 84, 96, 108, and 120. 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 long-term exposure period.

With the exception of the Week 120 and Week 124 visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every visit.

If any subject experiences intolerance, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period. At the investigator's discretion and in consultation with the medical monitor, subjects who were previously down titrated may be re-challenged during the follow-up treatment period.

Long-term Optional Follow-up Treatment Period

Subjects who either complete 124 weeks of treatment and/or are considered eligible for Protocol Amendment 5 may be eligible to receive further treatment under Protocol Amendment 5. Subjects who are eligible for re-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 are eligible to enter another LUM001 study,

ii. LUM001 is commercially available, or

iii. The sponsor stops the program or development of this indication.

Once Protocol Amendment 5 is implemented at the site and the subject consents to enter the long-term optional follow-up period, and the subject consents to enter the long-term optional follow-up period, the subject will be re-initiated at the same LUM001 dose they last received during LUM001-303 for approximately 12 weeks. The appropriate amount of study drug will be dispensed at the Protocol Amendment 5 Day 0/baseline visit, but daily dosing will not begin until the following day, Protocol Amendment 5, Study Day 1. At the Week 12 visit, a determination about afternoon dose escalation will be made based on efficacy (ItchRO[Obs] and sBA) and safety assessments. Study activities will proceed as follows:

- Protocol Amendment 5 Screening: Screening evaluations will be performed from Day -14 to Day -1. After obtaining informed consent (and/or assent when appropriate), subjects will undergo a physical examination including body weight, height, and vital signs, and have blood and urine samples taken for clinical laboratory testing. Females who are of childbearing potential will have a urine pregnancy test. The electronic diary will be issued and caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the screening visit. Eligibility criteria will be confirmed prior to the Baseline Visit. Concomitant medications and any adverse events will be recorded.
- Protocol Amendment 5 Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 14-day screening period, consideration may be given to rescreening at a later date. Screen failures are eligible for rescreening on a case by case basis following discussions between the investigator and the medical monitor. Screening procedures should be repeated at that time. Subject data pertaining to screening will be collected after the subject has been rescreened and determined to meet eligibility.
- Protocol Amendment 5 Day 0/Baseline Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. The clinician scratch scale, clinician xanthoma scale, and PedsQL questionnaire will be administered. ItchRO compliance will be assessed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug will be dispensed and concomitant medications and adverse events will be collected.
- Protocol Amendment 5 Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. Caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the Week 4 visit. The clinician scratch scale and the clinician xanthoma scale will be

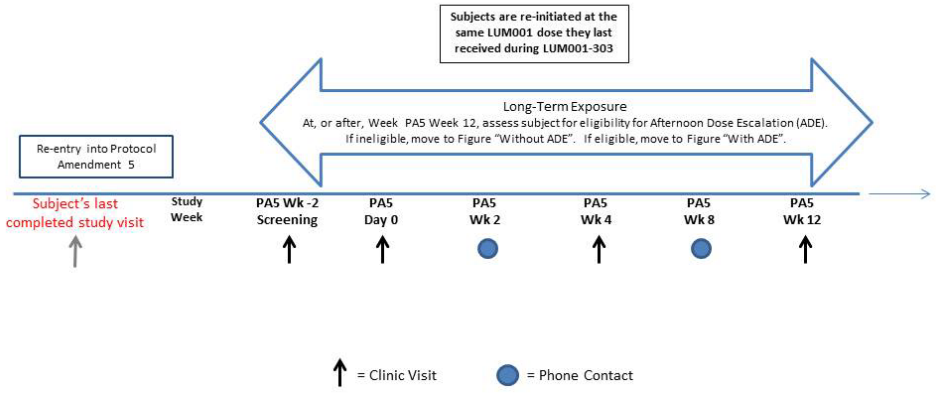
administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. The electronic diary will be issued and caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the Week 4 visit. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected.

- Protocol Amendment 5 Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.
- Protocol Amendment 5 Week 12: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. ItchRO compliance will be assessed, and the clinician scratch scale and clinician xanthoma scale will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected. Subjects will be assessed for afternoon dose escalation eligibility. The sBA value used for determination of afternoon dose escalation eligibility will be the most recent available value collected within the prior 12 weeks. The ItchRO(Obs) score used for afternoon dose escalation eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 8 weeks.

Subjects who are eligible for re-entry into the <u>long-term</u> optional follow-up treatment period will be consented and initiate treatment at the same dose level they last received during LUM001-303 (Synopsis Figure 4). After approximately 12 weeks of treatment, subjects will be evaluated for eligibility for afternoon dose escalation at Week 12. Once a decision about afternoon dose escalation has been made, the subject will then either:

- continue receiving the same dose of LUM001 QD (Synopsis Figure 5) if they do not meet the criteria for afternoon dose escalation *OR*
- initiate the afternoon dose escalation (Synopsis Figure 6).

<u>Synopsis Figure 4: Re-entry into Long-term Optional Follow-up Treatment under Protocol Amendment 5</u>

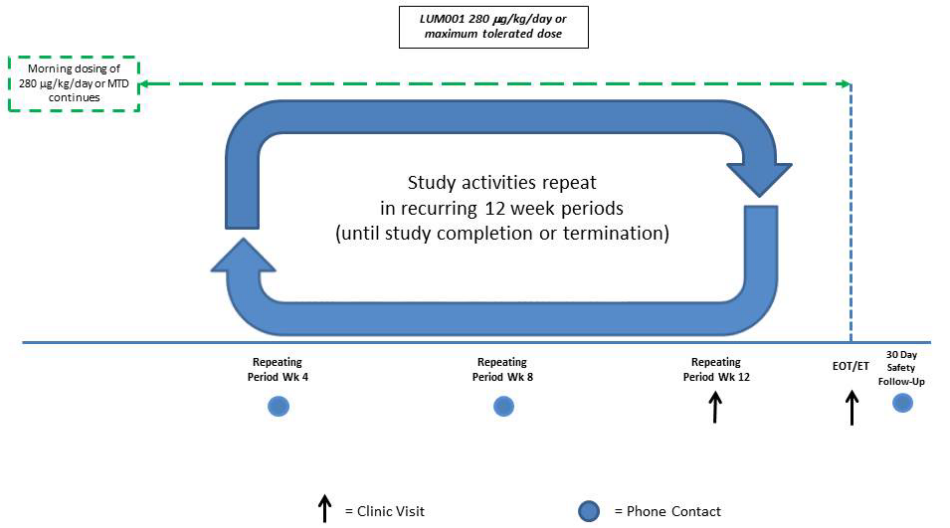


Subjects not eligible for afternoon dose escalation (subjects with normal sBA level AND ItchRO(Obs) score <1.5; Synopsis Figure 5), will be maintained at the same dose level

and will continue morning dosing only. Subjects will have study activities repeated in recurring 12-week periods as follows, until study completion or termination:

- Repeating Period Week 1 (not pictured in Synopsis Figure 5): subject deemed ineligible for afternoon dose escalation and continues QD dosing.
- Repeating Period Week 4 Telephone Contact: Collection of concomitant medications and any adverse events.
- Repeating Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.
- Repeating Period Week 12 Clinic Visit: Physical exam, body weight and height, vital signs, and blood samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of baseline fat-soluble vitamins. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected. Urine samples for clinical laboratory testing will be collected at every other visit.
- Subjects who do not qualify for afternoon dose escalation may be assessed at a later time point on a case by case basis following discussions between the investigator and medical monitor. Such re-evaluations may only occur at the Week 12 visit of any Repeating Period (RP) beginning with RP2 within Schedule F. If, in the course of the afternoon dose escalation re-evaluation, a subject is found to qualify for afternoon dose escalation, then the subject will move into Schedule G. During the follow-up treatment period, subjects will return to the clinic every 12 weeks.

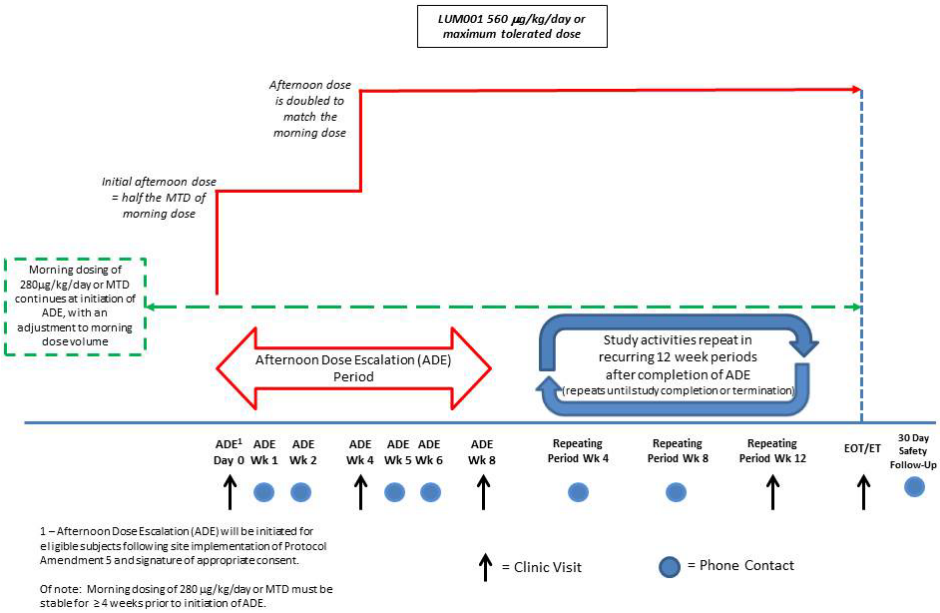
Synopsis Figure 5: Long-term Optional Follow-up Treatment under Protocol Amendment 5, without afternoon dose escalation



If the subject is eligible for afternoon dose escalation, ie, who has sBA level above normal AND/OR ItchRO(Obs) score ≥1.5, the subject will begin BID dosing (afternoon dose escalation) as follows:

	• On afternoon dose escalation Day 0, morning dosing will continue at 280 µg/kg or the maximum tolerated dose. However, the volume of the morning dose will be reduced by half. Of note: morning dosing must have been stable for ≥4 weeks prior to initiation of afternoon dose escalation. • On afternoon dose escalation Day 0, the afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose level for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled (ie, at afternoon dose escalation Week 4) to a maximum of 280 µg/kg/day (ie, up to a maximum 560 µg/kg/day or maximum tolerated dose). The following procedures will occur during the afternoon dose escalation period: • Afternoon dose escalation Day 0 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected. • Afternoon dose escalation Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions. • Afternoon dose escalation Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected. • Afternoon dose escalation Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions. • Afternoon dose escalation Week 8 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected.

Synopsis Figure 6: Long-term Optional Follow-up Treatment under Protocol Amendment 5, with afternoon dose escalation



Thereafter, subjects will have study activities repeated in recurring 12-week periods as described within Synopsis Figure 6, until study completion or termination.

If any subject experiences intolerance, the investigator, in consultation with the medical monitor, may lower the dose at any time during the entire follow-up treatment period. If the subject is on a twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose. At the investigator's discretion, and in consultation with the medical monitor, subjects who were previously down titrated may be re-challenged during the follow-up treatment period. During the long-term optional follow-Up treatment period, subjects will return to the clinic every 12 weeks.

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. In addition, the clinician scratch scale will be administered and study drug compliance will be assessed.

	The PedsQL will be administered at Protocol Amendment 5 Day 0/Baseline visit and every 24 weeks thereafter. Subjects/caregivers will receive follow-up phone calls as outlined in the repeating 12 week periods. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts. Palatability data will be collected at each clinic visit during the long-term optional follow up treatment period (including the EOT/ET visit), with the exception of the afternoon dose escalation visits. Twice-daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 consecutive weeks following the Protocol Amendment 5 Week 4 visit and at every clinic visit within the repeating 12 week periods. 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 long-term follow-up period. With the exception of the EOT/ET visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every 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 following assessments as outlined for the EOT/ET visit: physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory samples, including fasting lipid panel and pharmacokinetic sampling of LUM001. Blood will also be collected for determination of fat-soluble vitamins and AFP. Female subjects who are of child-bearing potential will have a urine pregnancy test. Study drug compliance will be assessed. Concomitant medications and adverse events will be collected. The clinician-administered pruritus scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, clinician xanthoma scale, and palatability questionnaire will also be completed. At completion of the long-term optional follow-up treatment period or early discontinuation, 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 terminated early. Concomitant medications and adverse events noted during this phone call will be recorded.
Drug Level Evaluations	Plasma levels of LUM001 will be evaluated at Baseline and Weeks 12, 24, 36, and 48 and 72. Blood will be drawn approximately 4 hours post-dosing for drug level analysis. Additionally, for subjects in which afternoon dose escalation is initiated, samples will also be drawn at 4 hours following the morning dose on afternoon dose escalation Day 0, afternoon dose escalation Week 4, afternoon dose escalation Week 8, and at the 3 scheduled clinic visits following completion of the afternoon dose escalation treatment period.
Safety and Tolerability Evaluations	The safety and tolerability of LUM001 will be assessed by determining the incidence, relationship to study drug, and severity of treatment-emergent AEs, withdrawals due to AEs, and changes in vital signs, laboratory and other safety parameters. A-fetoprotein (AFP), a marker of hepatocellular carcinoma will be measured every 6 months throughout the remainder of the study. Alterations in liver parameters assessed for the purposes of safety monitoring will be relative to the baseline (Day 0) of the LUM001-302 study in which the subject was enrolled. A Data Monitoring Committee (DMC) will review serious adverse event 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) to Week 48 in: • Fasting serum bile acid level. Secondary evaluations will be the mean change from Baseline (Day 0) to Week 48 and the change from Week 12 to Week 48 in: • Biochemical markers of cholestasis and liver disease [alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and total bilirubin]. • 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. • Xanthomas as measured by clinician xanthoma scale. Additional exploration, including behavior during the dose escalation and optimization phases will be specified in the statistical analysis plan.
Palatability Data	Palatability data will be collected at each clinic visit in the long-term optional follow up treatment period, with the exception of the afternoon dose escalation visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age). Assessments over time will be evaluated.
Statistical Considerations	<u>Sample Size</u> Approximately 18 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 LUM001-302 study. Because this is an extension study for the LUM001-302 study, the sample size is not based on statistical considerations. <u>Safety</u> 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 (baseline). 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. <u>Drug Level Analysis</u> Descriptive statistics analysis of LUM001 concentrations will be carried out on the plasma concentration data. <u>Interim Analysis</u> There may be one or more interim analysis (IA) conducted during the conduct of the study in order to guide the future of the development program. The IA may result in an interim report or publication.

	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. Special attention will be paid to change from baseline for those on placebo at baseline and during the first 12 weeks for those on active study drug at baseline and during the stable dosing period for all subjects at all dose levels. 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
7αC4, C4	7α-hydroxy-4-cholesten-3-one; an indirect method of bile acid synthesis
Ac	before meals
AE	adverse event
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
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
ATX	autotaxin
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	decilitre
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic case report form

Abbreviation	Definition
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
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
FIC1	familial intrahepatic cholestasis 1
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
HIV	human immunodeficiency virus
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl-CoA reductase; rate-controlling enzyme of the pathway that produces 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 Harmonisation
IEC	independent ethic committee
INR	international normalized ratio
IRB	institutional review board

Abbreviation	Definition
ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Itch Reported Outcome observer instrument
ItchRO(Pt)™	Itch Reported Outcome patient instrument
IU	international unit(s)
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
NBD	nasal biliary drainage
NCS	not clinically significant
ObsRO	observer reported outcome
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
PSC	primary sclerosing cholangitis
Pt	patient
PT	prothrombin time

Abbreviation	Definition
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 IBAT protein
SUSAR	suspected unexpected serious adverse reaction
TG	triglycerides
TGR5	a G protein-coupled receptor for bile acids
UDCA	ursodeoxycholic acid, ursodiol
ULN	upper limit of normal
US, USA	United States of America
WBC	white blood cell
WHO	World Health Organization
WMA	World Medical Association
yr(s)	year(s)
β-hCG	beta-subunit of human chorionic gonadotropin; pregnancy test
Mg	microgram
μM	micromolar

3 STUDY OBJECTIVES

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

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

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

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

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

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.

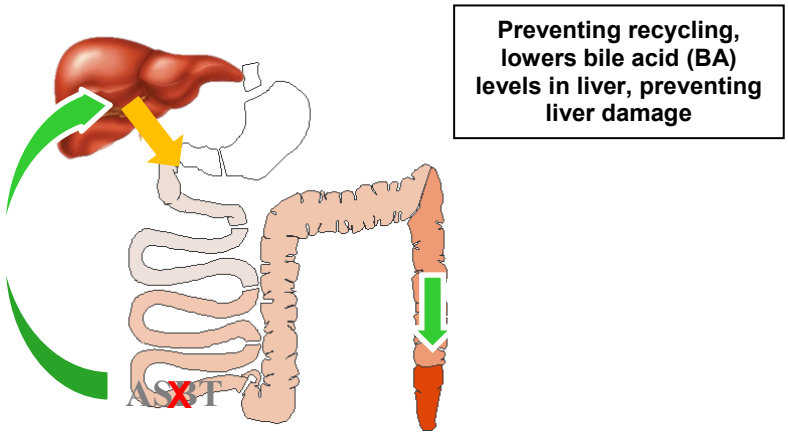
4.1 Therapeutic Rationale

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, Chen, Li, & Shneider, 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 or ileal exclusion. The current extension study will test this hypothesis.

4.2 Alagille Syndrome

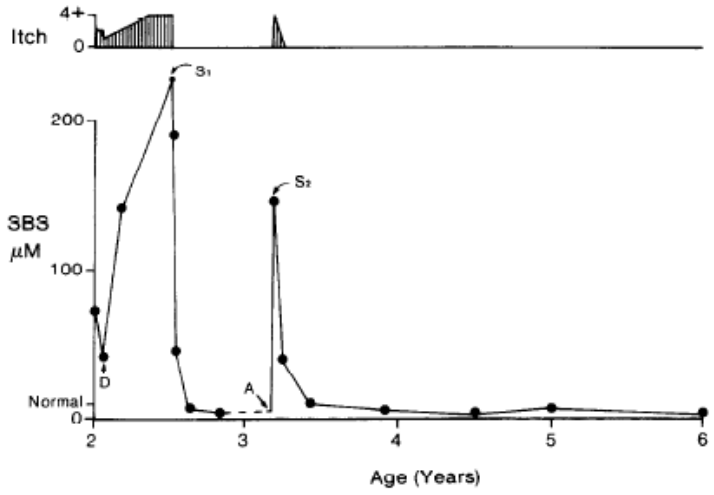
Alagille syndrome (ALGS) is an autosomal dominant with variable penetration multisystem disorder. The clinical diagnosis is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease, 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 & Whitington, 2002) (Modi, Suh, Jonas, Lillehei, & Kim, 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 (PEBD) and nasal biliary drainage (NBD) substantially reduces pruritus in ALGS (Emerick & Whitington, 2002), PFIC, and 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 (Whitington & 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 & 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 & 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.

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 patients 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 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 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.

4.5 Rationale for Dose and Schedule of Administration

The dosage of LUM001 chosen for the first studies in pediatric cholestatic subjects was based upon prior experience with this 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 GI AEs. These signs and symptoms were believed to be related to increased bile acid excretion and an increased concentration of free bile acids in the lower colon. In patients with cholestatic liver disease it is likely that bile flow is reduced compared to healthy volunteers and hypercholesterolemic patients and 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, 2001). 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 a pediatric subject 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)	Daily Exposure of LUM001 (mg)				
	Dose Level 1 (35 µg/kg/day)	Dose Level 2 (70 µg/kg/day)	Dose Level 3 (140 µg/kg/day)	Dose Level 4 (280 µg/kg/day)	Dose Level 5 (560 µg/kg/day)
10	0.35	0.70	1.40	2.80	5.60
15	0.53	1.05	2.10	4.20	8.40
20	0.70	1.40	2.80	5.60	11.20
25	0.88	1.75	3.50	7.00	14.00
30	1.05	2.10	4.20	8.40	16.80

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, Cappon, Hurtt, & Zoetis, 2005) (van den Anker, Schwab, & Kearns, 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 day 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.

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

Under Protocol Amendment 5, an afternoon dose is introduced for eligible subjects in the long-term optional follow-up treatment period. LUM001 doses will be escalated over a period of 4-8 weeks up to a maximum dose of 280 µg/kg BID (or maximum tolerated dose). The afternoon dose is only initiated and escalated in subjects with elevated sBA and/or ItchRO(Obs) ≥1.5 on the maximum (or maximum tolerated) morning dose.

If a subject experiences intolerance (such as gastrointestinal symptoms like diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose.

This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001. Twice daily dosing is used in this study based on the findings of a healthy volunteers study in adult males (Study SHP625-101), which demonstrated that bile acid

levels in feces increase with escalating doses and twice-daily regimen of LUM001 (up to 100 mg QD and 50 mg BID). In this study, subjects who were randomized to LUM001 treatment, received 1 of 4 doses of LUM001 (10, 20, 50, 100 mg) during 7 days. No titration was used in this study. There was a dose-dependent increase in total fecal BA excretion. In addition, BID dosing (ie, 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (ie, 100 mg QD). It is therefore hypothesized that twice-daily dosing has the potential to allow for more complete target engagement throughout the day at the level of the distal ileum.

The higher dosing level is also supported by favorable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (post-natal day [PND] 21 through PND63). As expected for a drug intentionally designed to be minimally absorbed, systemic LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies in adult rats. No adverse effects were observed on postnatal growth and development of offspring at the highest doses tested (200 mg/kg/day in males, 1000 mg/kg/day in females). This study was initiated in juvenile animals at PND21, which from a whole animal development perspective, is typically representative of a 2-year old child. However, given the fact that LUM001 is a minimally absorbed drug, of particular importance is the age at which the GI tract is considered functionally mature. In humans this is considered to have occurred by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs during the first 3 weeks of life. Therefore, results from this study can be used to support the dosing levels proposed here for children 12 months of age and older.

5 INVESTIGATIONAL PLAN

5.1 Study Design

This is a multicentre, double-blind study of LUM001 in children ≥12 months of age diagnosed with ALGS who have completed participation in the LUM001-302 study. All subjects will receive active drug LUM001 in this study. The study is divided into 5 parts: a dose escalation period, a dose optimization period, a stable dosing period, an optional 52-week follow-up period, and a long-term optional follow-up treatment period for eligible subjects who choose to stay on treatment with LUM001. During this long-term optional follow-up treatment period, subjects may have their dose of LUM001 increased to a maximum of 560 ug/kg/day (280 ug/kg BID), based on efficacy (sBA level and ItchRO Observer (Obs) score) and safety assessments. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occur: i) subjects are eligible to enter another LUM001 study, or ii) LUM001 is available commercially or (iii) the sponsor stops the program or development in this indication. Subjects who do not consent and/or are not eligible for Protocol Amendment 5 will continue their study participation in Protocol Amendment 4.

Dose Escalation Period

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

- Subjects who were randomized to receive placebo during the LUM001-302 study will receive weekly dose increases of LUM001 up to a target dose of 140 µg/kg/day.
- Subjects who were randomized to receive active drug during the LUM001-302 study will continue to receive the dose of LUM001 that they were taking at Week 13 of the LUM001-302 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 level will be increased or decreased in a double-blind manner. Increases in dose will be based on effect on efficacy (sBA and ItchRO[Obs] score) and safety assessments. Reductions in dose will be based on tolerability. At the investigator's discretion, the doses for 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 Period

Following completion of the 8-week dose optimization period, all subjects will enter the stable dosing period lasting 60 weeks. During the remainder of the study 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 medical monitor, may lower the dose to a previously tolerated dose.

Optional Follow-up Treatment Period:

At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the 52-week, follow-up treatment period. The 3 following possible scenarios may occur:

- For subjects who are eligible to roll over into the follow-up treatment period, those with <7 days since the last dose of LUM001, will be maintained at the same dose level.
- For subjects who are eligible to roll over into the follow-up treatment period having ≥7 days since the last dose of LUM001, will be dose escalated up to 280 µg/kg/day or the highest tolerated dose following a 4 week dose escalation beginning at 35 µg/kg/day.
- For subjects who do not wish to enter the follow-up treatment period, or are not eligible to enter the follow-up treatment period, a safety follow-up phone call will be made by the study site 30 days after the last dose of study drug.

Long-term optional Follow-up Treatment Period (Protocol Amendment 5):

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

5.2 Data Monitoring Committee

A Data Monitoring Committee (DMC) will review serious adverse event data, other key subject safety and study data at specified intervals for the duration of the study. The DMC will be composed of at least 2 members who are otherwise independent from the conduct of the study: one or more physicians and at least one biostatistician. The DMC's primary responsibility is to review the progress of the study, particularly with regard to safety and risk/benefit, and make recommendations to sponsor to stop or modify the study if safety concerns are identified. Further

details regarding the structure, function and operation of the DMC will be detailed in the DMC charter.

5.3 Number of Study Centers

This will be a multicentre study in the 3 clinical centers that participated in Study LUM001-302.

5.4 Number of Subjects

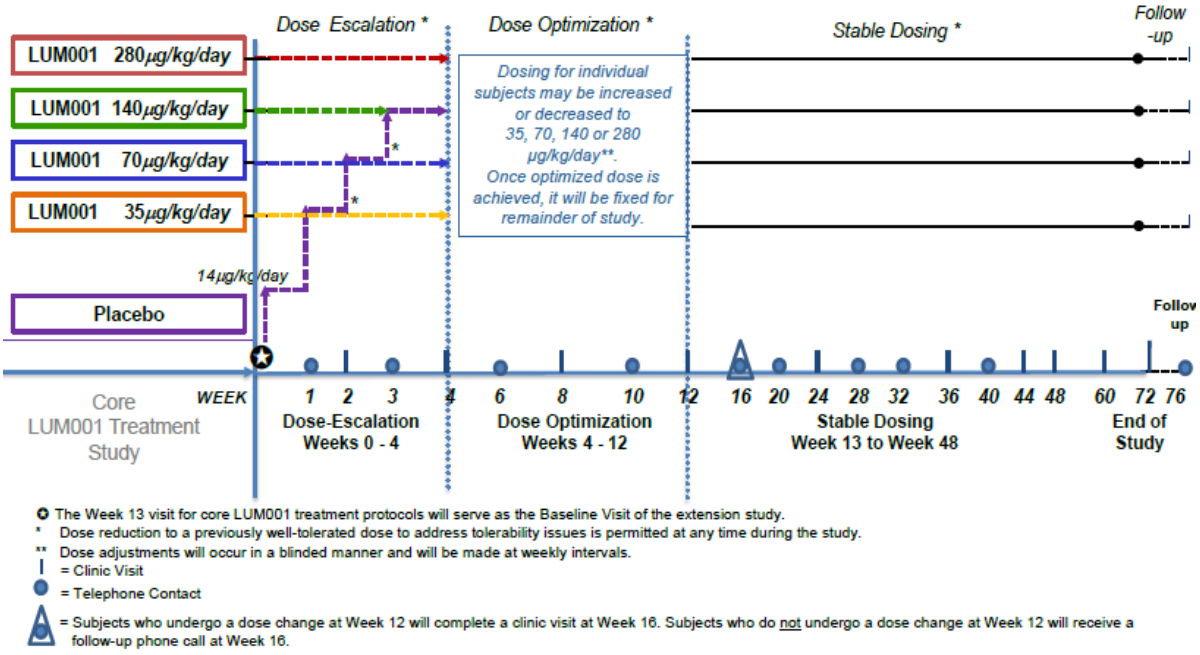
Approximately 18 subjects meeting the study's inclusion and exclusion criteria may be enrolled in the study.

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, an 8-week dose optimization period, a 60-week stable dosing period, an optional 52-week follow-up treatment period, and a long-term optional follow-up treatment period. A safety follow-up phone call will be made by the study site 30 days after the last dose of study drug.

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

Figure 3: Study Design for LUM001-303 (Up to and including Week 72)



✪ The Week 13 visit for core LUM001 treatment protocols will serve as the Baseline Visit of the 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.

Figure 4: Follow-up Treatment Scheme (no interruption in LUM001 dosing or interruption <7 days)

Applies to the following population:

- Subjects who experienced no interruption in LUM001 dosing, or interruption <7 days between Protocol Amendment 3 and Protocol Amendment 4.

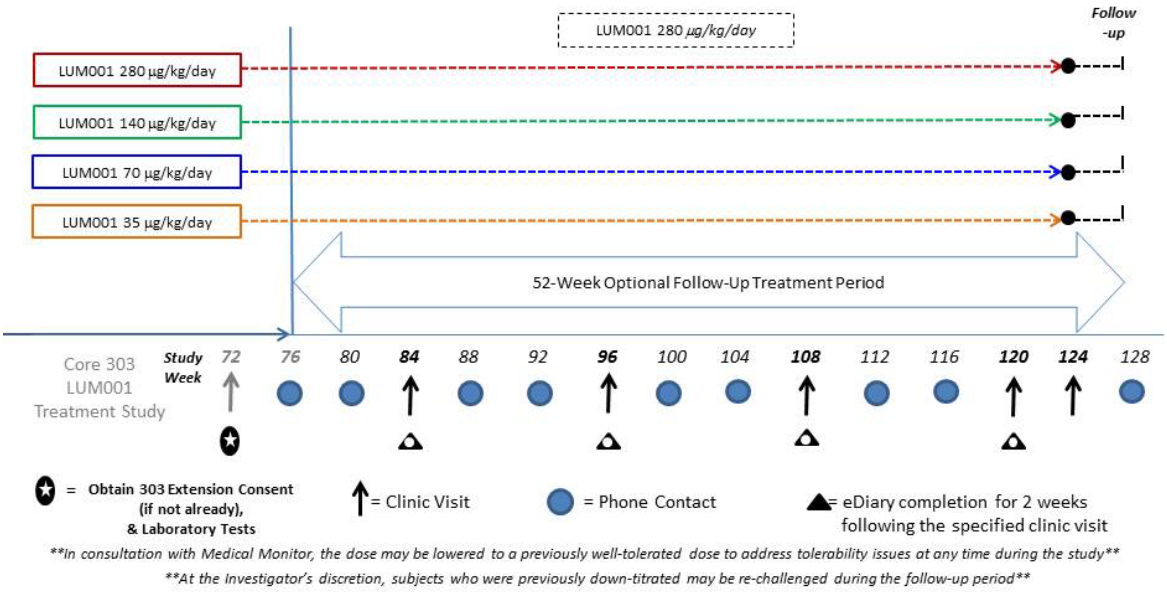
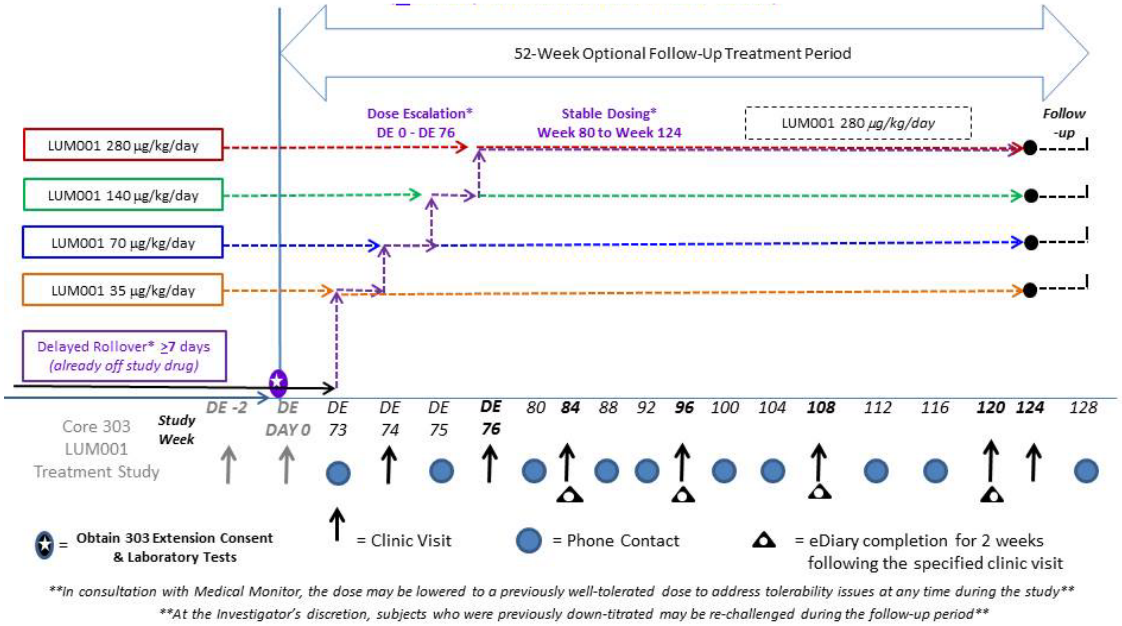


Figure 5: Follow-up Treatment Scheme (interruption in LUM001 dosing ≥7 days)

Applies to the following population:

- Subjects who experienced an interruption in LUM001 dosing ≥7 days between Protocol Amendment 3 and Protocol Amendment 4.



Abbreviations: DE=dose escalation

Figure 6: Re-Entry into Long-term Optional Follow-up Treatment under Protocol Amendment 5

Applies to the following population:

- Subjects who either complete 124 weeks of treatment and/or are considered eligible for Protocol Amendment 5

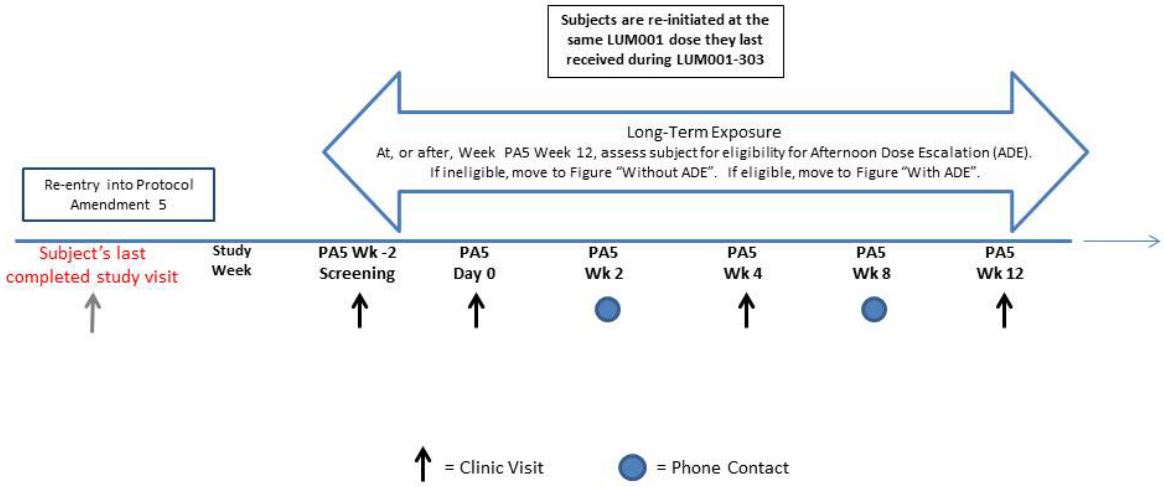
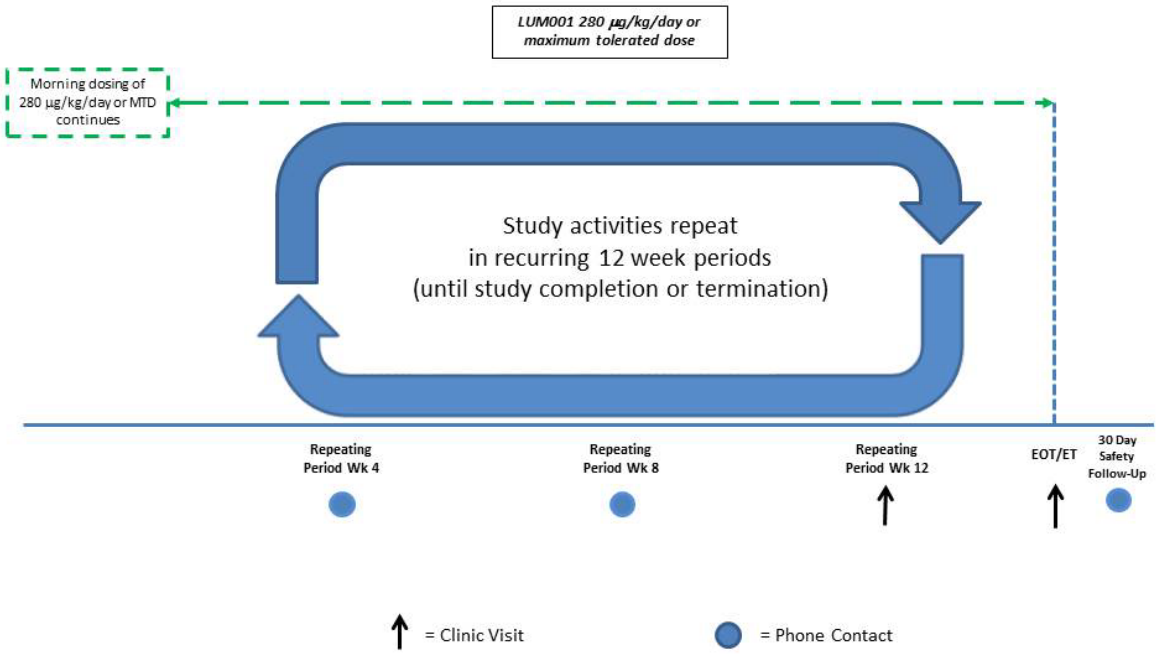


Figure 7: Long-term Optional Follow-up Treatment under Protocol Amendment 5, without afternoon dose escalation

Applies to the following population:

- Subjects deemed ineligible for afternoon dose escalation.

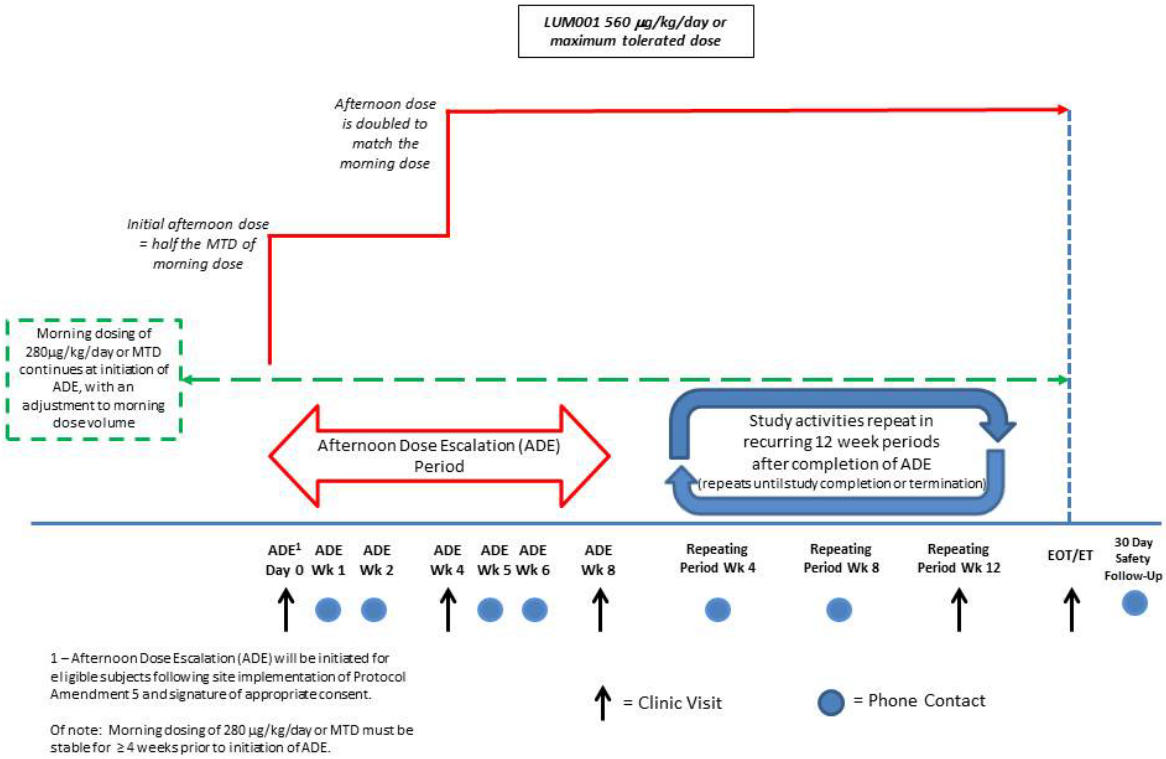


Abbreviations: EOT=end of treatment; ET=early termination; MTD=maximum tolerated dose; Wk=Week

Figure 8: Long-term Optional Follow-up Treatment under Protocol Amendment 5, with afternoon dose escalation

Applies to the following population:

- Subjects whose sBA levels have not normalized and/or whose ItchRO(Obs) score is ≥1.5 and therefore qualify for introduction of afternoon dosing.



Abbreviations: ADE=afternoon dose escalation; MTD=maximum tolerated dose; Wk=Week

5.5.1 Treatment

The Week 13 visit from the LUM001-302 study will also serve as the Baseline Visit for the LUM001-303 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 ≥10% will require a dose adjustment. 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. During the course of the study, it may be necessary to instruct the subject/caregiver to return to the site for an unscheduled dispensation of study drug. 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 will receive a grape-flavored solution containing LUM001 administered orally once a day (QD) or BID using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the dose should be taken approximately at the same time each day for the duration of the treatment period.

5.5.1.1 Dose Escalation Period

For subjects randomized to placebo in the LUM001-302 study, or those who complete the LUM001-302 more than 7 days prior to enrollment into this study, the 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 LUM001-302 study LUM001 doses will remain the same as the dose taken at Week 13 of the LUM001-302 study. Study treatment for each subject will remain blinded and will be prepared by the unblinded central pharmacist according to a specified dose-escalation regimen. This regimen will represent a *real* dose escalation for 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

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

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

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

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

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

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

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

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 period. However, if at any time during the study, a subject experiences intolerance due to gastrointestinal symptoms, the physician investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose.

The maximum daily dose of LUM001 in this period is 280 µg/kg/day, up to a maximum daily dose of 20 mg. Blinded investigators may request dose adjustment for any subject based on an assessment of tolerability and effect on pruritus. Caregivers and age-appropriate 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 subject, 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 during this period.

5.5.1.3 Stable Dosing Period

At the end of the Dose Optimization Period, subjects will continue dosing to complete 72 weeks of cumulative LUM001 exposure in this study.

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

To ensure the safety of subjects participating in this study, a DMC will review serious adverse event data, other key subject safety and study data at specified intervals for the duration of the study.

5.5.1.4 Optional Follow-up Treatment Period

Subjects who are eligible to roll over on to the optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will continue to receive study drug at the dose they were receiving at Week 72 for up to 52 weeks of additional treatment or in the event that a new study opens to enrollment, whichever occurs first.

Subjects who are eligible to roll over into the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level.

Subjects with ≥7 days since last dose of LUM001 will be dose escalated up to 280 µg/kg/day or to the highest tolerated dose starting at 35 µg/kg/day. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001 and allows for subjects to reach 280 µg/kg/day or a highest tolerated dose within a 4-week period. The dose escalation (DE) period will proceed as follows:

5.5.1.5 Follow-up

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

5.5.1.6 Long-term Optional Follow-up Treatment Period

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

- Subjects with normal sBA level AND ItchRO(Obs) score <1.5 will be maintained at the same dose level and will continue morning dosing only.
- Subjects with sBA level above normal AND/OR ItchRO(Obs) score ≥1.5 will start BID dosing (afternoon dose escalation) as follows:
    - The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated in order to limit the amount of propylene glycol in the diluent administered.
    - The afternoon dose will be initiated at half the dose level of the morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be doubled to match the morning dose.
- Subjects with abnormal sBA level AND ItchRO(Obs) score ≥1.5 who had normal sBA level and ItchRO(Obs) score <1.5 prior to dose interruption will remain on the maximum tolerated morning dose (the dose they received last during LUM001-303) for an additional 2 weeks until their efficacy and safety assessments are repeated for eligibility assessment for afternoon dose escalation.
- The sBA value used for determination of afternoon dose escalation eligibility will be the most recent available value collected within the prior 16 weeks. The ItchRO(Obs) score

used for afternoon dose escalation eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 16 weeks.

- The maximum daily dose will be 280 µg/kg BID, ie, 560 µg/kg/day (up to a maximum possible daily dose of 50 mg/day).
- 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 study drug.

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, the subject is considered to have completed the study if they participated in the EOT visit per Scheduled H.

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

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 LUM001-302 study will be used to identify the subject in the LUM001-303 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 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 the long-term optional follow-up period under Protocol Amendment 5 after the subject consents and the investigator has determined the subject meets study entry eligibility criteria per Protocol Amendment 5. However, any subject who consents to Protocol Amendment 5 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. Screen failures are eligible for rescreening on a case by case basis following discussions between the investigator and the medical monitor. Final consent and eligibility determined for subjects rescreened will be collected in the case report form.

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 the LUM001-303 protocol has been locked. Sponsor personnel and CRO personnel will remain blinded to all subjects' dose levels until after the study database for the LUM001-302 study has been locked. Once the treatment assignments for these core studies have been unblinded, access to the unblinded treatment assignments for subjects participating in LUM001-303 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 LUM001-302 treatment 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 serious adverse event (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.

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 study LUM001-302.
4. Females of childbearing potential must have a negative urine pregnancy test [β human chorionic gonadotropin (β-hCG)] at the Baseline Visit.
5. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and for 30 days following the last dose of study drug, must agree to use acceptable contraception during the study. Effective methods of contraception are described in Section 8.6.1.
6. Subjects are expected to have consistent caregiver(s) for the duration of the study.
7. Caregiver (and age appropriate subjects) must be able to read and understand English.
8. Caregivers (and age appropriate subjects) must have access to phone for scheduled calls from study site.
9. 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.
10. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the ItchRO electronic diary software at the outset of the study.

7.2 Exclusion Criteria

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

1. Experienced an adverse event or serious adverse event (SAE) related to the study drug during the LUM001-302 study that led to the discontinuation of the subject from the LUM001-302 study.
2. Any conditions or abnormalities (including laboratory abnormalities) which, in the opinion of the investigator or the medical monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study.
3. History or presence of gallstones or kidney stones.
4. History of non-adherence during the subject's participation in the LUM001-302 study, or earlier in the LUM001-303 study. Non-adherence is defined by dosing compliance[1] of less than 80% in the LUM001-302 study, or earlier in the LUM001-303 study.
5. Unlikely to comply with the study protocol, or unsuitable for any other reason, as judged by the investigator.

Eligible subjects for the 52-week optional follow-up treatment period:

Subjects will be considered eligible for the 52-week optional follow-up treatment period if they have completed the protocol through the Week 72 visit with no safety concerns. Subjects who were discontinued due to safety reasons can be re-challenged if blood tests are back to relatively normal values for this patient population and subject does not meet any of the protocol's stopping rules; the decision will be made by the investigator in consultation with the medical monitor. Subjects who have undergone a surgical disruption of the enterohepatic circulation will not be eligible to enter into the follow-up treatment period. Subjects who were discontinued for other reasons will be considered on an individual basis.

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

Inclusion Criteria:

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

1. The subject has either:
    a. Completed the protocol through either the Week 124 or the ET visit with no major safety concerns.

    OR

    b. Discontinued due to safety reasons judged unrelated to the study drug, and laboratory results have returned to levels acceptable for this patient population or individual and subject does not meet any of the protocol's stopping rules at the time of entry into the follow-up period. The decision will be made by the investigator in consultation with the medical monitor. Subjects who were discontinued for other reasons will be considered on an individual basis.
2. Females of childbearing 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.

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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.

3. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug, must agree and use acceptable contraception during the study.
4. Informed consent and assent (per IRB/EC) as appropriate.
5. 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:

All exclusion criteria mentioned for the original study LUM001-303 apply upon re-entry into the long-term optional follow-up treatment period.

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 LUM001-302 study will also serve as the evaluations for the Baseline Visit for the LUM001-303 extension study. Informed consent (and/or assent when appropriate) for participation in the extension study must be obtained for all participating subjects. 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. Blood will also be collected for PK analysis. The clinician scratch scale will be administered, as will the PedsQL. Females who are of childbearing potential will have a urine pregnancy test and concomitant medications and any adverse events 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 adverse events 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 adverse events 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 72)

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 medical monitor, may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted.

During the stable dosing period, subjects will return to the clinic at Weeks 24, 36, 44, 48, 60 and 72. 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 will be administered and study drug compliance will be assessed. The PedsQL will be completed at Weeks 24, 48 and 72 and the Caregiver Impression of Change (CIC) will be completed at Weeks 48 and 72. Subjects/caregivers will receive follow-up phone calls at Weeks 16, 20, 28, 32 and 40. Concomitant medications and any adverse events 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.

Additional study drug will be supplied at each clinic visit.

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

8.1.5 Week 72

At the Week 72 visit, 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. Blood will also be collected for PK analysis. The clinician scratch scale, PedsQL and CIC will be administered and the degree and severity of xanthomatosis will be evaluated using the clinician xanthoma scale. Females who are of childbearing potential will have a urine pregnancy test and concomitant medications and any adverse events will be recorded. Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected.

8.1.6 Early Termination for Subjects without Participation in the 52-week Optional Follow-up Treatment Period

Any subject who withdraws from the study prior to completion of all treatment period clinic visits up to Week 72 or who is not eligible or willing to roll into the 52-week optional treatment period, should undergo the procedures specified for the Week 72 Visit. 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 bile acids, other cholestasis biochemical markers, fat soluble vitamins) and blood collection for PK analysis. In addition, the following assessments should be completed: the clinician scratch scale, the PedsQL, CIC and the clinician xanthoma scale. Females who are of childbearing potential will have a urine pregnancy test and concomitant medications and any adverse events 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. 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 Optional Follow-up Treatment Period (post Week 72 to Week 124):

Subjects who are eligible to roll over into the follow-up treatment period will continue to receive study drug at the dose they were receiving at Week 72 for up to 52 weeks or until a new study opens to enrollment, whichever occurs first.

Subjects who are eligible to roll over into the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level.

Subjects with ≥7 days since last dose of LUM001 will be dose escalated up to 280 µg/kg/day or to the maximum tolerated dose starting at 35 µg/kg/day. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001 and allows for subjects to reach 280 µg/kg/day or a maximum tolerated dose within a 4-week period. The dose escalation (DE) period will proceed as follows:

- DE Week -2 Clinic Visit: obtain consent, obtain weight, and draw labs.
- DE Day 0 Clinic Visit: investigator evaluates laboratory results, study drug is dispensed and subject begins at 35 µg/kg/day dose level.
- DE Week 73 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated.
- DE Week 74 Clinic Visit: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated.
- DE Week 75 Telephone Contact: subject escalates to 280 µg/kg/day dose, if prior dose level was tolerated.
- DE Week 76 Clinic Visit: subject continues in Follow-up Treatment Period at 280 µg/kg/day, or highest tolerated dose.

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. In addition, the clinician scratch scale will be administered and study drug compliance will be assessed. The PedsQL will be administered at DE Day 0 (for subjects requiring dose escalation) and at Weeks 84, 96, 108, 120, and 124 or ET visit. The Caregiver Impression of Change (CIC) assessment will be completed at Weeks 108, 120, and 124 or ET visit. Subjects/caregivers will receive follow-up phone calls at Weeks 76, 80, 88, 92, 100, 104, 112, 116, and at 30 days following the last dose of study drug. Concomitant medications and any AEs 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 84, 96, 108, and 120. 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 long-term exposure period.

With the exception of the Week 120 and Week 124 visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every visit.

If any subject experiences intolerance, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period. At the investigator's discretion and in consultation with the medical monitor, subjects who were previously down titrated may be re-challenged during the follow-up treatment period.

8.1.8 Long-term Optional Follow-up Treatment Period

Subjects who either complete 124 weeks of treatment and/or are considered eligible for re-entry into Protocol Amendment 5 may be eligible to receive further treatment under Protocol Amendment 5. Subjects who are eligible for re-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 are eligible to enter another LUM001 study,
ii. LUM001 is commercially available, or
iii. The sponsor stops the program or development of this indication.

Refer to Section 5.5 for schematics describing the flow of study visits within this period.

Once Protocol Amendment 5 is implemented at the site, and the subject consents to enter the long-term optional follow-up period, the subject will be re-initiated at the same LUM001 dose they last received during LUM001-303 for approximately 12 weeks. The appropriate amount of study drug will be dispensed at the Protocol Amendment 5 Day 0/baseline visit, but daily dosing will not begin until the following day. Protocol Amendment 5, Study Day 1. At the Week 12 visit, a determination about afternoon dose escalation will be made based on efficacy (ItchRO[Obs] and sBA) and safety assessments. Study activities will proceed as follows:

- Protocol Amendment 5 Screening: Screening evaluations will be performed from Day -14 to Day -1. After obtaining informed consent (and/or assent when appropriate), subjects will undergo a physical examination including body weight, height, and vital signs, and have blood and urine samples taken for clinical laboratory testing. Females who are of childbearing potential will have a urine pregnancy test. The electronic diary will be issued and caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the screening visit. Eligibility criteria will be confirmed prior to the Baseline Visit. Concomitant medications and any adverse events will be recorded.
- Protocol Amendment 5 Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 14-day screening period, consideration may be given to rescreening at a later date. Screen failures are eligible for rescreening on a case by case basis following discussions between the investigator and the medical monitor. Screening procedures should be repeated at that time. Subject data pertaining to screening will be collected after the subject has been rescreened and determined to meet eligibility.
- Protocol Amendment 5 Day 0/Baseline Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. The clinician scratch scale, clinician xanthoma scale, and PedsQL questionnaire will be administered. ItchRO compliance will be assessed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug will be dispensed and concomitant medications and adverse events will be collected.
- Protocol Amendment 5 Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid

panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. Caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the Week 4 visit. The clinician scratch scale and the clinician xanthoma scale will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. The electronic diary will be issued and caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the Week 4 visit. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected.

- Protocol Amendment 5 Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.
- Protocol Amendment 5 Week 12: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. ItchRO compliance will be assessed, and the clinician scratch scale and clinician xanthoma scale will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected. Subjects will be assessed for afternoon dose escalation eligibility. The sBA value used for determination of afternoon dose escalation eligibility will be the most recent available value collected within the prior 12 weeks. The ItchRO(Obs) score used for afternoon dose escalation eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 8 weeks.

Subjects who are eligible for re-entry into the long-term optional follow-up treatment period will be consented and initiate treatment at the same dose level they last received during LUM001-303 (Figure 6). After approximately 12 weeks of treatment, subjects will be evaluated for eligibility for afternoon dose escalation at Week 12. Once a decision about afternoon dose escalation has been made, the subject will then either continue receiving the same dose of LUM001 QD (Figure 7) if they do not meet the criteria for afternoon dose escalation, or initiate the afternoon dose escalation (Figure 8).

Subjects not eligible for afternoon dose escalation (subjects with normal sBA level AND ItchRO(Obs) score <1.5; (Figure 7), will be maintained at the same dose level and will continue morning dosing only. Subjects will have study activities repeated in recurring 12-week periods as follows, until study completion or termination:

- Repeating Period Week 1 (not pictured in Figure 7): subject deemed ineligible for afternoon dose escalation and continues QD dosing.
- Repeating Period Week 4 Telephone Contact: Collection of concomitant medications and any adverse events.
- Repeating Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.
- Repeating Period Week 12 Clinic Visit: Physical exam, body weight and height, vital signs, and blood samples for clinical laboratory testing, including fasting lipid panel. Blood will

also be collected for determination of baseline fat-soluble vitamins. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected. Urine samples for clinical laboratory testing will be collected at every other visit.

- Subjects who do not qualify for afternoon dose escalation may be assessed at a later time point on a case by case basis following discussions between the investigator and medical monitor. Such re-evaluations may only occur at the Week 12 visit of any Repeating Period beginning with RP2 within Schedule F. If, in the course of the afternoon dose escalation re-evaluation, a subject is found to qualify for afternoon dose escalation, then the subject will move into Schedule G as outlined in Section 16.1. During the follow-up treatment period, subjects will return to the clinic every 12 weeks.

Subjects eligible for afternoon dose escalation (ie, who have sBA level above normal AND/OR ItchRO(Obs) score ≥1.5) will begin BID dosing (afternoon dose escalation) as follows:

- On afternoon dose escalation Day 0, morning dosing will continue at 280 µg/kg or the maximum tolerated dose. However, the volume of the morning dose will be reduced by half. Of note: morning dosing must have been stable for ≥4 weeks prior to initiation of afternoon dose escalation.
- On afternoon dose escalation Day 0, the afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose level for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled (ie, at afternoon dose escalation Week 4) to a maximum of 280 µg/kg/day (ie, up to a maximum 560 µg/kg/day or maximum tolerated dose).

The following procedures will occur during the afternoon dose escalation period:

- Afternoon dose escalation Day 0 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected.
- Afternoon dose escalation Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.
- Afternoon dose escalation Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma

sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected.

- Afternoon dose escalation Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.
- Afternoon dose escalation Week 8 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected.

Thereafter, subjects will have study activities repeated in recurring 12-week periods as described within Figure 8, until study completion or termination.

If any subject experiences intolerance, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period. At the investigator's discretion and in consultation with the medical monitor, subjects who were previously down titrated may be re-challenged during the follow-up treatment period. During the long-term optional follow-up treatment period, subjects will return to the clinic every 12 weeks.

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. In addition, the clinician scratch scale will be administered and study drug compliance will be assessed. The PedsQL will be administered at Protocol Amendment 5 Day 0/Baseline visit and every 24 weeks thereafter. Subjects/caregivers will receive follow-up phone calls as outlined in the repeating 12-week periods. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.

Palatability data will be collected at each clinic visit during the long-term optional follow up treatment period (including the EOT/ET visit), with the exception of the afternoon dose escalation visits. Plasma samples will be obtained for LUM001 pharmacokinetics at the afternoon dose escalation Day 0, afternoon dose escalation Week 4, afternoon dose escalation Week 8 visits, and at the 3 scheduled clinic visits following completion of the afternoon dose escalation period.

Twice-daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 consecutive weeks following the Protocol Amendment 5 Week 4 visit and at every clinic visit within the repeating 12-week periods. 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 long-term follow-up period.

With the exception of the EOT/ET visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every 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 following assessments as outlined for the EOT/ET visit: physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory samples, including fasting lipid panel and pharmacokinetic sampling of LUM001. Blood will also be collected for determination of fat-soluble vitamins and AFP. Female subjects who are of child-bearing potential will have a urine pregnancy test. Study drug compliance will be assessed. Concomitant medications and adverse events will be collected. The clinician-administered pruritus scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, clinician xanthoma scale, and palatability questionnaire will also be completed.

8.1.9 End of Treatment or Early Termination

Any subject who completes or withdraws from the study should undergo all procedures specified for the EOT/ET visit (see Schedule H). The following assessments are to be completed at the EOT/ET visit: safety and clinical laboratory evaluations, including determination of serum bile acids, lipid panel, other cholestasis biochemical markers, fat soluble vitamins and AFP. Female subjects who are of childbearing potential will have a urine pregnancy test. Study drug compliance will be assessed. Concomitant medications and adverse events will be collected. In addition, the following assessments should be completed: the clinician scratch scale, clinician xanthoma scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, as defined for Early Termination (see Schedule of Procedures, Section 16.1).

8.1.10 Safety Follow-up 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 adverse events noted during this phone call will be recorded.

8.2 Genetic Testing

JAGGED1 and *NOTCH2* mutations are predictive of ALGS. For subjects who do not have complete documentation of a *JAGGED1* or *NOTCH2* mutation, blood samples for genotyping will be collected at the screening visit. The appropriate genetic counseling in accordance with local laws will be provided to any subject and their legal caregivers at a study visit following the

receipt of results of genetic testing, at no cost to the subject. Subjects for whom prior genotyping was performed may need to have an optional repeat analysis performed if the original information collected at screening was insufficient for complete documentation of the diagnosis of ALGS including the type of mutation recorded. For those participants for which the type of mutation cannot be documented, genetic testing may be conducted and the results recorded.

8.3 Physical Examination, Weight and Height, Vital Signs

A physician investigator will conduct a physical examination on each subject at Baseline, at Weeks 24, 36, 48, 60 and 72 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 52-week optional and long-term optional follow-up treatment periods, physical examinations will be conducted as outlined in the Schedule of Procedures in Section 16.1.

Body weight, height, and vital signs, including body temperature, blood pressure, respiration and pulse, will be determined at every study clinic visit. A change in weight that is ≥10% of the weight used to calculate the subject's current LUM001 dose will result in a dose adjustment. This dose adjustment will be made by the central pharmacy when they make the subject's next LUM001 preparation.

8.4 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 11.4.3 regarding laboratory abnormalities.

8.5 Pruritus and Quality of Life Assessments

8.5.1 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 a core LUM001 treatment 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. The electronic diary will be returned to the study centre during the Week 12 visit.

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 centre 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. For subjects who enter into the 52-week optional and long-term optional follow-up treatment periods, daily completion of the diary will occur as outlined in the Schedule of Procedures in Section 16.1.

8.5.2 Clinician Scratch Scale

A clinician's assessment of pruritus will be made by the principle 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 and 72). For subjects who enter into the 52-week optional and long-term optional follow-up treatment periods, the clinician scratch scale will be administered as outlined in the Schedule of Procedures in Section 16.1.

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.

8.5.3 Clinician Xanthoma Scale

A clinician's assessment of xanthomatosis will be made by the principle 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 and 72.

For subjects who enter into the 52-week optional and long-term optional follow-up treatment periods, the clinician's assessment of xanthomatosis will be administered as outlined in the Schedule of Procedures in Section 16.1.

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 & Whitington, 2002).

8.5.4 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL™ is a questionnaire that will be administered to subjects and or caregivers at the Baseline (Day 0) and Weeks 24, 48 and 72 clinical visits using the age-appropriate PedsQL module (Section 16.6). For subjects who enter the 52-week optional follow-up treatment period, the PedsQL will also be administered at Weeks 84, 96, 108, 120, and 124. For subjects with interruptions in LUM001 dosing of ≥7 days, the PedsQL will also be administered at DE Day 0. The PedsQL is a validated, modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescent (Varni, Seid, & Kurtin, 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 and 72 clinical visits using the age-appropriate module, see Section 16.6. For subjects who enter into the 52 week optional and long-term optional follow-up treatment periods, the multidimensional fatigue and family impact questionnaires will be administered as outlined in the Schedule of Procedures in Section 16.1. Age at the LUM001-302 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.

8.5.5 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 Week 48 and Week 72 visit, see Section 16.1. For subjects who enter into the 52 week optional follow-up treatment periods, the CIC will be administered as outlined in the Schedule of Procedures in Section 16.1.

8.5.6 Palatability

A palatability questionnaire (see Section 16.9) will be completed by the subject and/or caregiver (dependent on age) at clinic visits at time points as outlined in the Schedule of Procedures in Section 16.1.

8.6 Restriction on the Lifestyle of Subjects

8.6.1 Contraception Requirements

Sexually active female subjects of childbearing potential must continue to use acceptable contraception with their partners, or refrain from sexual activity, from the time of enrollment throughout the study period and for 30 days following the last dose of study drug.

If hormonal contraceptives are used, they should be administered according to the package insert.

Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of the IP.

Acceptable methods of contraception are:

a. Hormonal contraceptives (eg, oral contraceptive pill, depot, patch, intramuscular implant or injection, or vaginal ring), stabilized for at least 30 days if first use, plus condoms; and/or
b. Barrier method, eg, (i) condom (male or female) or (ii) diaphragm, with spermicide; or
c. Intrauterine device (IUD); or
d. A sexual partner who is surgically sterilized.

Male Contraception:

Contraception is required for all sexually-active male subjects and their partners. All male subjects agree not to donate sperm, and to use 1 of the following approved methods of contraception until 30 days following study discharge:

a. Male condom with spermicide
b. Intrauterine device with spermicide (use by female sexual partner)
c. Female condom with spermicide (use by female sexual partner)
d. Contraceptive sponge with spermicide (use by female sexual partner)
e. Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide) (use by female sexual partner)
f. Oral, implantable, transdermal, or injectable hormonal contraceptive (use by female sexual partner).

8.6.2 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 5 mL, or 0.25 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 compositions of LUM001 study drug 1.0 mL, 0.5 mL, and 0.25 mL oral solutions are described, respectively, in Table 5, Table 6, and Table 7.

Table 5: Composition of LUM001 1.0 mL Oral Solution

Component	Function	Quantity per 1.0 mL
LUM001	Active Ingredient	up to 50.0 mg
Propylene Glycol	Co-solvent	250.0 mg
Sucralose	Sweetener	7.5 mg
Grape Flavoring Agent	Taste Masking Agent	5.0 mg
Water	Vehicle	q.s. to 1.0 mL

q.s = quantity sufficient

Table 6: Composition of LUM001 0.5 mL Oral Solution

Component	Function	Quantity per 0.5 mL
LUM001	Active Ingredient	up to 25.0 mg
Propylene Glycol	Co-solvent	125.0 mg
Sucralose	Sweetener	3.75 mg
Grape Flavoring Agent	Taste Masking Agent	2.5 mg
Water	Vehicle	q.s. to 0.5 mL

q.s = quantity sufficient

Table 7: Composition of LUM001 0.25 mL Oral Solution

Component	Function	Quantity per 0.25 mL
LUM001	Active Ingredient	up to 12.5 mg
Propylene Glycol	Co-solvent	62.5 mg
Sucralose	Sweetener	1.875 mg
Grape Flavoring Agent	Taste Masking Agent	1.25 mg
Water	Vehicle	q.s. to 0.25 mL

q.s = quantity sufficient

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 that is ≥10% of the weight used to calculate the subject's current LUM001 dose will result in a dose adjustment. This dose adjustment will be made by the central pharmacy when they make the subject's next LUM001 preparation. The dose may also be down-titrated, at the investigator's discretion and in consultation with the medical monitor, for subjects experiencing intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) to a given dose. If the subject is on twice daily dosing regimen, dose reduction should first be attempted with the afternoon dose. Subjects who were previously down-titrated may be re-challenged during the long-term exposure period.

Study drug (LUM001 with diluent) will be prepared by a central pharmacy based on the subject's last recorded weight from the LUM001-302 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.

Subjects will receive a grape-flavored solution containing LUM001, administered orally QD or BID using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the doses should be taken approximately at the same time each day for the duration of the treatment period. See Section 5.5.1 for information regarding dosing during the treatment periods, respectively.

Study Drug Administration under Protocol Amendment 5:

QD Dosing Regimen

For QD dosing, the required dose will be delivered in 0.5 mL volume for subjects who weigh less than 10 kg and in 1.0 mL for subjects who weigh 10 kg or more.

BID Dosing Regimen

For BID dosing, the required dose is delivered in half the dosing volume: 0.25 mL BID for subjects who weigh less than 10 kg and 0.50 mL BID for subjects who weigh 10 kg or more.

For subjects weighing less than 10 kg at study re-entry, once a weight of 10 kg is reached while in the study, the subject will be moved from 0.5 mL total daily dosing volume (0.25 mL BID) to 1.0 mL total daily dosing volume (0.50 mL BID).

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 and, for subjects who receive a BID regimen, when they ate dinner (evening meal).

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 of LUM001-303 entry until completing the final required assessment while enrolled in LUM001-303).

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. All modifications to concomitant medications must be carefully documented in the relevant case report forms

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 adverse events and the potential relationship to study drug it is important to note that due to their liver disease many patients 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 CTCAE Grade 3 treatment emergent laboratory abnormality, with the exception of the specific rules outlined below (Section 10.5) dosing can be suspended or continued as per the investigator's judgment and following discussion with the medical monitor. If suspended, the investigator and 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 re-test should be conducted by the central laboratory but may also be conducted at a local laboratory on an as needed basis. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). The results from the retest must be available prior to the next scheduled clinic visit or phone follow-up.

Stopping Rule Guidance: Subject dosing must be suspended until the retest results are available. If any of the stopping criteria described below (refer to Section 10.5.2.2 and Section 10.5.2.5) are confirmed, the investigator in consultation with the medical monitor or appropriately qualified designee, 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 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), in particular whether the event should be considered as an important medical event, ie, an event that would have met one of the other seriousness criteria in the absence of appropriate medical interventions.

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 LUM001-302 study.

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 ideally within 14 days of the initial collection.

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)	3 mg increase over historical baseline level

[1] Historical baseline values are those reported at baseline of the LUM001-302 study.

Frequency of Repeat Measurements: Subjects with confirmed a 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 ALT or total bilirubin level, as described above, appropriate additional diagnostic investigations should be considered by the investigator, in consultation with 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 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 -302 study.

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 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 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 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; later attempts to escalate the dose are permitted. If the subject is on a twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose. This decision should be made in consultation with the 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 serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonisation (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 adverse events to allow the sponsor, or designee, to identify potential study-related, study drug- or dose-related adverse events.

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 DMC will be notified of any SAE as specified in the DMC 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 adverse event (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 adverse event does not 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 adverse event caused by the study drug.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. 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 adverse event is any adverse event 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 will be collected as medical history unless the AE started within 30 days of last dose. Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. 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 centre'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 informed consent form 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 Common Terminology Criteria for Adverse Events (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 adverse event, 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 study 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.

- Serious adverse event (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 and 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 database lock.

Approximately 18 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 preceding LUM001-302 study. Because this is an extension study for LUM001-302, 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.

Special attention will be paid to change from baseline for those on placebo at baseline and during the first 12 weeks for those on active study drug at baseline and during the stable dosing period for all subjects at all dose levels.

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

12.1 Sample Size Considerations

Approximately 18 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 LUM001-302 study, 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 Demographic and Baseline Characteristics

12.2.2.1 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 when entering the study as well as after the dose optimization period.

The number and percentage of subjects receiving study drug following the protocol specified dose escalation procedure and stable dosing regimen will be tabulated by treatment group. 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. Duration of the follow-up period will be tabulated.

12.2.2.2 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 descriptively for each treatment group and overall.

Baseline for this study will be considered Day 0.

Medical history information will be presented in listings.

12.2.3 Efficacy Analyses

12.2.3.1 Efficacy Variables

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

- Fasting serum bile acid level.

Secondary evaluations will be the mean change from Baseline (Day 0) to Week 48 and the change from Week 12 to Week 48 in:

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

Change from Week 12 to Week 48 in fasting serum bile acid will also be examined.

Efficacy variables will be presented for each time point at which they are measured (see Section 16.1). Additional exploration, including behavior during the dose escalation and optimization phases, will be specified in the SAP.

12.2.3.2 Primary Efficacy Analysis

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

The difference between treatment groups in change from baseline to Week 48 in the serum bile acids will be evaluated using an ANCOVA model with treatment and baseline serum bile acid as a covariate.

12.2.3.3 Secondary, Exploratory and Other Efficacy 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 and will be compared between treatment groups using the chi-square test.

P-values from the secondary and exploratory efficacy analyses will be considered nominal.

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

12.2.4 Safety Analyses

Safety analyses will be performed on the Safety Population.

12.2.4.1 Safety Assessments

The following assessments will be used to monitor safety:

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

Safety variables will be presented for each time point at which they are measured (see Section 16.1).

12.2.5 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 and by treatment group for the safety population. Individual subject listings will be prepared for all safety data.

12.2.5.1 Adverse Events

Frequencies (number and percentage) of subjects with one or more treatment emergent AEs will be summarized by treatment group, 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 and stable dose 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.

12.2.5.2 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 using descriptive statistics by study visit and treatment group. Change 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, 60, 72, and at additional time points during the 52-week optional follow-up treatment and long-term optional treatment periods using methods to be specified in the SAP.

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.

12.2.5.3 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 using descriptive statistics by clinical visit and treatment group. 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. In general this will be the Day 0 visit.

12.2.5.4 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.

12.2.5.5 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.

12.2.5.6 Serum Alpha-fetoprotein

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

12.2.6 Palatability Analyses

Palatability data will be collected at each clinic visit in the long-term optional follow up treatment period, with the exception of the afternoon dose escalation visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age). Assessments over time will be evaluated.

12.2.7 Interim Analyses

There may be one or more interim analysis (IA) conducted during the conduct of the study in order to guide the future of the development program. The IA may result in an interim report or publication.

12.2.8 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. 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 study.

13.2 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 site's investigator(s) for the study and other possible participants, their professional background (eg, investigator, coordinator, and technician) and their role in the study. The investigator should ensure that all appropriately qualified persons to whom he/she has delegated study duties are recorded on a sponsor-approved Delegation of Site Responsibilities Form.

13.3 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.

13.4 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 centre 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 adverse events occurring at the study centre and other adverse event 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.

13.5 Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms 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 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.

14.2 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 study. 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.

14.3 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 study'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.

14.4 Study Documentation and Storage

Source documents are original documents, data, and records from which the subject's case report form 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 case report forms must be maintained and be readily available.

The investigator and the study centre 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 case report forms (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 centre, 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 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 study (eg, case report forms 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 case report forms. 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.

14.6 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.

14.7 Compensation for Injury

The sponsor maintains appropriate insurance coverage for clinical studies 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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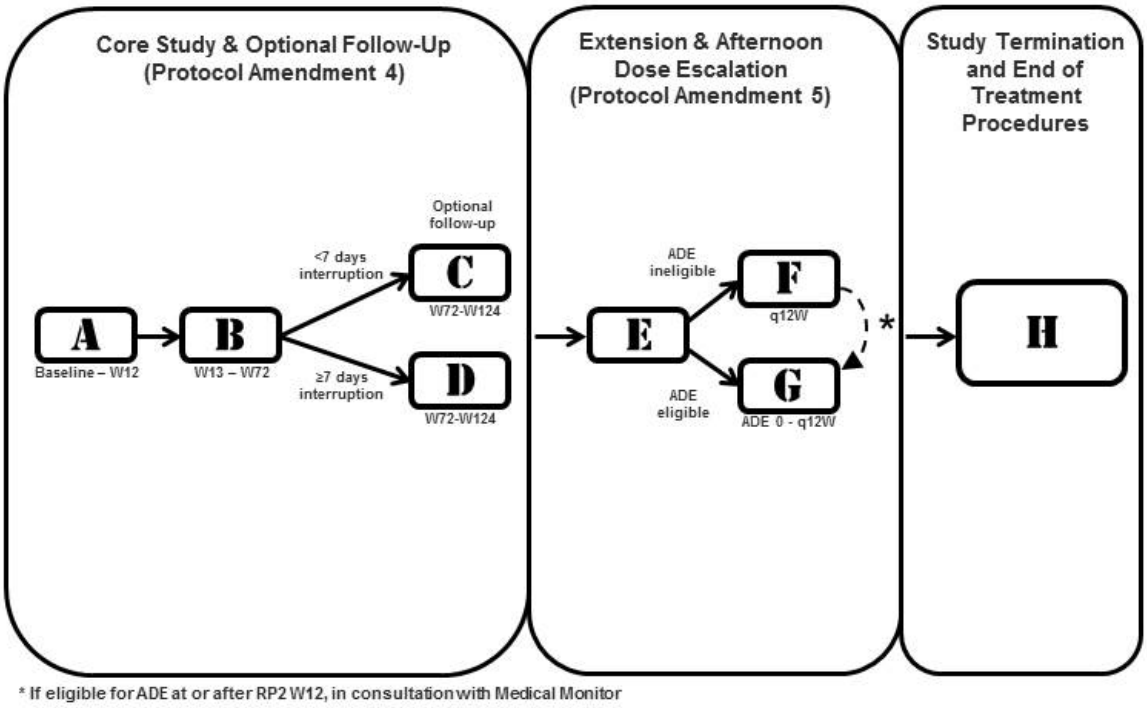
16 APPENDICES

16.1 Schedule of Procedures

Overall Scheme and Corresponding Schedule of Procedures

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

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



16.1.1 Schedule of Procedures A – (Baseline - Week 12)

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

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

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

[i] Subjects should be dosed for at least 7 days at each dose level.

	Clinic Visit
	Phone Contact

16.1.2 Schedule of Procedures B - Stable Dosing: Week 16 – Week 72 / Study Termination

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

Study Period	Treatment Period (continued) Stable Dosing										Study Termination[h]	Follow-Up[i]
Study Week	16[f]	20	24	28	32	36	40	44	48	60	Week 72 (or Early Term[g])	30 days after final dose[h]
Study Day	112	140	168	196	224	252	280	308	336	420	504	
Window (in days)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±5)

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] 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.
[c] Subjects are required to fast at least 4 hr (only water permitted prior to collection).
[d] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[e] Subjects must be available to receive a phone call from study staff.
[f] 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.
[g] Subjects who withdraw early should complete all evaluations at this visit.
[h] Subjects who roll directly into the Week 76 visit will not have a follow-up visit until after Week 124.
[i] Follow-up visit is only for subjects who exit the study at the Study Termination Visit.
[j] At the indicated visits during the treatment period, oxalate will be part of the urinalysis
[k] During the stable dosing period, twice daily completion of the eDiary (ItchRO) for 4 consecutive weeks will be required following the Week 24 and Week 44 clinic visits.

	Clinic Visit
	Phone Contact

16.1.3 Schedule of Procedures C – 52-Week Optional Follow-Up Treatment Period for those subjects < 7 days from last dose of LUM001 (Protocol Amendment 4)

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

16.1.3 Schedule of Procedures C – 52-Week Optional Follow-Up Treatment Period for those subjects < 7 days from last dose of LUM001 (Protocol Amendment 4)

Study Period	52-week FU Treatment Period												Study Termination[j]	Follow-Up[k]
Study Week	76	80	84	88	92	96	100	104	108	112	116	120	124[i]	30 days after final dose
Study Day	553	560	588	616	644	672	700	728	756	336	812	840	868	
Window (in days)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±14)	(±5)

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

	Clinic Visit
	Phone Contact

16.1.4 Schedule of Procedure D – 52-Week Optional Follow-up Treatment Period: DE-2 –Week 176 for Subjects with ≥7days from last dose of LUM001 (Protocol Amendment 4). Includes Evaluation of Eligibility for Afternoon Dose Escalation Dosing Regimen

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

16.1.4 Schedule of Procedure D – 52-Week Optional Follow-up Treatment Period: DE-2 –Week 176 for Subjects with ≥7days from last dose of LUM001 (Protocol Amendment 4). Includes Evaluation of Eligibility for Afternoon Dose Escalation Dosing Regimen

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

16.1.4 Schedule of Procedure D – 52-Week Optional Follow-up Treatment Period: DE-2 –Week 176 for Subjects with ≥7days from last dose of LUM001 (Protocol Amendment 4). Includes Evaluation of Eligibility for Afternoon Dose Escalation Dosing Regimen

Study Period	Treatment Period (continued)																	Study Termination[k]	Follow-Up[l]
	Follow-up Treatment Period Dose Escalation (DE)						Follow-up Treatment												
FTP Study Week	DE -2	DE Day 0	DE 73	DE 74	DE 75	DE 76	80	84	88	92	96	100	104	108	112	116	120	Week 124 (or ET[k])	30 days after final dose
Study Day	-14	0	511[a]	518[a]	525[a]	532[a]	560[a]	588[a]	616[a]	644[a]	672[a]	700[a]	728[a]	756[a]	784[a]	812[a]	840[a]	868[a]	
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±14)	(±5)

[a] Calculation of Study Day includes subject's participation through the first 72 weeks.
[b] Once necessary approvals are received for Protocol Amendment 5 and associated consent/assent are available, site will consent/assent subject for Protocol Amendment 5 at the next clinic visit.
[c] Depending on the outcome of afternoon dose escalation eligibility assessment, the subject will move into either Schedule of Procedures For G. Note: It is possible that subject will not necessarily complete up through Week 124 before they move to Schedule of Procedures F or G.
[d] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[e] See Section 16.2 for detailed list of laboratory analytes.
[f] Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
[g] Blood samples must be drawn before administration of vitamin supplementation.
[h] Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation type in support of the diagnosis of ALGS.
[i] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[j] Subjects must be available to receive a phone call from study staff.
[k] Subjects who withdraw early should complete all evaluations at this visit.
[l] Follow-up visit is only for subjects who exit the study at the Study Termination Visit.
[m] At indicated visits during treatment period, oxalate will be part of the UA.
[n] During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 74, Week 84, Week 96, Week 108, and Week 120 visits .

Clinic Visit
Phone Contact

16.1.5 Schedule of Procedure E – Long-term Optional Follow-up Treatment Period: Protocol Amendment 5 Screening (Week -2) and on LUM001. Includes Evaluation of Eligibility for Afternoon Dose Escalation Dosing Regimen at Protocol Amendment 5, Week 12

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

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

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

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

Study Period	Treatment Period (continued)					
	Long-Term Optional Follow-up Treatment Period					
FTP Study Week	Screening PA5 (Week -2)	PA 5 Day 0/Baseline	PA 5 Week 2	PA 5 Week 4	PA 5 Week 8	PA 5 Week 12
Study Day	-14	0	518[a]	532[a]	546[a]	560[a]
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)

Clinic Visit
Phone Contact

16.1.6 Schedule of Procedure F-G: Re-entry under Protocol Amendment 5

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

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

a Blood pressure (BP), heart rate (HR), temperature, respiration rate.
b See Section 16.2 for detailed list of laboratory analytes.
c Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
d Blood samples must be drawn before administration of vitamin supplementation.
e Females of childbearing potential, result must be reviewed prior to dispensing study drug.
f Study drug may be dispensed at unscheduled clinic visits.
g Subjects must be available to receive a phone call from study staff.
h Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
i At indicated visits during treatment period, oxalate will be part of the UA.
j Sample will be drawn at every other clinic visit starting with RP1 Week 12.
k Starting at Week 12 RP2 subjects should be re-assessed for ADE eligibility

Clinic Visit
Phone Contact

Schedule of Procedures G – Extension of Long-term Optional Follow-up Treatment Period, for subjects eligible for afternoon dose escalation

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

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

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

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 hr (only water permitted) prior to collection.
d Blood samples must be drawn before administration of vitamin supplementation.
e Pharmacokinetic sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose escalation period.
f Females of childbearing potential, result must be reviewed prior to dispensing study drug.
g Study drug may be dispensed at unscheduled clinic visits.
h Subjects must be available to receive a phone call from study staff.
i Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
j At indicated visits during treatment period, oxalate will be part of the UA.
k Sample will be drawn at every other clinic visit starting with RP1 Week 12.

Clinic Visit
Phone Contact

16.1.7 Schedule of Procedures H – Study Termination and End of Treatment Procedures

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

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

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

Clinic Visit
Phone Contact

16.2 List of Laboratory Analytes

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

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

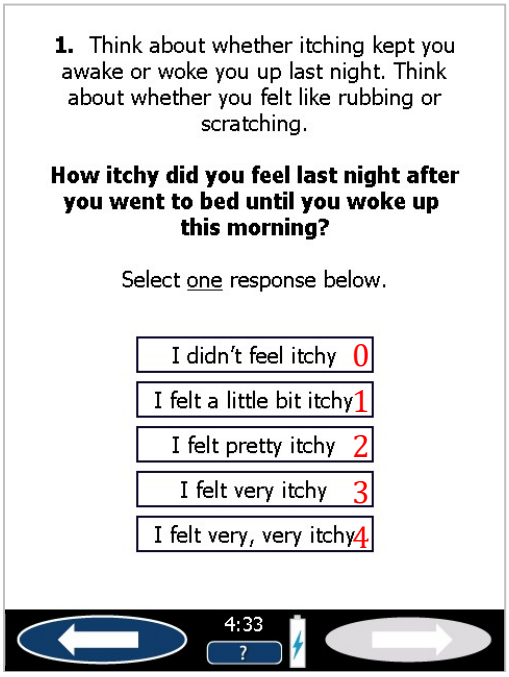
16.3 Itch Reported Outcome Instrument (ItchRO™)

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.

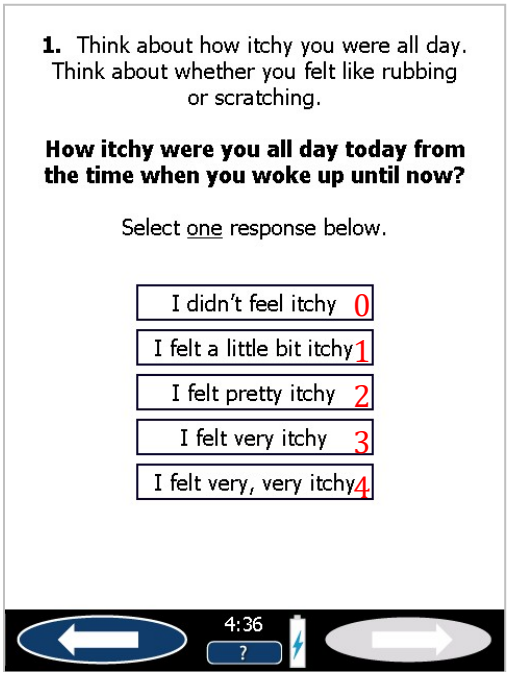
16.3.1 Patient Itch Reported Outcome Instrument, ItchRO(Pt)™

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.

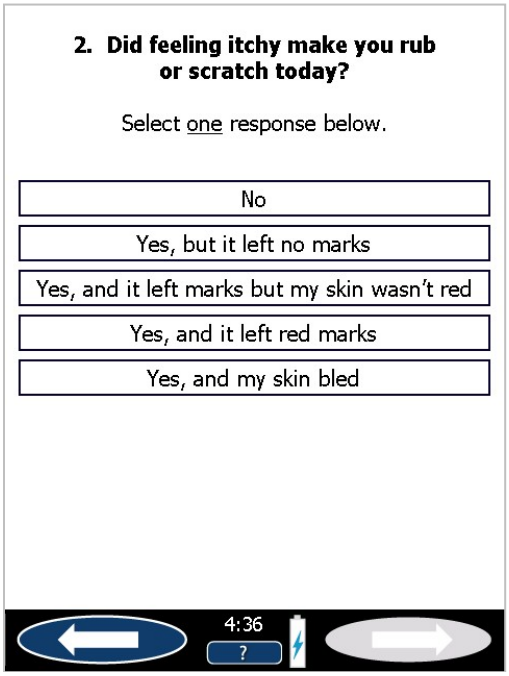


If the patient selects "I didn't feel itchy at all" the morning diary is complete, if not the following screens will be shown on the eDiary:

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.

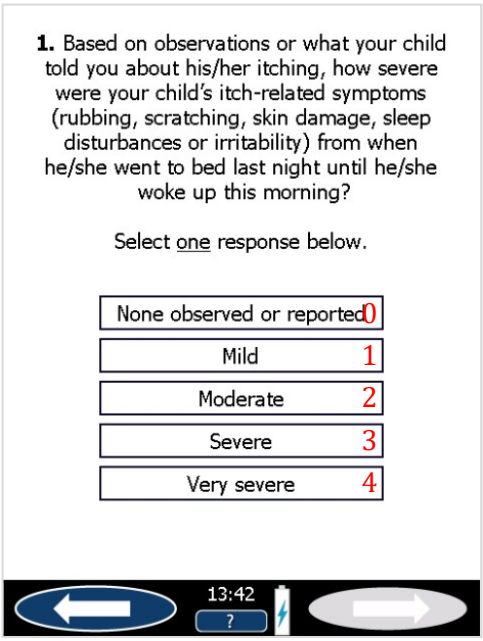


If the patient selects "I didn't feel itchy" the evening diary is complete, if not the following screen will be shown on the eDiary:

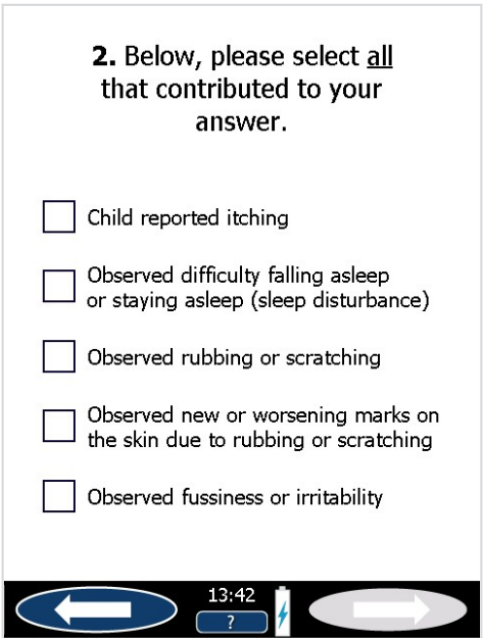


16.3.2 Observer Itch Reported Outcome Instrument, ItchRO(Obs)™

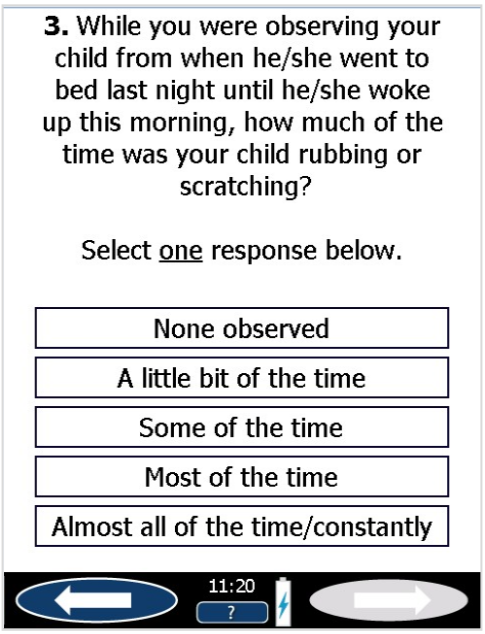
A screen shot from the ItchRO(Obs) morning report is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) morning report score is 0 and the maximum score is 4.



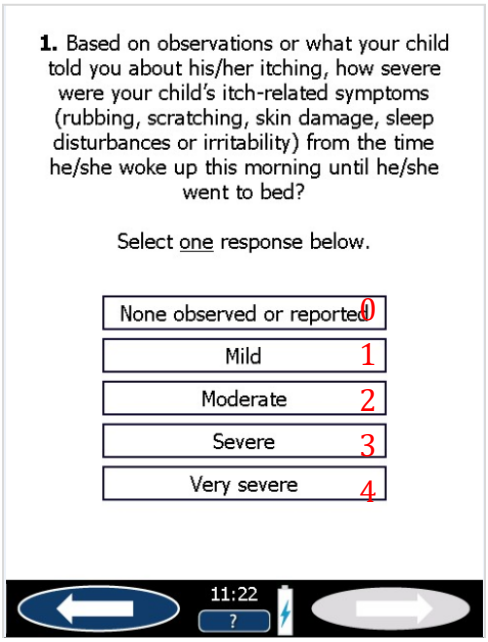
If the caregiver selects "None observed or reported" the morning diary is complete, if not the following screen will be shown on the eDiary:



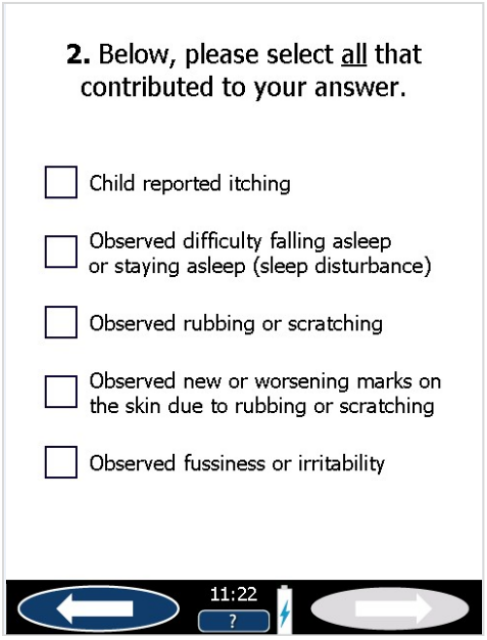
All caregivers will also be required to answer the following question on the ItchRO(Obs) morning report:



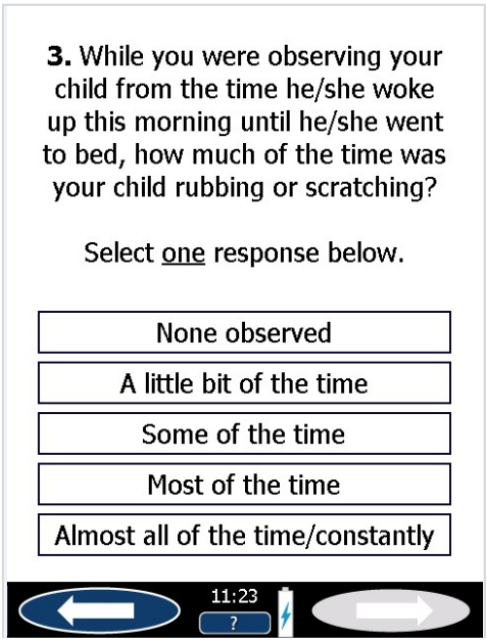
A screen shot from the ItchRO(Obs) evening report is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) evening report score is 0 and the maximum score is 4.



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 & 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 & 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. Subjects will continue to fill out the same questionnaire used at baseline for continuity of data collection, regardless of subsequent birthdays after the baseline visit.

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

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

ID#_____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Infant Scales

English (United Kingdom)

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. Regurgitating (spitting up) after eating	0	1	2	3	4
3. Difficulty breathing	0	1	2	3	4
4. Having an upset 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 diarrhoea	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 making a fuss 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 making a fuss 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 13-24 months)

ID#_____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Infant Scales

English (United Kingdom)

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. Regurgitating (spitting up) after eating	0	1	2	3	4
3. Difficulty breathing	0	1	2	3	4
4. Having an upset 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 diarrhoea	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 making a fuss 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 making a fuss 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-Infant-(13-24Months) - United Kingdom/English - Version of 31 Jul 13 - Mapi.
ID7346 / PedsQL-Infant-(13-24Months)_AU1.0_eng-GB.doc

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)

ID#_____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 – UK English

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 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 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 and exercise	0	1	2	3	4
4. Lifting heavy things	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 aches or pains	0	1	2	3	4
8. Feeling tired	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	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Having 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 children 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 nursery or day care***

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

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

ID#_____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 English (United Kingdom)

PARENT REPORT for YOUNG CHILDREN (ages 5-7)

INSTRUCTIONS

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 100 metres	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activities 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 aches or pains	0	1	2	3	4
8. Feeling tired	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	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 on with other children	0	1	2	3	4
2. Other children 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 being 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

16.6.5 Parent Report for Children (ages 8-12)

ID#_____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 English (United Kingdom)

PARENT REPORT for CHILDREN (ages 8-12)

INSTRUCTIONS

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 100 metres	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activities 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 aches or pains	0	1	2	3	4
8. Feeling tired	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	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 on with other children	0	1	2	3	4
2. Other children 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 being 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 Parent Report for Teenagers (ages 13-18)

ID#_____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 English (United Kingdom)

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

INSTRUCTIONS

On the following page is a list of things that might be a problem for **your teenager**.
Please tell us **how much of a problem** each one has been for **your teenager** 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 teenager had with …*

PHYSICAL FUNCTIONING ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. Walking 100 metres	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activities 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 aches or pains	0	1	2	3	4
8. Feeling tired	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	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 on with other teenagers	0	1	2	3	4
2. Other teenagers not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teenagers	0	1	2	3	4
4. Not being able to do things that other teenagers his or her age can do	0	1	2	3	4
5. Keeping up with other teenagers	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

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

ID# _____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 – UK English

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 click your fingers?	☺	😐	☹

Ask the child to demonstrate clicking 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 lift big things?	0	2	4
5. Is it hard for you to have a bath or shower?	0	2	4
6. Is it hard for you to help in the home (like picking up your toys)?	0	2	4
7. Do you have aches and pains? (*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 angry?	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. Do you have trouble getting on with other children?	0	2	4
2. Do other children say they do not want to play with you?	0	2	4
3. Do other children tease you?	0	2	4
4. Can other children do things you cannot do?	0	2	4
5. Is it hard for you to keep up when you play with other children?	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. Do you have trouble keeping up with schoolwork?	0	2	4
4. Do you miss school because of not feeling well?	0	2	4
5. Do you miss school to go to the doctor or hospital?	0	2	4

How much of a problem is this for you?

Not at all

Sometimes

A lot

PedsQL 4.0 – (5-7)
f:\institute\ustadapt\project\pg2161\etude2161\final_versions\april\pedsql4-core-yo-uk-baseline.doc-20/04/2004
APRIL 2004

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

ID# _____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 – UK English

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 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 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 a couple of streets (about 100 metres)	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 activities or exercise	0	1	2	3	4
4. It is hard for me to lift heavy things	0	1	2	3	4
5. It is hard for me to have 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 have aches and pains	0	1	2	3	4
8. I feel tired	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	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 ON WITH OTHERS ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting on with other children	0	1	2	3	4
2. Other children do not want to be my friend	0	1	2	3	4
3. Other children tease me	0	1	2	3	4
4. I cannot do things that other children my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other children	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

PedsQL 4.0 – (8-12)
f:\institut\cultadap\project\pg2161\etude2161\final_versions\format_jmvaml\uk\pedsql4-core-c-uk.doc
APRIL 2004

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

ID# _____

Date:_____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 – UK English

TEENAGER 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 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 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 a couple of streets (about 100 metres)	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 activities or exercise	0	1	2	3	4
4. It is hard for me to lift heavy things	0	1	2	3	4
5. It is hard for me to have 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 have aches and pains	0	1	2	3	4
8. I feel tired	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	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 ON WITH OTHERS ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting on with other teenagers	0	1	2	3	4
2. Other teenagers do not want to be my friend	0	1	2	3	4
3. Other teenagers tease me	0	1	2	3	4
4. I cannot do things that other teenagers my age can do	0	1	2	3	4
5. It is hard to keep up with other teenagers my age	0	1	2	3	4

ABOUT SCHOOL / COLLEGE ***(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 school / college work	0	1	2	3	4
4. I miss school / college because of not feeling well	0	1	2	3	4
5. I miss school / college to go to the doctor or hospital	0	1	2	3	4

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version - English (UK)

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

MENTAL 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 Young Children (ages 5-7)

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version - English (UK)

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

MENTAL 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 Children (ages 8-12)

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version - English (UK)

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

MENTAL 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 Parent Report for Teenagers (ages 13-18)

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version - English (UK)

PARENT REPORT for **TEENAGERS** (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

MENTAL 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

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

ID# _____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version - UK English

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 feeling 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.

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

How much of a problem is this for you?

Not at all

Sometimes

A lot

16.6.15 Multidimensional Fatigue Scale Child Report (ages 8-12)

ID# _____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version - UK English

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

16.6.16 Multidimensional Fatigue Scale Teen Report (ages 13-18)

ID# _____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version - UK English

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

16.6.17 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

*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 and Week 72 visit. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the CIC will be completed as outline in the Schedule of Procedures in Section 16.1.

The questionnaire is designed for self-administration and uses a 7-point scale in which 1 designates the best outcome and 7 designate 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)

16.7.1 Caregiver Global Therapeutic Benefit (CGTB)

Caregiver Global Therapeutic Benefit (CGTB)

The Caregiver Global Therapeutic Benefit (CGTB) questionnaire is designed to assess the caregiver's perception of the treatment benefits on the subject's itching compared to the side effects experienced with study drug. The CGTB will be completed by all caregivers at the Week 13 visit.

The questionnaire is designed for self-administration and uses a 5-point scale in which 1 designates the best outcome and 5 designates the worst outcome.

CGTB

Considering all aspects of your child's treatment, do you feel that the benefits of this treatment outweigh the side-effects?

- ☐ Definitely (1)
- ☐ Somewhat (2)
- ☐ About the same (3)
- ☐ Maybe not (4)
- ☐ Definitely not (5)

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 Palatability Questionnaire

LUM001 304 Palatability Questionnaire
Caregiver Only

Clinic Site Staff to capture the patient body weight: _____ and target dose (µg/kg):_____

Questionnaire to be completed by:

- Caregiver only for non-collaborating child (generally <4 years of age)

1. On the basis of reaction / facial expression of your child, do you think that the taste of the medication is acceptable?
   Mark an X on the box below which best describes your answer.

Yes	Not sure	No
		

2. Do you sometimes have problems in giving the medication to your child because he/she refuses to take it because of the taste?
   Mark an X on the box below which best describes your answer.

Yes	Not sure	No

3. Based on its taste in the mouth, how easy or difficult it is for your child to take this medicine every day to treat the disease condition?
   Mark an X on the box below which best describes your answer.

Very Easy	Easy	Neither Easy or Difficult	Difficult	Very Difficult
				

Version 1.0, 01 Dec 2016

LUM001 304 Palatability Questionnaire

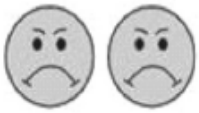
Child Only or Child and Caregiver

Clinic Site Staff to capture the patient body weight: _____ and target dose (µg/kg):_____

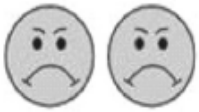
Questionnaire to be completed by:

- Child only if >8 years age or
- Caregiver & collaborating child if 4 to 8 years of age

1. How does the medication taste immediately when you swallow it?
   Mark an X on the box below which best describes your answer.

Very Good	Good	Nor good or bad	Bad	Very Bad
				

2. How does the medication taste approximately 5 min after swallowing it?
   Mark an X on the box below which best describes your answer.

Very Good	Good	Nor good or bad	Bad	Very Bad
				

3. Based on the taste of this medication and how you felt in the mouth, would you take this medication every day to treat the disease condition?
   Mark an X on the box below which best describes your answer.

Yes	Not sure	No
		

Version 1.0, 01 Dec 2016

Caregiver Global Therapeutic Benefit (CGTB)

The Caregiver Global Therapeutic Benefit (CGTB) questionnaire is designed to assess the caregiver's perception of the treatment benefits on the subject's itching compared to the side effects experienced with study drug. The CGTB will be completed by all caregivers at the Week 13 visit.

The questionnaire is designed for self-administration and uses a 5-point scale in which 1 designates the best outcome and 5 designates the worst outcome.

CGTB

Considering all aspects of your child's treatment, do you feel that the benefits of this treatment outweigh the side-effects?

- ☐ Definitely (1)
- ☐ Somewhat (2)
- ☐ About the same (3)
- ☐ Maybe not (4)
- ☐ Definitely not (5)

16.10 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	13 Sep 2013	
Amendment 1	05 Nov 2013	Global
Amendment 2	28 Feb 2014	Global
Amendment 3	17 Sep 2014	Global
Amendment 4	04 Nov 2015	Global
Amendment 5	16 May 2017	Global

16.10.1 Protocol Amendment 5 Summary of Changes

Protocol Number: LUM001-303

Protocol Title: A MULTICENTRE 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: 16 May 2017

The LUM001-303 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 are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.

This amendment also describes the way in which eligible subjects who had previously discontinued from the study may re-enter and receive study treatment in the long-term optional follow-up treatment period (after Week 124).

Additional objectives for the long-term optional follow-up treatment period have been added, as follows:

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

Lastly, this amendment updates the contraceptive requirements to align with the *Heads of Medicine Clinical Trials Facilitation Group Recommendations Related to Contraception and Pregnancy Testing* (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf).

The following changes have been made to the Protocol Amendment 4 (4 November 2015). 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
Cover page, Sponsor; Title Page, Sponsor; Sponsor Signature Page, Sponsor; Protocol Signature page, Sponsor	**Changed from:** Lumena Pharmaceuticals, Inc. 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**
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:** **Thomas Jaecklin, MD, MSc** Shire Zahlerweg 10 6300 Zug Switzerland **Phone: +41(0) 79 850 77 18** **Email: thomas.jaecklin@shire.com**
Emergency Contact Information	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	Description of Change
Synopsis, Objectives; Section 3, Study Objectives	Objectives of ~~Optional Follow-up Treatment Period (after Week 72)~~ **the long-term optional follow-up treatment period for subjects who are eligible for Protocol Amendment 5**: • To offer eligible subjects in the LUM001-303 study continued **study** treatment at ~~Week 72~~ until the first of the following occurs: ~~(i) up to 52 weeks of additional treatment (Week 100) or (ii) in the event that a new study opens to enrollment~~ **(i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.** • **To explore twice a day (BID) dosing regimen and higher daily dosing of LUM001.** • **To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma.** • **To assess palatability of the LUM001 formulation.**
Synopsis, Study Design; Section 5.1, Study Design	The study is divided into ~~4~~ **5** parts: a dose escalation period, a dose optimization period, a stable dosing period, ~~and~~ an optional 52-week optional follow-up treatment period, **and a long-term optional follow-up treatment period** for eligible subjects who choose to stay on treatment with LUM001. **A minimum period of 7 days must elapse between increases in dose.** Dose Optimization Period Study drug dose **level** will be increased or decreased in a double-blind manner. Increases in dose will be based on effect on ~~pruritus~~ **efficacy (sBA and ItchRO[Obs] score) and safety assessments.** **Long-term optional Follow Up Treatment Period (Protocol Amendment 5):** **The long-term optional follow up treatment period is for eligible subjects who choose to stay on treatment with LUM001. During this long-term optional follow-up treatment period, subjects may have their dose of LUM001 increased to a maximum of 560 µg/kg/day (280 µg/kg BID), based on efficacy (sBA and ItchRO score) and safety assessments. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occur: i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.**
Synopsis, Inclusion Criteria; Section 7.1, Inclusion Criteria	5. **Males and females of child-bearing potential who are** sexually active ~~females~~, **or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug,** must ~~be prepared to~~ **agree and** use ~~an effective method (≤ 1% failure rate) of~~ **acceptable** contraception during the **study**. Effective methods of contraception are ~~considered to be~~ **described in Section 8.6.1.** ~~a. Hormonal (e.g., contraceptive pill, patch, intramuscular implant or injection); or~~ ~~b. Barrier method, e.g., (a) condom (male or female) or (b) diaphragm, with spermicide; or~~ ~~c. Intrauterine device (IUD).~~ 6. **Subjects are expected to have consistent caregiver(s) for the duration of the study.** 7. ~~Subjects above the age of assent and caregivers and children~~ **Caregiver (and age appropriate subjects)** must be able to read and understand English.

Section	Description of Change
Synopsis, Exclusion Criteria; Section 7.2, Exclusion Criteria	4. History of non-adherence during the subject's participation in the LUM001-302 ~~protocol~~ **study**, **or earlier in the LUM001-303 study**. Non-adherence is defined by dosing compliance of less than 80% in the LUM001-302 ~~protocol~~ **study or earlier in the LUM001-303 study.** **Eligible subjects for the 52-week optional follow-up treatment period:** Subjects will be considered eligible for the **52-week** optional ~~52-week~~ follow-up treatment period if they have completed the protocol through the Week 72 visit with no safety concerns. Subjects who were discontinued due to safety reasons can be re challenged if blood tests ~~do not satisfy~~ **are back to relatively normal values for this patient population and the subject does not meet any of** the protocol's stopping rules; the decision will be made by the investigator in consultation with the sponsor medical monitor. … **Protocol Amendment 5: Eligible Subjects for the long-term optional follow-up treatment period:** **Inclusion Criteria:** **Subjects will be considered eligible for the long-term optional follow-up treatment period if they meet the following criteria:** **1. The subject has either:** **o Completed the protocol through the Week 124 or the ET visit with no major safety concerns.** **OR** **o Discontinued due to safety reasons judged unrelated to the study drug, and laboratory results have returned to levels acceptable for this patient population or individual and subject does not meet any of the protocol's stopping rules at the time of entry into the follow-up period. The decision will be made by the investigator in consultation with the sponsor medical monitor. Subjects who were discontinued for other reasons will be considered on an individual basis.** **2. Females of childbearing potential must have a negative urine or serum pregnancy test (β-hCG) at the time of entry into the long-term optional follow-up treatment period.** **3. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug, must agree and use acceptable contraception during the study.** **4. Informed consent and assent (per IRB/EC) as appropriate.** **5. 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:** **All exclusion criteria mentioned for the original study LUM001-303 apply upon re-entry into the long-term optional follow-up period.**
Synopsis, Treatment Groups	**After Week 124 and/or implementation of this amendment, whichever occurs first, subjects will be considered for a long-term optional follow-up treatment period, if eligible, receiving up to 560 µg/kg/day (given as twice daily doses of 280 µg/kg), or to a maximum possible daily dose of 50 mg/day.**

Synopsis, Study Drug Dosage and Administration; Section 10.1, Study Drug Administration	**Subjects will receive a grape-flavored solution containing LUM001, administered orally once a day (QD) or BID using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the doses should be taken approximately at the same time each day for the duration of the treatment period.** ~~Subjects who weight 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 over a 124-week treatment period. 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.~~

Synopsis, Long-term Optional Follow-up Treatment Period; Section 5.5.1.6, Long-term Optional Follow-up Treatment Period	**Long-term Optional Follow-up Treatment Period:**
	Upon completion of the 52-week optional follow-up treatment period and/or implementation of this amendment, whichever occurs first, subjects will be assessed by the investigator to determine their willingness and eligibility for entry into the long-term optional follow-up treatment period. All subjects will be re-initiated at the same LUM001 dose they last received during LUM001-303. The appropriate amount of study drug will be dispensed at the Protocol Amendment 5 Day 0/baseline visit, but daily dosing will not begin until the following day, Protocol Amendment 5, Study Day 1. Eligibility assessment for afternoon dose escalation will then occur in all subjects based on efficacy (ItchRO[Obs] and sBA) and safety assessments following approximately 12 weeks of dose re-initiation as follows:
	• **Subjects with normal sBA level AND ItchRO(Obs) score <1.5 will be maintained at the same dose level and will continue morning dosing only.**
	• **Subjects with sBA level above normal AND/OR ItchRO(Obs) score ≥1.5 will start BID dosing (afternoon dose escalation) as follows:**
	  ○ **The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated in order to limit the amount of propylene glycol in the diluent administered.**
	  ○ **The afternoon dose will be initiated at half the dose level of the morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be doubled to match the morning dose.**
	• **Subjects with abnormal sBA level AND ItchRO(Obs) score ≥1.5 who had normal sBA level and ItchRO(Obs) score <1.5 prior to dose interruption will remain on the maximum tolerated morning dose (the dose they received last during LUM001-303) for an additional 2 weeks until their efficacy and safety assessments are repeated for eligibility assessment for afternoon dose escalation.**
	• **The sBA value used for determination of afternoon dose escalation eligibility will be the most recent available value collected within the prior 16 weeks. The ItchRO(Obs) score used for afternoon dose escalation eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 16 weeks.**
	• **The maximum daily dose will be 280 µg/kg BID, ie, 560 µg/kg/day (up to a maximum possible daily dose of 50 mg/day).**

Section	Description of Change
Synopsis, Study Drug Dosage and Administration; Section 10.1, Study Drug Administration	• **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 study drug.** **<u>Study Drug Administration under Protocol Amendment 5</u>** **QD Dosing Regimen** **For QD dosing, the required dose will be delivered in 0.5 mL volume for subjects who weigh less than 10 kg and in 1.0 mL for subjects who weigh 10 kg or more.** **BID Dosing Regimen** **For BID dosing, the required dose is delivered in half the dosing volume: 0.25 mL BID for subjects who weigh less than 10 kg and 0.50 mL BID for subjects who weigh 10 kg or more.** **For subjects weighing less than 10 kg at study re-entry, once a weight of 10 kg is reached while in the study, the subject will be moved from 0.5 mL maximum daily dosing volume (0.25 mL BID) to 1.0 mL maximum daily dosing volume (0.50 mL BID).**

Section	Description of Change
Synopsis, Rationale for Dose and Schedule Selection; Section 4.5, Rationale for Dose and Schedule of Administration	**The study drug may be adjusted if there is a change of ≥10% in body weight since the screening visit or if there is a change of ≥10% in weight since the last weight based medication adjustment to maintain the target dose.** **Under Protocol Amendment 5, an afternoon dose is introduced for eligible subjects in the long-term optional follow-up treatment period. LUM001 doses will be escalated over a period of 4-8 weeks up to a maximum dose of 280 µg/kg BID (or maximum tolerated dose). The afternoon dose is only initiated and escalated in subjects with elevated sBA and/or ItchRO(Obs) ≥1.5 on the maximum (or maximum tolerated) morning dose.** **If a subject experiences intolerance (such as gastrointestinal symptoms like diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator, in consultation with the sponsor medical monitor, may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose.** **This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001. Twice daily dosing is used in this study based on the findings of a healthy volunteers study in adult males (Study SHP625-101), which demonstrated that bile acid levels in feces increase with escalating doses and twice-daily regimen of LUM001 (up to 100 mg QD and 50 mg BID). In this study, subjects who were randomized to LUM001 treatment, received 1 of 4 doses of LUM001 (10, 20, 50, 100 mg) during 7 days. No titration was used in this study. There was a dose-dependent increase in total fecal BA excretion. In addition, BID dosing (ie, 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (ie, 100 mg QD). It is therefore hypothesized that twice-daily dosing has the potential to allow for more complete target engagement throughout the day at the level of the distal ileum.** **The higher dosing level is also supported by favorable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (post-natal day [PND] 21 through PND63). As expected for a drug intentionally designed to be minimally absorbed, systemic LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies in adult rats. No adverse effects were observed on postnatal growth and development of offspring at the highest doses tested (200 mg/kg/day in males, 1000 mg/kg/day in females). This study was initiated in juvenile animals at PND21, which from a whole animal development perspective, is typically representative of a 2-year old child. However, given the fact that LUM001 is a minimally absorbed drug, of particular importance is the age at which the GI tract is considered functionally mature. In humans this is considered to have occurred by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs during the first 3 weeks of life. Therefore, results from this study can be used to support the dosing levels proposed here for children 12 months of age and older.**

Synopsis, Study Visit Schedule and Procedures; Section 5.5, Overall Study Duration and Follow-up	Clarified titles of study design schemes, updated figures and updated text to reflect the addition of the extended follow-up treatment period beyond what was previously described in Protocol Amendment 4. ~~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 60-week stable dosing period. Subjects who complete 72 weeks of treatment may be eligible to receive treatment for up to 52 weeks during the optional follow-up treatment period. Planned participation for each subject enrolled in the optional follow-up treatment study is 128 weeks, inclusive of a 4-week follow-up phone call. .~~
Synopsis, Study Visit Schedule and Procedures; Section 8.1.7, Optional Follow-up Treatment Period	With the exception of the Week 120 and Week 124 visit ~~(Study Termination), additional study drug will be supplied at each clinic visit during the follow-up treatment period,~~ **additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every visit.** **If any subject experiences intolerance, the investigator, in consultation with the sponsor medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period. At the investigator's discretion and in consultation with the sponsor medical monitor, subjects who were previously down titrated may be re-challenged during the follow-up treatment period.**
Synopsis, Study Visit Schedule and Procedures; Section 8.1.8, Long-term Optional Follow-up Treatment Period	**<u>Long-term Optional Follow-up Treatment Period</u>** **Subjects who either complete 124 weeks of treatment and/or are considered eligible for Protocol Amendment 5 may be eligible to receive treatment under Protocol Amendment 5. Subjects who are eligible for re-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 are eligible to enter another LUM001 study,** **ii. LUM001 is commercially available, or** **iii. The sponsor stops the program or development of this indication.** **Once Protocol Amendment 5 is implemented at the site, and the subject consents to enter the long-term optional follow-up period, the subject will be re-initiated at the same LUM001 dose they last received during LUM001-303 for approximately 12 weeks. The appropriate amount of study drug will be dispensed at the Protocol Amendment 5 Day 0/baseline visit, but daily dosing will not begin until the following day, Protocol Amendment 5, Study Day 1. At the Week 12 visit, a determination about afternoon dose escalation will be made based on efficacy (ItchRO[Obs] and sBA) and safety assessments. Study activities will proceed as follows:** • **Protocol Amendment 5 Screening: Screening evaluations will be performed from Day -14 to Day -1. After obtaining informed consent (and/or assent when appropriate), subjects will undergo a physical examination including body weight, height, and vital signs, and have blood and urine samples taken for clinical laboratory testing. Females who are of childbearing potential will have a urine pregnancy test. The electronic diary will be issued and caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the screening visit. Eligibility criteria will be confirmed prior to the Baseline Visit. Concomitant medications and any adverse events will be recorded.** • **Protocol Amendment 5 Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 14-day screening period, consideration may be given to rescreening at a later date. Screen failures are eligible for rescreening on a case by case basis following**

	discussions between the investigator and the medical monitor. Screening procedures should be repeated at that time. Subject data pertaining to screening will be collected after the subject has been rescreened and determined to meet eligibility. • **Protocol Amendment 5 Day 0/Baseline Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. The clinician scratch scale, clinician xanthoma scale, and PedsQL questionnaire will be administered. ItchRO compliance will be assessed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug will be dispensed and concomitant medications and adverse events will be collected.** • **Protocol Amendment 5 Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. Caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the Week 4 visit. The clinician scratch scale and the clinician xanthoma scale will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. The electronic diary will be issued and caregivers and age-appropriate subjects will be asked to complete the diary twice daily during the 2 weeks following the Week 4 visit. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected.** • **Protocol Amendment 5 Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.** • **Protocol Amendment 5 Week 12: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel and cholestasis biomarkers. Blood will also be collected for determination of baseline fat-soluble vitamins. ItchRO compliance will be assessed, and the clinician scratch scale and clinician xanthoma scale will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected. Subjects will be assessed for afternoon dose escalation eligibility. The sBA value used for determination of afternoon dose escalation eligibility will be the most recent available value collected within the prior 12 weeks. The ItchRO(Obs) score used for afternoon dose escalation eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 8 weeks.** **Subjects who are eligible for re-entry into the long-term optional follow-up treatment period will be consented and initiate treatment at the same dose level they last received during LUM001-303 (Synopsis Figure 4). After approximately 12 weeks of treatment, subjects will be evaluated for eligibility for afternoon dose escalation at Week 12. Once a decision about afternoon dose escalation has been made, the subject will then either:** - **continue receiving the same dose of LUM001 QD (Synopsis Figure 5) if they do not meet the criteria for afternoon dose escalation OR** - **initiate the afternoon dose escalation (Synopsis Figure 6).**

	Subjects not eligible for ADE (subjects with normal sBA level AND ItchRO(Obs) score <1.5; Synopsis Figure 5), will be maintained at the same dose level and will continue morning dosing only. Subjects will have study activities repeated in repeating 12-week periods as follows, until study completion or termination: • **Repeating Period Week 1 (not pictured in Synopsis Figure 5): subject deemed ineligible for afternoon dose escalation and continues QD dosing.** • **Repeating Period Week 4 Telephone Contact: Collection of concomitant medications and any adverse events.** • **Repeating Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.** • **Repeating Period Week 12 Clinic Visit: Physical exam, body weight and height, vital signs, and blood samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of baseline fat-soluble vitamins. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected. Urine samples for clinical laboratory testing will be collected at every other visit.** • **Subjects who do not qualify for afternoon dose escalation may be assessed at a later time point on a case by case basis following discussions between the investigator and medical monitor. Such re-evaluations may only occur at the Week 12 visit of any Repeating Period (RP) beginning with RP2 within Schedule F. If, in the course of the afternoon dose escalation re-evaluation, a subject is found to qualify for afternoon dose escalation, then the subject will move into Schedule G as outlined in Section 16.1. During the follow-up treatment period, subjects will return to the clinic every 12 weeks.** **If the subject is eligible for afternoon dose escalation,(ie, who has sBA level above normal AND/OR ItchRO(Obs) score ≥1.5), the subject will begin BID dosing (afternoon dose escalation) as follows:** • **On afternoon dose escalation Day 0, morning dosing will continue at 280 µg/kg or the maximum tolerated dose. However, the volume of the morning dose will be reduced by half. Of note: Morning dosing must have been stable for ≥4 weeks prior to initiation of afternoon dose escalation.** • **On afternoon dose escalation Day 0, the afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose level for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled (ie, at afternoon dose escalation Week 4) to a maximum of 280 µg/kg/day (ie, up to a maximum 560 µg/kg/day or maximum tolerated dose).** **The following procedures will occur during the ADE period:** • **Afternoon dose escalation Day 0 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects**

	who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected. • **Afternoon dose escalation Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.** • **Afternoon dose escalation Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and any adverse events will be collected.** • **Afternoon dose escalation Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.** • **Afternoon dose escalation Week 8 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and any adverse events will be collected.** **Thereafter, subjects will have study activities repeated in recurring 12-week periods as described within Synopsis Figure 6, until study completion or termination.** **If any subject experiences intolerance, the investigator, in consultation with the sponsor medical monitor, may lower the dose at any time during the entire follow-up treatment period. If the subject is on a twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose. At the investigator's discretion, and in consultation with the sponsor medical monitor, subjects who were previously down titrated may be re-challenged during the follow-up treatment period. During the long-term optional Follow-Up Treatment Period, subjects will return to the clinic every 12 weeks.** **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. In addition, the clinician scratch scale will be administered and study drug compliance will be assessed. The PedsQL will be administered at Protocol Amendment 5 Day 0/Baseline visit and every 24 weeks thereafter.** **Subjects/caregivers will receive follow-up phone calls as outlined in the repeating 12 week periods. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.** **Palatability data will be collected at each clinic visit during the long-term optional follow up treatment period (including the EOT/ET visit), with the exception of the afternoon dose escalation visits. Plasma samples will be obtained for LUM001**

Section	Description of Change
	pharmacokinetics at the afternoon dose escalation Day 0, afternoon dose escalation Week 4, afternoon dose escalation Week 8 visits, and at the 3 scheduled clinic visits following completion of the afternoon dose escalation period. **Twice-daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 consecutive weeks following the Protocol Amendment 5 Week 4 visit and at every clinic visit within the repeating 12 week periods. 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 long-term follow-up period.** **With the exception of the EOT/ET visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every 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 following assessments as outlined for the EOT/ET visit: physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory samples, including fasting lipid panel and pharmacokinetic sampling of LUM001. Blood will also be collected for determination of fat-soluble vitamins and AFP. Female subjects who are of child-bearing potential will have a urine pregnancy test. Study drug compliance will be assessed. Concomitant medications and adverse events will be collected. The clinician-administered pruritus scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, clinician xanthoma scale, and palatability questionnaire will also be completed.** **At completion of the long-term optional follow-up treatment period or early discontinuation, 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 terminated early. Concomitant medications and adverse events noted during this phone call will be recorded.**
Synopsis, Drug Level Evaluations	**Additionally, for subjects in which afternoon dose escalation is initiated, samples will also be drawn at 4 hours following the morning dose on afternoon dose escalation Day 0, afternoon dose escalation Week 4, afternoon dose escalation Week 8, and at the 3 scheduled clinic visits following completion of the afternoon dose escalation treatment period.**
Synopsis, Safety and Tolerability	**Alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma, will be measured every 6 months throughout the remainder of the study.**
Synopsis, Palatability Data; Section 12.2.6, Palatability Analyses Section 16.9, Palatability Questionnaire	**Palatability data will be collected at each clinic visit in the long-term follow-up treatment period, with the exception of the afternoon dose escalation visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age). Assessments over time will be evaluated.** Added palatability questionnaire
Section 8.5.6, Palatability	**A palatability questionnaire (see Section 16.9) will be completed by the subject and/or caregiver (dependent on age) at clinic visits at time points as outlined in the Schedule of Procedure in Section 16.1.**

Section	Description of Change
Synopsis, Statistical Considerations; Section 12.2.7, Interim Analyses	**Interim Analysis** **There may be one or more interim analysis (IA) conducted during the conduct of the study in order to guide the future of the development program. The IA may result in an interim report or publication.**
Section 4.5, Rationale for Dose and Schedule of Administration	*Updated Sample Daily Exposure (mg/day) in Pediatric Subjects table.* ~~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 (~17µg/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.~~
Section 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~~ **an** 8 ~~weeks of~~ **week** dose optimization ~~and~~ **period**, a 60-week stable dosing period~~**Subjects who complete 72 weeks of treatment may be eligible to receive treatment for up to 52 weeks during the follow-up treatment period (see Figure 4 and Figure 5). Planned participation for each subject enrolled in the optional follow-up treatment study is 128 weeks, inclusive of a 4-week follow-up phone call (see Figure 3).~~ **, an optional 52-week follow-up treatment period, and a long-term optional follow-up treatment period. A safety follow-up phone call will be made by the study site 30 days after the last dose of study drug.**
Section 5.5.1, Treatment	Study drug will be dispensed to subjects/caregivers ~~at the study site~~. **During the course of the study, it may be necessary to instruct the subject/caregiver to return to the site~~.~~ for an unscheduled dispensation of study drug.** ~~Subjects who weigh 10 kg or more at screening will receive a 1.0 mL grape-flavored solution per day containing LUM001 Subjects who weigh less than 10 kg at screening will receive a 0.5 mL grape-flavored solution per day containing LUM001. The daily volume administered will not change during the course of the study. Dosing will occur over a 48-week treatment period. 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.~~ **Subjects will receive a grape-flavored solution containing LUM001 administered orally once a day (QD) or twice a day (BID) using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the dose should be taken approximately at the same time each day for the duration of the treatment period.**
Long-term Exposure Period	Moved text describing individual study procedures to be performed during this period to Section 8.1.7.
Section 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**

Section	Description of Change
	optional follow-up treatment period, the subject is considered to have completed the study if they participated in the EOT visit per Scheduled H.
Section 6.1, Enrollment	**Subjects will be enrolled in the 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 the long-term optional follow-up period under Protocol Amendment 5 after the subject consents and the investigator has determined the subject meets study entry eligibility criteria per Protocol Amendment 5. However, any subject who consents to Protocol Amendment 5 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. Screen failures are eligible for rescreening on a case by case basis following discussions between the investigator and the medical monitor. Final consent and eligibility determined for subjects rescreened will be collected in the case report form.**
Section 8.1.9, End of Treatment or Early Termination	**Any subject who completes or withdraws from the study should undergo all procedures specified for the EOT/ET visit (see Schedule H). The following assessments are to be completed at the EOT/ET visit: safety and clinical laboratory evaluations, including determination of serum bile acids, lipid panel, other cholestasis biochemical markers, fat soluble vitamins and AFP. Female subjects who are of childbearing potential will have a urine pregnancy test. Study drug compliance will be assessed. Concomitant medications and adverse events will be collected. In addition, the following assessments should be completed: the clinician scratch scale, clinician xanthoma scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, as defined for Early Termination (see Schedule of Procedures, Section 16.1).**
Section 8.1.10, Safety Follow-up Period	Text moved from former Section 8.1.7. **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 adverse events noted during this phone call will be recorded.**
Section 8.3, Physical Examination, Weight and Height, Vital Signs; Section 8.5.1, Itch Reported Outcome (ItchRO™); Section 8.5.2, Clinician Scratch Scale; Section 8.5.3, Clinician Xanthoma Scale; Section 8.5.4, Pediatric Quality of Life Inventory (PedsQL); Section 8.5.5, Caregiver Impression of Change	Edited text to indicate all assessments will be performed as outlined in the Schedule of Procedures in Section 16.1.

Section	Description of Change
Section 8.6.1, Contraception Requirements	Sexually active female subjects of childbearing potential must continue to use **acceptable** contraception with their partners, or refrain from sexual activity, from the time of enrollment~~until the end of the study~~, **throughout** the study **period and for 30 days following the last dose of the study drug.** **If hormonal contraceptives are used they should be administered according to the package insert.** **Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of the IP.** **Acceptable methods of contraception are:** 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.~~ **a. Hormonal contraceptives (eg, oral contraceptive pill, depot, patch, intramuscular implant or injection, or vaginal ring), stabilized for at least 30 days if first use, plus condoms; and/or** **b. Barrier method, eg, (i) condom (male or female) or (ii) diaphragm, with spermicide; or** **c. Intrauterine device (IUD); or** **d. A sexual partner who is surgically sterilized.** **Male Contraception:** **Contraception is required for all sexually-active male subjects and their partners. All male subjects agree not to donate sperm, and to use 1 of the following approved methods of contraception until 30 days following study discharge:** **a. Male condom with spermicide** **b. Intrauterine device with spermicide (use by female sexual partner)** **c. Female condom with spermicide (use by female sexual partner)** **d. Contraceptive sponge with spermicide (use by female sexual partner)** **e. Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide) (use by female sexual partner)** **f. Oral, implantable, transdermal, or injectable hormonal contraceptive (use by female sexual partner).**
Section 8.6.2, Fasting Requirements	On these visit days study drug should be administered as usual (1 mL, **5 mL**, or 0.~~5 mL~~**25** qAM, ac), in the morning 30 minutes before breakfast.
Section 9.1.1, LUM001	Added new composition of LUM001 1.0 mL, 0.5 mL, and 0.25 mL Oral Solution tables.
Section 10.1, Study Drug Administration	**The dose may also be down-titrated, at the investigator's discretion and in consultation with the sponsor medical monitor, for subjects experiencing intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) to a given dose. If the subject is on twice daily dosing regimen, dose reduction should first be attempted with the afternoon dose. Subjects who were previously down-titrated may be re-challenged during the long-term exposure period.** **…** ~~Each subject dose for subjects who weigh 10 kg or more will be~~ **Subjects will receive a grape-flavored solution containing LUM001**, administered orally ~~as a 1.0 mL solution containing study drug (LUM001)~~ **QD or BID** using the syringe provided. ~~Each subject dose for subjects who weigh less than 10 kg will be administered orally as a 0.5 mL~~

Section	Description of Change
	~~solution containing study drug (LUM001)using the syringe provided. Study drug~~ **The first dose** should be taken at least 30 minutes prior to the first meal of the day ~~(qAM, ac) and should be administered~~ **and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the doses should be taken** approximately at the same time each day for the duration of the treatment period. ~~See Sections 5.5.1, 5.5.1.1, and 5.5.1.2~~ **See Section 5.5.1** for information regarding dosing during the ~~dose escalation and stable dosing~~ **treatment** periods, respectively.
Section 10.2, Treatment Compliance	Subjects and/or caregivers will be asked to complete a paper diary indicating when they took their study medication and when they ate breakfast **and, for subjects who receive a BID regimen, when they ate dinner (evening meal).**
Section 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 **of LUM001-303 entry** until ~~**the 30-day post-treatment follow-up visit**~~**completing the final required assessment while enrolled in LUM001-303**).
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 (Sections 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 ~~Sponsor Medical Monitor~~. ~~The Investigator and Sponsor Medical Monitor~~ **sponsor medical monitor. If suspended, the investigator 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 re-test should be conducted by the central laboratory, but may also be conducted at a local laboratory on an as needed basis.** **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), in particular whether the event should be considered as an important medical event, ie. an event that would have met one of the other seriousness criteria in the absence of appropriate medical interventions.**
Section 10.6, Adjustment of Dose	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; **later attempts to escalate the dose are permitted. If the subject is on twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose.**
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 will be collected as medical history unless the AE started within 30 days of last dose.**
Section 11.3.1, Serious Adverse Events	The collection of SAEs will begin after the subject signs the informed consent/assent form and stop ~~at the end of the subject's follow-up period which is defined as Week 52 for subjects who do not roll over into the optional treatment follow-up period, Week 100 for subjects who do roll over into the optional treatment follow-up period, or 28 days after the last dose of study drug for those subjects that terminate prior to the Week 96 visit~~ 30 days after the last dose of study drug.
Section 11.3.2, Non-serious Adverse Events	The recording of non-serious AEs will begin after the subject signs the informed consent/assent form and will stop ~~at the end of the subject's follow-up period, which is defined as Week 52 for subjects who do not roll over into the optional treatment follow-up period, Week 100 for subjects who do roll over into the optional treatment follow-up~~

Section	Description of Change
	~~period, or 30 days after the last dose of study drug for those subjects that terminate prior to the Week 96 visit~~ 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.**
Section 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…
Section 12.2.4.1, Safety Assessments	**Serum alpha-fetoprotein (AFP)**
Section 12.2.5.2, Laboratory Tests	Changes within a treatment group for selected safety measures will be assessed at Weeks 8, 12, 24, 36, 48, ~~and at the final study evaluation visit ((Week 72)~~60, 72,**and at additional time points during the 52-week and long-term optional treatment periods…**
Section 12.2.5.6, Serum Alpha-fetoprotein	(new section) **Assessments of serum AFP will be listed for individual subjects and summarized using descriptive statistics by study visit.**
Section 16.1, Schedule of Procedures E-H	Added Overall Scheme and Corresponding Schedule of Procedures Added Schedule of Procedures E - Long-term Optional Follow-up Treatment Period: Protocol Amendment 5 Screening (Week -2) and on LUM001. Includes Evaluation of Eligibility for Afternoon Dose Escalation Dosing Regimen at Protocol Amendment 5, Week 12. • Any subject who re-enters the study under Protocol Amendment 5. The subject returns to their last previously administered dose for 12 weeks and then moves to either Schedule F or G, depending on afternoon dose eligibility. • Proceed to Schedule H for Early Termination or End of Treatment Procedures. Added Schedule of Procedures F-G: Re-entry under Protocol Amendment 5: Schedule of Procedures F – Extension of Long-term Optional Follow-up Treatment Period, for subjects ineligible for ADE. Schedule of Procedures G – Extension of Long-term Optional Follow-up Treatment Period, for subjects eligible for ADE. Added Schedule of Procedures H - Study Termination and End of Treatment Procedures
Section 16.2, List of Laboratory Analytes	Added alpha-fetoprotein (AFP) under marker of hepatocellular carcinoma
Section 8.5.4, Pediatric Quality of Life Inventory (PedsQL™)	**Subjects will continue to fill out the same questionnaire used at baseline for continuity of data collection, regardless of subsequent birthdays after the baseline visit.**

16.10.2 Protocol Amendment 4 Summary of Changes

Protocol Number: LUM001-303

Protocol Title: A MULTICENTRE 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: 04 Nov 2015

The LUM001-303 protocol is being amended to include an Optional Follow-up Treatment Period (After Week 72) that is intended to offer the opportunity to eligible subjects treated in the LUM001-303 study to continue on treatment after Week 72 until the first to occur of the following: (i) up to 52 weeks of additional treatment (Week 124), or (ii) in the event that a new study opens to enrollment.

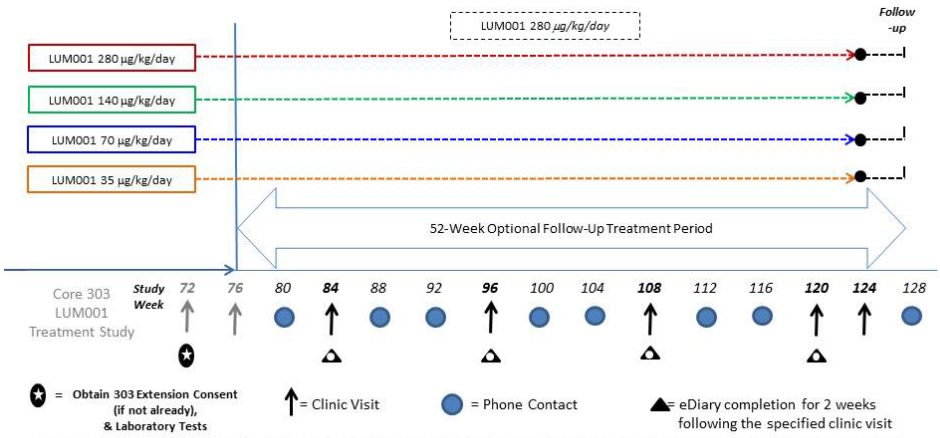
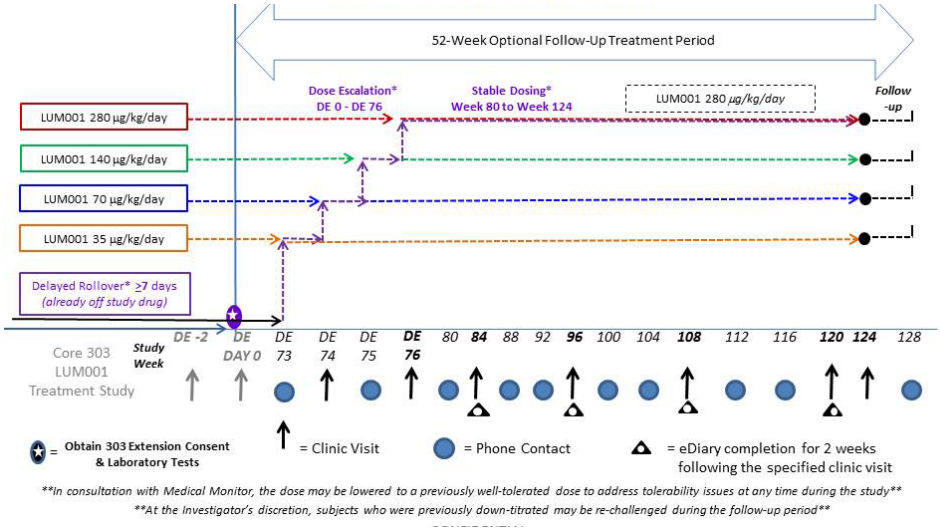
The following changes have been made to Protocol Amendment 4. Note that correction of typos and grammatical errors are not captured in the below table.

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

Section	Description of Change
Title page; Sponsor Medical Monitor	**Added:** **Sponsor Medical Monitor:** **Susanne Schmidt, MD, PhD** **Premier Research** **Office: +1 215 282 5406** **Cell: +1 267 838 2380** **Email: medmonitorLUM303@premier-research.com**
Title Page, Medical Lead	**Changed from:** Ciara Kennedy, PhD Lumena Pharmaceuticals, Inc. Phone: 00-1-858-337-7922 Email: cikennedy@shire.com **To:** **Beatriz Caballero, MD** **Shire, Inc.** **Zahlerweg 10** **6300 Zug** **Switzerland** **Phone: +41(0) 41 288 42 30** **Email: bcaballero@shire.com**

Section	Description of Change
Study Synopsis, Objectives; Section 3, Study Objectives	The primary objective of the study **(up to and including Week 72)** is to: • Evaluate the long-term safety and tolerability of LUM001 in pediatric subjects with ALGS. Secondary objectives of the study **(up to and including Week 72)** are to: • … **Objectives of Optional Follow-up Treatment Period (after Week 72):** • **To offer eligible subjects in the LUM001-303 study continued treatment after Week 72 until the first of the following occur: (i) up to 52 weeks of additional treatment (Week 124), or (ii) in the event that a new study opens to enrollment.** • **To obtain safety and efficacy data in subjects treated long term on LUM001 including genotyping characteristics.**
Study Synopsis, Study Design; Section 5.1, Study Design	This is a multicentre, double-blind study of LUM001 in children ≥12 months of age diagnosed with ALGS who have completed participation in the LUM001-302 study. All subjects will receive active drug (LUM001) in the study. The study is divided into ~~3~~**4** parts: a dose escalation period, a dose optimization period, ~~and~~ a stable dosing period**, and an optional 52-week follow-up period for eligible subjects who choose to stay on treatment with LUM001. Subjects' participation in the optional follow-up treatment period will continue until the first of the following occur: i) completion of 52 weeks of additional treatment or ii) in the event that a new study of LUM001** ~~is 76 weeks, including a 4 week follow-up~~ **opens to enrollment.** **Planned participation for each subject enrolled in the optional follow-up treatment study is ~~76~~128 weeks, inclusive of a 4 week follow-up phone call.** … **Optional Follow-up Treatment Period:** **At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the optional 52-week, follow-up treatment period to receive study drug at the dose they were receiving at Week 72.**
Study Synopsis, Study Population; Section 7.2, Exclusion Criteria	**Eligible subjects for 52-week optional follow-up treatment period:** **Subjects will be considered eligible for the 52-week optional follow-up treatment period if they have completed the protocol through the Week 72 visit with no safety concerns. Subjects who were discontinued due to safety reasons can be re-challenged if blood tests do not satisfy the protocol's stopping rules; the decision will be made by the investigator in consultation with the Sponsor Medical Monitor. Subjects who have undergone a surgical disruption of the enterohepatic circulation will not be eligible to enter into the follow-up treatment period. Subjects who were discontinued for other reasons will be considered on an individual basis.**
Study Synopsis, Study Drug Dosage and Administration Section 5.1, Study Design; Section 5.5.1.1, Dose Escalation Period; Section 5.5.1.3, Stable Dosing Period	… Dosing will occur over a ~~72~~**124-**week treatment period. 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. … Dose Escalation Period … ~~The primary anticipated adverse reaction or intolerance is gastrointestinal in nature (e.g., 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).~~

Section	Description of Change
	If a subject experiences intolerance due to gastrointestinal symptoms **(eg, diarrhea, abdominal pain, cramping) at any time during the study**, the investigator, in consultation with the Sponsor Medical Monitor, may lower the dose to a previously tolerated dose. **Optional Follow-up Treatment Period:** **At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the 52-week, follow-up treatment period. The three following possible scenarios may occur:** • **For subjects who are eligible to roll over into the follow-up treatment period, those with <7 days since the last dose of LUM001, will be maintained at the same dose level.** • **For subjects who are eligible to roll over into the follow-up treatment period having ≥7 days since the last dose of LUM001, will be dose escalated up to 280 µg/kg/day or the highest tolerated dose following a 4-week dose escalation beginning at 35 µg/kg/day.** • **For subjects who do not wish to enter the follow-up treatment period, or are not eligible to enter the follow-up treatment period, a safety follow-up phone call will be made by the study site 30 days after the last dose of study drug.**
Study Synopsis, Rationale for Dose and Schedule Selection	…**The dose may also be down-titrated, at the investigator's discretion and in consultation with the Sponsor Medical Monitor, for subjects experiencing intolerance to a given dose. During the follow-up treatment period, the dose will be escalated for those subjects who had been off treatment for ≥7 days. The dose will be escalated over the first 4 weeks up to 280 µg/kg/day or to the highest tolerated dose starting at 35 µg/kg/day. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001 and allows for subjects to reach 280 µg/kg/day or a highest tolerated dose within a 4-week period.**
Study Synopsis, Study Visit Schedule and Procedures; Section 5.5, Overall Study Duration and Follow-up; Section 5.5.1.4, Optional Follow-up Treatment Period; Section 8.1.8, Optional Follow-up Treatment Period (post Week 72 to Week 124); Statistical Considerations, Section 12; Section	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 60-week stable dosing period. **Subjects who complete 72 weeks of treatment may be eligible to receive treatment for up to 52 weeks during the optional follow-up treatment period.** Planned participation for each subject enrolled in the **optional follow-up treatment** study is ~~76~~**128** weeks, **inclusive of** a 4 week follow-up **phone call.** Study activities will be conducted as described in the Schedule of Procedures (Section 16.1). **Study Scheme (**~~as described below~~Up to and including Week 72**):**

Section	Description of Change
12.2.3.1, Efficacy Variables	**Follow-up Treatment Scheme** **(no interruption in LUM001 dosing, or interruption <7 days)**  **Follow-up Treatment Scheme** **(interruption in LUM001 dosing ≥7 days):**  … Week 72~~/ Study Termination: At the Study Termination Visit,~~ **Week 72: Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the optional 52-week treatment period. Eligible subjects must have documented consent in order to continue in the optional follow-up treatment period.** … Follow-up Period: **For subjects who do not roll over into the optional follow-up treatment period,** a safety follow-up phone call will be made by the study site 30 days after the last dose of study drug. 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 adverse events noted during this phone call will be recorded.

Section	Description of Change
	<u>Optional Follow-up Treatment Period (post Week 72 to Week 124):</u> **Subjects who are eligible to roll over into the follow-up treatment period will continue to receive study drug at the dose they were receiving at Week 72 for up to 52 weeks or until a new study opens to enrollment, whichever occurs first.** **Subjects who are eligible to roll over into the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level.** **Subjects with ≥7 days since last dose of LUM001 will be dose escalated up to 280 µg/kg/day or to the highest tolerated dose starting at 35µg/kg/day. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001 and allows for subjects to reach 280 µg/kg/day or a highest tolerated dose within a 4-week period. The dose escalation (DE) period will proceed as follows:** • **DE Week -2 Clinic Visit: obtain consent, obtain weight, and draw labs.** • **DE Day 0 Clinic Visit: PI evaluates laboratory results, study drug is dispensed and subject begins at 35 µg/kg/day dose level.** • **DE Week 73 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated.** • **DE Week 74 Clinic Visit: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated.** • **DE Week 75 Telephone Contact: subject escalates to 280 µg/kg/day dose, if prior dose level was tolerated.** • **DE Week 76 Clinic Visit: subject continues in Follow-up Treatment Period at 280 µg/kg/day, or highest tolerated dose.** **If any subject experiences intolerance, the investigator, in consultation with the Sponsor Medical Monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period. At the investigator's discretion and in consultation with the Sponsor Medical Monitor, subjects who were previously down titrated may be re-challenged during the optional follow-up treatment period.** **During the follow-up treatment period, subjects will return to the clinic every 3 months, at Weeks 84, 96, 108, 120, and 124.** **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. In addition, the clinician scratch scale will be administered and study drug compliance will be assessed. The PedsQL will be administered at DE Day 0 (for subjects requiring dose escalation) and at Weeks 84, 96, 108, 120, and 124. The Caregiver Impression of Change (CIC) assessment will be completed at Weeks 108, 120, and 124. Subjects/caregivers will receive follow-up phone calls at Weeks 76, 80, 88, 92, 100, 104, 112, and 116. Concomitant medications and any AEs 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 consecutive weeks following the Week 84, 96, 108, and 120 clinic visits. 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 long-term exposure period.**

Section	Description of Change
	With the exception of the Week 120 and Week 124 visit (Study Termination), additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every visit. … Efficacy Evaluations 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 48 and the change from Week 12 to Week 48 in: … Additional exploration ~~of evaluations of safety~~**, including behavior during the dose escalation** and ~~durability of therapeutic effect~~ **optimization phases** will be specified in the statistical analysis plan. … Efficacy …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. **Rationale for removing durability of effect from efficacy evaluations:** The efficacy evaluation of durability of effect of LUM001 in subjects was removed as this cannot be assessed as this study is not placebo-controlled and an effect has not yet been established (through historical control for example).
Section 5.5.2, Follow-up	**Study drug will be discontinued at Week 72 if the subject chooses not to participate in the optional follow-up treatment period.** … ~~This call~~ **For those patients that choose to roll over in to the follow-up treatment period, a follow-up phone call will take place at Week 128, 30 days after the last dose of study drug. Follow-up phone calls** will be made for all subjects who complete the study, as well as any subject who terminates from the study early.
Section 5.6, Study Termination	~~Subjects will be dosed to complete a cumulative LUM001 exposure of at least one year.~~
Section 8.1.5, Week 72	Week 72~~/Study Termination (End of Study)~~ At the Week 72~~/Study Termination Visit~~, a physical exam (including collection of vital signs, height and weight measurements) will be performed. … ~~Study drug will be discontinued at this visit.~~
Section 8.1.6, Early Termination	Any subject who withdraws from the study prior to completion of all treatment period clinic visits **up to Week 72 or who is not eligible or willing to roll into the 52-week optional treatment period** should undergo the procedures specified for the Week 72~~/Study Termination~~ Visit.

Section	Description of Change
Section 8.1.7, Follow-up Period (30 days After Last Dose)	**Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in an optional follow-up treatment period.**
Section 8.2, Genetic Testing	***JAGGED1*** **and** ***NOTCH2*** **mutations are predictive of ALGS. For subjects who do not have complete documentation of a** ***JAGGED1*** **or** ***NOTCH2*** **mutation, blood samples for genotyping will be collected at the screening visit. The appropriate genetic counseling in accordance with local laws will be provided to any subject and their legal caregivers at a study visit following the receipt of results of genetic testing, at no cost to the subject. Subjects for whom prior genotyping was performed may need to have an optional repeat analysis performed if the original information collected at screening was insufficient for complete documentation of the diagnosis of ALGS including the type of mutation recorded. For those participants for which the type of mutation cannot be documented, genetic testing may be conducted and the results recorded.**
Section 8.3, Physical Examination, Weight and Height, Vital Signs	… **For subjects who enter into the 52-week optional follow-up treatment period, physical examinations will also be conducted at Weeks 84, 96, 108, 120, and 124. For subjects with interruptions in LUM001 dosing of ≥7 days, additional physical examinations will be conducted during the DE period at DE -2, DE Day0, DE Week 74, and DE Week 76.** …
Section 8.5.1, Itch Reported Outcome (ItchRO™)	… **For subjects who enter the 52-week optional follow-up treatment period, daily completion of the diary will also be during the 2 weeks following the Weeks 84, 96, 108, and 120 clinic visits.** …
Section 8.5.2, Clinician Scratch Scale	… **For subjects who enter the optional follow-up treatment period, the clinician scratch scale will also be administered at Weeks 84, 96, 108, 120, and 124. For subjects with interruptions in LUM001 dosing of ≥7 days, assessments will be conducted during the DE period at DE -2, DE Day 0, DE Week 74, and DE Week 76.**
Section 8.5.3, Clinician Xanthoma Scale	… **For subjects who enter the 52-week optional follow-up treatment period, the clinician's assessment of xanthomatosis will also be administered at Weeks 84, 96, 108, 120, and 124.** **For subjects with interruptions in LUM001 dosing of ≥7 days, the assessment will also be conducted during the DE period at DE Week 76. …**
Section 8.5.4, Pediatric Quality of Life Inventory (PedsQL)	… **For subjects who enter the 52-week optional follow-up treatment period, the PedsQL will also be administered at Weeks 84, 96, 108, 120, and 124. For subjects with interruptions in LUM001 dosing of ≥7 days, the PedsQL will also be administered at DE Day 0….** **For subjects who enter the optional follow-up treatment period, the multidimensional fatigue and family impact questionnaires will also be administered at Weeks 84, 96, 108, 120, and 124.** …

Section	Description of Change
Section 8.5.5, Caregiver Impression of Change	… **For subjects who enter the 52-week optional follow-up treatment period, the CIC will also be administered at Weeks 108, 120, and 124**.
Section 11.3; Monitoring and Recording of Adverse Events	**Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.**
Section 11.3.1; Serious Adverse Events	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 76 **for subjects who do not roll over into the 52-week optional treatment follow-up period, Week 124 for subjects who do roll over into the optional treatment follow-up period,** or 30 days after the last dose of study drug for those subjects that terminate prior to the Week ~~72~~ 76 **or Week 124** 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 76 **for subjects who do not roll over into the 52-week optional treatment follow-up period, Week 124 for subjects who do roll over into the 52-week optional treatment follow-up period, or 30 days after the last dose of study drug for those subjects that terminate prior to the Week 76 or Week 124 visit.**
Section 16.1; Schedule of Procedures	**Added:** Two new Schedules of Procedures for the Optional Follow-up Treatment Period (Week 72-Week 124) for: • Subjects with no interruption in LUM001 dosing or interruption <7 days • Subjects with interruption in LUM001 dosing ≥7 days
Section 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 ~~visit.~~ **and Week 72 visit. For subjects who enter the 52-week optional follow-up treatment period, the CIC will also be administered at Weeks 108, 120, and 124.**

16.10.3 Protocol Amendment 3 Summary of Changes

Protocol Number: LUM001-303

Protocol Title: A MULTICENTRE 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: **3**

Date: September 17, 2014

The following changes have been made to protocol amendment 3. The following table provides a summary list of changes to the protocol:

Section	Description of Change
Synopsis (Section 1), Study Design Overall Study Duration and Follow-up (Section 5.5)	Changed treatment (duration) period to collect additional long-term safety data from 48 weeks to 76 weeks, including a 4 week follow-up. Treatment period changed from 48 weeks to 72 weeks.
Synopsis (Section 1), Study Visit Schedule and Procedures Study Design (Section 5.1)	Changed stable dosing period from 36 weeks to 60 weeks and study duration to 76 weeks, including a 4 week follow-up. Added study visits at Weeks 60 and 72. Changed Study Termination (End of Study) from Week 48 to Week 72. Added PedsQL evaluation at Week 72. Added Caregiver Impression of Change evaluation at week 72. Changed Study Termination from Week 48 to Week 72.
Synopsis (Section 1), Number of Subjects Number of Subjects (Section 5.4) Statistical Considerations (Section 12)	Changed from 42 to 18
Synopsis (Section 1), Drug Level Evaluations	Added evaluation at week and 72
Synopsis (Section 1), Study Population Subject Eligibility (Section 7)	Clarified that core LUM001 treatment protocol refers to Study LUM001-302 for eligibility in this study

Section	Description of Change
Synopsis (Section 1), Efficacy Evaluations Efficacy Evaluations (Section 12.2.3.1)	Modification of biochemical markers of cholestasis and liver disease to include deletion of alkaline phosphatase (ALP) and modification of bilirubin (total and direct) to total bilirubin in secondary evaluations for the durability of the therapeutic effect as mean change from Baseline (Day 0) to Week 48 and the change from Week 12 to Week 48.
Number of Study Centers (Section 5.3)	Changed from 14 to 3
Stable Dosing Period (Sections 5.5.1.3, 8.1.4)	Changed stable dosing period from 36 weeks to 60 weeks and study duration to 72 weeks
Study Termination (Section 8.1.5)	Changed Study Termination (End of Study) from Week 48 to Week 72
Early Termination (Section 8.1.6)	Changed Study Termination (End of Study) from Week 48 to Week 72
Physical Examination, Weight and Height, Vital Signs (Section 8.2)	Added assessments at Weeks 60 and 72
Clinician Scratch Scale (Section 8.4.2)	Added assessments at Weeks 60 and 72
Clinician Xanthoma Scale (Section 8.4.3)	Added assessments at Weeks 60 and 72
Pediatric Quality of Life Inventory PedsQL (Section 8.4.4)	Added assessment at Week 72; clarified that age at baseline visit will be used as the age for the determination of the appropriate questionnaire to be used for the duration of the study, regardless of subsequent birthdays during the study.
Caregiver Impression of Change (Section 8.4.5)	Added assessment at Week 72
Schedule of Procedures (Section 16.1)	Modified to reflect changes listed above
Administrative Changes	To correct typographical and grammatical errors; replaced core LUM001 treatment protocol with Study LUM001-302

16.10.4 Protocol Amendment 2 Summary of Changes

Protocol Number: LUM001-303

Protocol Title: A MULTICENTRE 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 28, 2014

The following changes have been made to protocol amendment 2. The following table provides a summary list of changes to the protocol:

Section	Description of Change
Inclusion Criteria (Synopsis and Section 7.1)	Lowered eligibility age from 2 years of age to 12 months to 18 years
Synopsis (Section 1), Number of Subjects (Section 5.4)	Changed from 60 to 42
Synopsis (Section 1), Treatment (Section 5.5.1), Study Drug Administration (Section 10.1)	Text has been revised to indicate that subjects who weigh 10 kg or more will receive a 1.0 mL solution containing LUM001 or placebo. Subjects who weigh less than 10 kg will receive a 0.5 mL solution containing LUM001 or placebo. The volume administered will not change during the course of the study.
Section 4.5, (Rationale for Dose and Schedule of Administration)	Edited age criteria from 2 to 18 years to 12 months to18 years
Study Drug Description (Section 9.1)	Tabular descriptions of the composition of the LUM001 0.5 mL solution and the 0.5 mL placebo solution have been included. Correction made to maximum LUM001 dose.
Section 11.4.2 (dosing errors)	Clarified that dosing errors are captured in eCRF and in paper dosing diaries
Section 16.6 (PedsQL)	Added PedQL for infants

16.10.5 Protocol Amendment 1 Summary of Changes

Protocol Number: LUM001-303

Protocol Title: A MULTICENTRE 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: November 5, 2013

The following changes have been made to the original protocol:

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

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

Section	Description of Change
Exclusion Criteria 3 (Synopsis and Section 7)	History or presence of gallstones or kidney stones added
Dose Escalation Period (Synopsis and Section 5.5.1.1)	Clarification added regarding dose escalation for subjects who may be unable to begin LUM001-303 the same day of the last day of their LUM001 treatment protocol
Abbreviations	Removal of unused abbreviations
Study Scheme (Synopsis, Figure 4 and protocol titles in Sections 8.1.3 and 8.1.4)	Updated “Dose Optimization Period to Weeks 5-12”, and “Stable Dosing Period to Weeks 13-48”
Section 8.1.1 and Schedule of Events	Addition of Medical History
Schedule of Events	Subscript “c” added with clarity around dose escalation. Window visit updated during dose escalation period. Correction made to Week 8 (was Day 63, corrected to Day 56)