CLINICAL PROTOCOL

PROTOCOL NUMBER: LUM001-501

INDIGO STUDY

OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN AP**I**CAL SODIUM-DEPE**N**DENT BILE ACI**D** TRANSPORTER **I**NHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PRO**G**RESSIVE FAMILIAL INTRAHEPATIC CH**O**LESTASIS

Protocol Amendment 4.1: 08 February 2019

Protocol History

Protocol Amendment 4:	20 December 2016
Protocol Amendment 3:	02 November 2015
Protocol Amendment 2:	05 November 2014
Protocol Amendment 1 (United Kingdom & Europe):	07 May 2014
Protocol Amendment 1 (United States):	10 December 2013
Original Protocol:	23 October 2013

Developed in Collaboration with ChiLDREN

THE CHILDHOOD LIVER DISEASE RESEARCH AND EDUCATION NETWORK

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

SPONSOR SIGNATURE PAGE

LUM001-501

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Protocol Amendment 4:	20 December 2016

Sponsor:
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TITLE PAGE

Study Drug:	LUM001
Protocol Number:	LUM001-501
Amendment Number:	4.1
Date:	08 February 2019
EudraCT No:	2013-003833-14
IND No:	119916
Study Phase:	Phase 2
Protocol Title:	Open Label Study of the Efficacy and Long Term Safety of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis
Sponsor:	Mirum Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, California 94025 USA
Medical Monitor:	Cagil Ozen, MD Premier Research Office: +1 215 282 5406 Cell: +1 267 838 2380 Email: medmonitorLUM501@premier-research.com
Medical Lead:	Thomas Jaecklin, MD Mirum Pharmaceuticals AG Innere Margarethenstrasse 5 4051 Basel Switzerland Phone: +41(0) 79 850 77 18 Email: tjaecklin@mirumpharma.com
Compliance Statement:	This study will be conducted in accordance with all applicable clinical research guidelines including the International Conference on Harmonization (ICH) Guidelines for current Good Clinical Practice (GCP). Study documents will be maintained in accordance with applicable regulations.

PROTOCOL SIGNATURE PAGE

Sponsor's (Mirum) Approval

Signature:	**Date:** 6.2.2019
Thomas Jaecklin, MD 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:

OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS.

Protocol Number:	LUM001-501
Amendment Number:	4.1
Date:	08 February 2019
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:
medmonitorLUM501@premier-research.com

PRODUCT QUALITY COMPLAINTS

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 4.1

Protocol Number: LUM001-501

Protocol Title: OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Amendment: **4.1**

Date: **08 February 2019**

The LUM001-501 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 4 (20 December 2016). 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	**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; Sponsor Signature page, Sponsor (Mirum) Approval	**Changed from:** **Medical Lead:** Thomas Jaecklin, MD 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:
<table>
<tr><td>Origin of Product Quality Complaint</td><td>E-mail Address</td></tr>
<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>10.3 Concomitant Medications</td><td>Changed From: No new medications used to treat pruritus may be added during the course of the study.

To:
No new medications used to treat pruritus may be added during the period from Baseline (Day 0) until Week 13 (timepoint for primary analysis).</td></tr>
<tr><td>Schedule of Procedures D</td><td>Added clarifying footnote regarding baseline reference value for participants re-entering in Protocol Amendment 3 after dose interruption of ≥ 7 days:
11 For participants re-entering under Protocol Amendment 3, Baseline laboratory values are considered those collected at re-entry visit DE-2 weeks</td></tr>
<tr><td>Schedule of Procedures G</td><td>Added clarifying footnote regarding baseline reference value for participants re-entering in Protocol Amendment 4 after dose interruption of ≥ 7 days::
8 For participants re-entering under Protocol Amendment 4, Baseline laboratory values are considered those collected at re-entry visit PA4 DE-2 weeks</td></tr>
</table>

PROTOCOL AMENDMENT 4

Protocol Number: LUM001-501

Protocol Title: OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Amendment: **4**

Date: **20 December 2016**

The LUM001-501 protocol is being amended to allow continued participation in the Optional Follow-Up Treatment Period, beyond what was previously described in Protocol Amendment 3. Study treatment in the Optional Follow-up Treatment Period will continue until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.

This amendment also describes the way in which eligible subjects who had previously discontinued from the study may re-enter and receive study treatment in the optional follow-up treatment period (After Week 72).

Additional objectives for the Optional Follow-up Treatment Period have been added, as follows:

- exploration of a twice daily (BID) dosing regimen and higher daily dosing of LUM001;
- identification of genetic indicators of treatment response, including use of exome sequencing;
- assessment of alpha-fetoprotein (AFP) levels, a marker of hepatocellular carcinoma;
- assessment of the palatability of the LUM001 formulation in all patients, by-proxy in patients <4 years old and by patient questionnaire in children ≥4 years old; and
- an exploratory objective to allow the possibility of analysis of serum markers of treatment response using metabolomic and proteomic analysis on previously collected serum samples.

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 3 (02 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	**Changed from:** Lumena Pharmaceuticals LLC 12531 High Bluff Drive, Suite 110 San Diego, CA 92130 USA **To:** Lumena Pharmaceuticals LLC* **300 Shire Way** **Lexington, MA 02421** USA ***Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc**
Title Page, Medical Lead; Sponsor 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** 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.
Synopsis, Objectives; Section 3, Study Objectives	Objectives of Optional Follow-up Treatment Period (After Week 72): • To offer eligible subjects in the LUM001-501 study continued study treatment ~~at~~ **beyond** Week 72 until the first of the following occurs: (i) ~~up~~ **the subjects are eligible** to ~~52 weeks of additional treatment (Week 124),~~ **enter another LUM001 study** or (ii) ~~in the event that a new study opens to enrollment~~ **LUM001 is available commercially.**
Synopsis, Objectives; Section 3, Study Objectives	Objectives of Optional Follow-up Treatment Period (After Week 72): • To obtain safety and efficacy data in subjects treated long-term on LUM001 ~~including genotyping characteristics.~~
Synopsis, Objectives; Section 3, Study Objectives	• **To explore a twice a day (BID) dosing regimen and higher daily dosing of LUM001.**

Section	Description of Change
Synopsis, Objectives; Section 3, Objectives	• **To identify genetic indicators of treatment response, including use of exome sequencing.**
Synopsis, Objectives; Section 3, Study Objectives	• **To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma.**
Synopsis, Objectives; Section 3, Objectives	• **To assess palatability of the LUM001 formulation.**
Synopsis, Objectives; Section 3, Study Objectives	**Exploratory Objective:** • **To allow the possibility of analysis of serum markers of treatment response using metabolomic and proteomic analysis on previously collected serum samples.**
Synopsis, Study Design; Section 5.1, Study Design	The study is divided into 5 parts: …. and an optional ~~52 week~~ follow-up **treatment** period for eligible subjects who choose to stay on treatment with LUM001. **During this 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 ongoing efficacy (sBA level and ItchRO score) and safety assessment.**
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 trial. Effective methods of contraception are ~~considered to be~~ **described in Section 8.7.1.** ~~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).~~
Synopsis, Inclusion Criteria; Section 7.3, Exclusion Criteria	Eligible Subjects for ~~52-week~~ Optional Follow-up Treatment Period: Inclusion Criteria Subjects will be considered eligible for the ~~52-week~~ Optional Follow-up Treatment Period if they have meet the following criteria: 1. The subject has either: • completed the protocol through the Week 72 visit with no **major** safety concerns. ~~Subjects who were~~ , **OR** • • discontinued due to safety reasons **judged unrelated** to ~~relatively normal values for this patient population~~ **the study drug, and blood tests have returned to levels acceptable for this patient population/individual** and subject does not meet any of the protocol's stopping rules **at re-entry. …** ~~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.**]** **2. Females of childbearing potential must have a negative urine or serum pregnancy test (β-hCG) at the time of entry into the optional follow-up treatment period.** **3. Informed consent and assent (per IRB/EC) as appropriate.** **Exclusion Criteria**

Section	Description of Change
	Subjects will be excluded from the Optional Follow-up Treatment Period if they meet any of the following criteria: **1. Surgical disruption of the enterohepatic circulation.** **2. Investigational drug other than LUM001, biologic, or medical device within 30 days prior to re-entry, or 5 half-lives of the study agent, whichever is longer.**
Synopsis, Treatment Groups; Section 5.5.2, Treatment; Section 10.1, Study Drug Administration	All subjects will receive LUM001, up to ~~280~~ **560** µg/kg/day **(given as twice-daily doses of 280 µg/kg)** or a maximum daily dose of ~~20~~ **25** mg/~~day~~ **BID.**
Synopsis, Study Drug Dosage and Administration; Section 10.1, Study Drug Administration Section 5.5.2, Treatment	Subjects ~~who weigh 10 kg or more at screening~~ will receive a ~~1.0 mL~~ grape-flavored solution containing LUM001. ~~Subjects who weigh less than 10 kg at screening will receive 0.5 mL grape-flavored solution containing LUM001. The volume administered, either 1.0 mL or 0.5 mL will not change during the course of the study~~. Each ~~daily~~ **subject** dose will be administered ~~in the morning~~ **orally once a day (QD) or twice a day (BID) using the syringe provided. The first dose should be taken** ~~at least 30 minutes before breakfast (qAM, ac). Study drug should be administered~~ **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 at** approximately **the** same time ~~every day~~ **each day for the duration of the treatment period.** **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 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).** **Study Drug Dosage** **Baseline through Week 72:** **For the first 72 weeks of the study,** each subject will receive either 1.0 mL or 0.5 mL of solution containing LUM001 orally as follows**, administered as a daily morning dose:** • Dose Level 1: 14 µg/kg/day. • Dose Level 2: 35 µg/kg/day. • Dose Level 3: 70 µg/kg/day. ~~(up to a maximum daily dose of 5mg).~~ • Dose Level 4: 140 µg/kg/day. ~~(up to a maximum daily dose of 10mg).~~ • Dose Level 5: 280 µg/kg/day. ~~(up to a maximum daily dose of 20mg)~~.

Section	Description of Change
Section 5.5.2.4, Optional Follow-up Treatment Period (Post-Week 72) Synopsis; Section 5.5.2.3, Long-term Exposure Period	At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the optional follow-up treatment period. ~~Following the completion of the Week 72 study visit, subjects who choose to participate in the optional follow-up treatment period will enter under one of the following LUM001 dosing scenarios:~~ **Optional Follow-up Treatment Period (Post-Week 72):** **Subjects ~~who are~~ eligible for the optional follow-up treatment period will continue treatment under dosing scenarios based on whether their LUM001 dosing will continue without interruption or interruption of <7 continuous days, or with interruption ≥7 days. Eligibility for BID dosing will be determined based on efficacy as measured by sBA level and ItchRO score.** **Subjects who enter the optional follow-up treatment period without LUM001 dosing interruption or with** an interruption of **<7 continuous days will be dosed in the following manner:** • **Subjects with normal sBA level AND ItchRO score <1.5** will be maintained at the same dose level **and will continue morning dosing only.** • **Subjects with sBA level above normal AND/OR ItchRO score ≥1.5 will start BID dosing (afternoon dose escalation; ADE) as follows:** o **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.** o **The afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled, to a maximum dose of280 µg/kg (or up to the maximum tolerated dose).** o **The maximum daily dose will be 280 µg/kg BID, i.e. 560 µg/kg/day(max. 25 mg BID)**. Subjects who a~~re eligible to roll over into the optional follow-up treatment period with a LUM001 dosing 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 Dose Level 2 (35 µg/kg/day). Subjects who do not wish to~~ enter the optional follow-up treatment period **with a LUM001 dosing interruption of ≥7 days initially will receive morning dosing only and will undergo dose escalation (DE) in the following manner:** • **The morning dose will be initiated at Dose Level 2 (35 µg/kg) and doubled in weekly intervals to a maximum dose of 280 µg/kg, or up to the maximum tolerated dose.** • **Once the morning dose of 280 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO score will be evaluated.** • **Subjects with normal sBA AND ItchRO score <1.5 after morning dose escalation will be maintained at the same dose level and will continue morning dosing only.** • **Subjects with sBA above normal AND/OR ItchRO score ≥1.5 will begin BID dosing (afternoon dose escalation) as outlined above.** **Subjects will continue to receive study drug until they are eligible to enter another LUM001 study or until LUM001 is available commercially, whichever occurs first.**

Section	Description of Change
	The maximum daily dose will be 280 µg/kg BID, i.e. 560 µg/kg/day (maximum 25 mg). If a subject experiences intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician Investigator in consultation with the Sponsor Medical Monitor may lower the dose for the remainder of the study. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose. **The sBA value used for determination of ADE eligibility will be the most recent available value. The ItchRO score used for ADE eligibility will be derived from the most recent 2 week electronic diary collection period.** ~~If a subject experiences intolerance due to gastrointestinal symptoms (eg, 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 for the remainder of the study.~~
Synopsis, Rationale for Dose and Schedule Selection	To reduce the risk of loose stools, diarrhea and abdominal pain/cramps ~~in this study up to Week 72, the~~ LUM001 doses will be escalated over ~~the first a~~ **period of** ~~4~~**-8 weeks.** ~~Dosing will start at 14~~ **up to a maximum dose of 280** µg/kg~~/day, and will then be increased at 7 day intervals to 140 µg/kg/day (equivalent to 10 mg daily dose in a 70 kg adult). At the Week 8 visit, study drug~~ **BID (or maximum tolerated dose). The morning dose** ~~will be further~~ **is initiated and** escalated~~ to 280 µg/kg/day. For subjects in the 52 week optional follow up treatment period with ≥7 days since the last~~ **first; the afternoon dose** ~~of LUM001, dosing will start at 35 µg/kg/day,~~ **is only initiated** and ~~will then be increased over the first 4 weeks up to 280 µg/kg/day~~ **escalated in patients with elevated sBA level and/**or ~~to~~ **ItchRO ≥1.5 on** ~~the maximum~~ **(or maximum** ~~tolerated)~~ **morning** ~~dose starting at Dose Level 2 (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.~~ **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 (i.e. 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (i.e. 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 (PND21 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**

Section	Description of Change
	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. **If the subject is on a 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.**
Synopsis, Study Visit; Schedule and Procedures	Clarified titles of study design schemes and updated figures to reflect the addition of the extended follow-up treatment period beyond what was previously described in Protocol Amendment 3.
Synopsis, Study Visit; Schedule and Procedures Synopsis; Section 8.1.7, Optional Follow-up Treatment Period (Post-Week 72)	~~At clinic visits during the treatment periods, blood sampling for study drug determination will be completed according to the region's sampling schedule (refer to Section 16.1).~~ Optional Follow-up Treatment Period (post-Week 72 ~~to Week 124):~~): Subjects who are eligible to roll over on to 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 of additional treatment or in the event that a new study opens to enrollment, whichever occurs first.~~ **until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially. Included below are schematics describing the flow of study visits within this period.** **Figure 2: Optional Follow-up Treatment Period (<7 days from last LUM001 dose between Protocol Amendment 2 and Amendment 3)** **Applies to the following subject population:** • **Subjects who experienced no interruption in LUM001 dosing, or interruption <7 days between Protocol Amendment 2 and Protocol Amendment 3.** *New figure added here* **----------** 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~~ **initially receive study drug at the dose they were receiving at Week 72. Once Protocol Amendment 4 is implemented at the site, a determination about Afternoon Dose Escalation (ADE) will be made. The subject then will move to Figure 5 or Figure 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.** **Figure 3: Optional Follow-up Treatment (≥7 days from last LUM001 dose between Protocol Amendment 2 and Protocol Amendment 3)** **Applies to the following subject population:** • **Subjects who experienced an interruption in LUM001 dosing ≥7 days between Protocol Amendment 2 and Protocol Amendment 3.** *New figure added here* **----------**

Section	Description of Change
	Once Protocol Amendment 4 is implemented at the site, a determination about Afternoon Dose Escalation (ADE) will be made. The subject will then move to Figure 5 or Figure 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation. **Figure 4: Optional Follow-up Treatment (≥7 days from last LUM001 dose between Protocol Amendment 3 and Protocol Amendment 4)** **Applies to the following subject population:** • **Subjects who experienced an interruption in LUM001 dosing ≥7 days between Protocol Amendment 3 and Protocol Amendment 4.** *New figure added here* **----------** **Subjects with ≥7 days since last dose of LUM001 prior to site implementation of Protocol Amendment 4 will be dose escalated up to 280 µg/kg/day or to the highest tolerated dose starting at Dose Level 2 (35 µg/kg/day), in a similar fashion as outlined in Figure 4.** **The dose escalation (DE) period will proceed as follows:** • **DE Week -2 Clinic Visit: obtain consent for Protocol Amendment 4, 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 1 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated.** • **DE Week 2 Clinic Visit: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated.** • **DE Week 3 Telephone Contact: subject escalates to 280 µg/kg/day dose, if prior dose level was tolerated.** • **DE Week 4 Clinic Visit: subject continues in follow-up treatment period at 280 µg/kg/day, or maximum tolerated dose.** • **At DE Week 8 Telephone Contact: eligibility for ADE will be assessed. The subject will then move to Figure 5 or 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.** **Figure 5: Optional Follow-up Treatment under Protocol Amendment 4, without Afternoon Dose Escalation (ADE)** **Applies to the following subject population:** • **Subjects deemed ineligible for ADE.** *New figure added here* **----------** **Subjects Deemed Ineligible for ADE:** **Subjects with normal sBA level AND ItchRO score <1.5 will be deemed ineligible for ADE; such patients will be maintained at the same dose level and will continue morning dosing only. Subjects will have study activities then repeated in recurring 12-week periods as follows, until study completion or termination:** • **Recurring Period Week 4 (i.e., beginning Week 88 or 4 weeks after consent to Protocol Amendment 4) Telephone Contact: Collection of concomitant medications and any adverse events.** • **Recurring Period Week 8 (e.g., Weeks 92, 104, 116, etc) Telephone Contact: Collection of concomitant medications and any adverse events.**

Section	Description of Change
	• **Recurring Period Week 12 (e.g., Weeks 96, 108, 120, etc) 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 fat-soluble vitamins. Urine samples for clinical laboratory testing will be collected at every visit. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale will be administered, 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 upon completion of other study procedures.** **Figure 6: Optional Follow-up Treatment under Protocol Amendment 4, with Afternoon Dose Escalation (ADE)** **Applies to the following subject population:** • **Subjects whose sBA levels have not normalized and/or whose ItchRO score is ≥1.5 and therefore qualify for introduction of afternoon dosing.** *New figure added here* **----------** **Subjects deemed eligible for ADE, i.e., who have sBA level above normal AND/OR ItchRO score ≥1.5, will begin BID dosing (afternoon dose escalation; ADE) as follows:** • **On ADE Day 0, morning dosing will continue at 280 µg/kg or the maximum tolerated dose. Dosing must have been stable for ≥4 weeks prior to initiation of ADE. The morning dose will be continued at the same dose level, 280 µg/kg or maximum tolerated dose; however, the volume of the morning dose will be reduced by half.** • **On ADE 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 (i.e., at ADE Week 4) to a maximum dose of 280 µg/kg (i.e., up to a maximum 560 µg/kg/day or maximum tolerated dose).** **The following procedures will occur during the ADE period:** • **ADE 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 PK. The clinician scratch 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.** • **ADE Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.** • **ADE 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**

Section	Description of Change
Section 8.1.7 (only, not synopsis), Optional Follow-up Treatment Period (Post-Week 72)	**determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 PK. The clinician scratch 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.** • **ADE Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.** • **ADE 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 PK. The clinician scratch 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 outlined within Figure 5, until study completion or termination.** 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**. If the subject is on a twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose.** During the follow-up treatment period, subjects will return to the clinic every 3 months~~, at Weeks 84, 96, 108, 120, and 124.~~ **At completion of the 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 terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded.** The PedsQL will be administered at DE Day 0 (for subjects requiring dose escalation) and at Weeks 84, 96, 108, 120, ~~and 124.~~ **every clinic visit within each recurring 12-week period, and at the EOT visit. Additionally, it will be collected at Protocol Amendment 4 DE Day 0, ADE Day 0, ADE Week 4, and ADE Week 8.** The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 108, 120, and ~~124.~~**the EOT visit.** Subjects/caregivers will receive follow-up phone calls at Weeks 80, 88, 92, 100, 104, 112, and 116, **and twice within each recurring 12-week period. and every 3 months hence for the subsequent visits.** 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 clinic

Section	Description of Change
	visits**. , at Protocol Amendment 4 DE Week 4, and every clinic visits (not including the EOT visit). visit within each recurring 12-week period.** With the exception of the ~~Week 120 and Week 124~~ **EOT** 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 ~~the Week 124~~**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 End of Treatment/Early Termination 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 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. The ItchRO, the clinician administered pruritus scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, and palatability questionnaire also will be completed.** **At completion of the 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 terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded**.
Synopsis, Drug Level Evaluations; Section 8.1.7, Optional Follow-up Treatment Period (Post-Week 72)	United States: … At all other blood draws, blood will be drawn approximately 4 hours post ~~dosing for drug level analysis.~~ **morning dosing for drug level analysis. Additionally, for subjects in which afternoon dose escalation is initiated, samples will also be drawn at ADE Day 0, ADE Week 4, ADE Week 8, and at the three scheduled clinic visits following completion of the ADE period.** United Kingdom, Europe and Australia: … At all other blood draws, blood will be drawn approximately 4 hours post ~~dosing for drug level analysis.~~ **morning dosing for drug level analysis. Additionally, for subjects in which afternoon dose escalation is initiated, samples will also be drawn at ADE Day 0, ADE Week 4, ADE Week 8, and at the three scheduled clinic visits following completion of the ADE period.**
Synopsis, Safety Evaluations; Section 12.2.4.1, Safety Assessments	• Clinical laboratory results, **including alpha-fetoprotein (AFP) as a screening for hepatocellular carcinoma.**
Synopsis, Efficacy Evaluations; Section 12.2.9.1, Efficacy Variables	The main focus for the analyses of efficacy is the period from Baseline (Day 0) to Week 13. The period from Baseline (Day 0) to ~~Week 48~~ **EOT** will be ~~analysed~~ **analyzed**. ~~The~~ Primary ~~efficacy evaluation will be mean~~ **endpoint:** • **Fasting serum bile acid level change** from Baseline / (Day 0) to Week 13 ~~in:• Fasting serum bile acid level.~~ Secondary ~~evaluations for~~ efficacy ~~will include the mean change from Baseline / Day 0 to Week 13 in~~ **endpoints:** • Alanine aminotransferase (ALT) and bilirubin (total and direct).) **change from Baseline (Day 0) to Week 13.** • Pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO). **change from Baseline (Day 0) to Week 13.** (For each subject, the average daily score will be calculated using the 7 days pre-treatment for Baseline / Day 0, and the last 7 days of treatment for Week 13.)

Section	Description of Change
	~~Pattern of change in serum bile acids from Baseline (Day 0) to Week 124 will be evaluated and its appropriate analysis methodology will be outlined in the Statistical Analysis Plan (SAP) for the study.~~ ~~Secondary evaluations will be the mean change from Baseline (Day 0) compared to Week 48 in:~~ ~~• Biochemical markers of cholestasis and liver disease including alanine aminotransferase (ALT), and bilirubin (total and direct).~~ ~~• Pruritus as measured by the ItchRO instruments (ItchRO(Obs)TM, caregiver instrument/ItchRO(Pt) TM patient instrument).~~ ~~Additional evaluations of safety and efficacy surrogates will be specified in the Statistical Analysis Plan.~~ **Exploratory efficacy endpoints:** • Change from Baseline (Day 0) in fasting serum bile acid level at Weeks 4, 8, 24, 36, 48 60, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the End of Treatment (EOT) visit.** • Change from Baseline (Day 0) in pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO) at Weeks 4, 8, 28, 48, 86, 98, 110, ~~and 122~~**. 122, and every three months thereafter.** • Change from Baseline (Day 0) for ALT, and bilirubin (total and direct) at Weeks 4, 8, 24, 36, 48, 60, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the EOT visit.** • Change from Baseline (Day 0) for other biochemical markers of cholestasis [total cholesterol, low-density lipoprotein cholesterol (LDL-C)] at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the EOT visit.** • Responder analysis: pruritus response rates as measured by ItchRO (Observer ItchRO/patient ItchRO) at Weeks 4, 8, 13, 28, 48, 86, 98, 110, ~~and 122~~ **122, and every three months thereafter, up to but not including the EOT visit.** • Change from Baseline (Day 0) in the Clinician Scratch Scale, at Weeks 2, 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the EOT visit.** • Change from Baseline (Day 0) in bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)] at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the EOT visit.** • Change from Baseline (Day 0) for PedsQL at Weeks 13, 24, 48, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the EOT visit**. • Patient Impression of Change (PIC) at Weeks 13, 48, 72, 108, 120, ~~and 124~~ **the EOT visit.** • Caregiver Impression of Change (CIC) at Weeks 13, 48, 72, 108, 120, ~~and 124~~ **the EOT visit.** • Caregiver Global Therapeutic Benefit (CGTB) assessment at Weeks 13, 48, ~~72, 108, 120, and 124~~ **at the EOT visit.** ~~In addition, the following evaluations may be explored:~~ • Change from Baseline (Day 0) for other biochemical markers [autotaxin and lysophosphatidic acid (LPA)] at Weeks 4, 8, 13, 36, 48, 60, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the EOT visit.** • Change from Baseline (Day 0) for measures of bile acid synthesis (FGF-19 and FGF-21) at Weeks 4, 8, 13, 36, 48, 60, 72, 84, 96, 108, 120, ~~and 124~~ **every three months thereafter, and at the EOT visit.**

Section	Description of Change
	For subjects entering the ~~52 week~~ optional **follow-up** treatment period with ≥7 days since last dose of LUM001, any of the above evaluations may also occur at clinic visits during the DE period.
Synopsis, Interim Analyses; Section 12.2.7, Interim Analyses	~~Two~~**The** following interim analyses are planned. … **A third interim analysis will be performed after all enrolled subjects have completed at least 6 months of treatment under Protocol Amendment 4 (or the Early Termination visit). This analysis will provide an assessment of the long-term safety and efficacy of LUM001. Subsequent interim analyses will be performed in yearly intervals.**
Synopsis, Exploratory Genetic Analyses; Section 12.2.10, Exploratory Genetic Analyses	**To better understand the role of genetics in treatment response, an additional blood sample will be taken for exome sequencing. The data analysis will focus initially on genetic variation in candidate genes that may have a role in treatment response, such as ASBT/SLC10A2 and genes in its pathway (ie upstream or downstream of ASBT/SLC10A2) and genes implicated in PFIC (ATP8B1, ABCB11 and ABCB4) with the goal of identifying genetic variation that may discriminate treatment responders from non-responders. Following examination of candidate genes, the data analysis may be expanded to evaluate genetic variation in additional regions of the exome. This genetic analysis is more comprehensive and may provide valuable information beyond the ATP8B1 and ABCB11 genes. The submission of this blood sample is voluntary. The results of this analysis may identify relevant genetic variants, only some of which will be of known clinical benefit.**
Synopsis, Exploratory Responder Analyses – Metabolomic and Proteomic Investigations; Section 8.6, Metabolomic and Proteomic Investigations; Section 12.2.11, Exploratory Responder Analyses (Metabolomic and Proteomic Investigations)	**As part of a comprehensive approach to identify serum markers in PFIC patients that respond well to treatment, previously collected serum samples will be analyzed using both metabolomic and proteomic biomarker discovery approaches. Metabolomics addresses the activity of small molecules (<10 kDa) produced by active and living cells during their life cycle. These molecules are not accessible by genomic, transcriptomic or proteomic approaches. Metabolomics monitors the chemical transformations in metabolic cascades and can be used to identify observable differences between patient populations. A targeted mass spectrometry proteomic approach will allow for the identification and quantitation of greater than 150 unique proteins in each serum sample. Serum samples from both responding and non-responding patients will be analyzed in both biomarker discovery platforms and the data will be evaluated for potential markers that can significantly delineate responders from non-responders.**
Synopsis, Palatability Data; Section 8.5.7, Palatability; Section 12.2.12, Palatability Analyses Section 16.11, Palatability Questionnaire	**Palatability data will be collected at each clinic visit in the follow up treatment period, with the exception of the DE and ADE visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age).** Added palatability questionnaire
Synopsis, Statistical Considerations	~~This plan will be finalized before the interim analysis of the Week 13 data takes place.~~ Safety measures including AEs, clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively by study phase

Section	Description of Change
Section 12, Statistical Considerations	(Weeks 0-13, 14-48, 49-72, 73-124) and over the entire study duration (Weeks 0-72, ~~0-124~~0-**EOT Visit**).
Section 4.4.1.3, Toxicology	As expected for a drug intentionally designed to work ~~in the intestinal lumen and~~ to be minimally absorbed, LUM001 exposure was very low and consistent with levels observed in adult rats. **The higher dosing level implemented with Protocol Amendment 4 is supported by favorable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (PND21 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.**
Section 4.5, Rationale for Dose and Schedule of Administration	*Updated Sample Daily Exposure (mg/day) in Pediatric Subjects table.* ~~To reduce the risk of loose stools and diarrhea in subjects in study LUM001-501 the LUM001 dose will be escalated over an up to 4-week period; dosing will start at 14 µg/kg/day, and will then be increased at 7-day intervals to 35 µg/kg/day, 70 µg/kg/day, 140 µg/kg/day and to a maximum of 280 µg/kg/day in the highest dose.~~ **To reduce the risk of loose stools and diarrhea in subjects in study LUM001-501, the 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). For BID dosing, the morning dose is initiated and escalated first; the afternoon dose is only initiated and escalated in patients with elevated sBA and/or ItchRO ≥1.5 on the maximum (or maximum tolerated) morning 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 (i.e. 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (i.e. 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 (PND21 through PND63). As expected for a drug intentionally designed to be minimally absorbed, systemic LUM001 exposure was very low and consistent with levels that**

Section	Description of Change
	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.
Section 5.1, Study Design	The study is divided into 5 parts: … and an optional ~~52-week~~ follow-up **treatment** period for eligible subjects who choose to stay on treatment with LUM001. **During the optional follow-up treatment period, subjects may be eligible for BID dosing based on efficacy as measured by sBA level and ItchRO score, and may have their dose of LUM001 increased to a maximum of 560 µg/kg/day (280 µg/kg BID).** Subjects' participation in the optional follow-up treatment period will continue until the first of the following ~~occur: i) completion of 52 weeks of additional treatment or ii) in the event that a new study of LUM001 opens to enrollment~~ **occurs: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.** **A second interim analysis will be performed** after all evaluable subjects have completed the Week 48 (or Early Termination) study visit. **A third interim analysis will be performed after all enrolled subjects have completed at least 6 months of treatment under Protocol Amendment 4 (or the Early Termination visit). Subsequent interim analyses will be performed in yearly intervals. See Section 12.2.7 for additional information.**
Section 5.5.2, Treatment	~~Study drug (LUM001) will be dispensed at the study site.~~ … ~~Subjects who weigh 10 kg or more at screening will receive a 1.0 mL grape-flavored solution containing LUM001. Subjects who weigh less than 10 kg at screening will receive a 0.5 mL grape-flavored solution containing LUM001. The volume administered will not change during the course of the study. 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 who are eligible to participate in the optional follow-up treatment period will be dosed according to the LUM001 dosing scenarios described in Section 10.1, and may be eligible for BID dosing based on efficacy, as assessed by sBA level and ItchRO score. The sBA value used for determination of ADE eligibility will be the most recent available value. The ItchRO score used for ADE eligibility will be derived from the most recent 2-week electronic diary collection period.**
Section 5.5.2.3, Long-term Exposure Period	However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the Sponsor Medical Monitor, may lower the dose ~~to a previously tolerated dose.~~ **for the remainder of the study.** **During the long-term exposure period, the dose may be adjusted to account for a change of ≥10% in weight since the screening visit (e.g. the amount of drug dosed may be increased to reflect the subject's weight increase).**
Section 5.5.2.4, Optional Follow-up Treatment Period	**Subjects eligible for the optional follow-up treatment period will continue treatment under dosing scenarios based on whether:** **-Their LUM001 dosing will continue without interruption or interruption of <7 continuous days, or** **-Their LUM001 dosing will continue with interruption ≥7 days.**

Section	Description of Change
	Eligibility for BID dosing will be determined based on efficacy as measured by sBA level and ItchRO score. **Subjects who enter the optional follow-up treatment period without LUM001 dosing interruption or with an interruption of <7 continuous days will be dosed in the following manner:** • **Subjects with normal sBA level AND ItchRO score <1.5 will be maintained at the same dose level and will continue morning dosing only.** • **Subjects with sBA level above normal AND/OR ItchRO score ≥1.5 will start BID dosing (afternoon dose escalation; ADE) as follows:** – **The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated.** – **The afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled, to a maximum dose of 280 µg/kg (or up to the maximum tolerated dose).** – **The maximum daily dose will be 280 µg/kg BID, i.e. 560 µg/kg/day (max. 25 mg BID).** **Subjects who enter the optional follow-up treatment period with a LUM001 dosing interruption of ≥7 days initially will receive morning dosing only and will undergo dose escalation (DE) in the following manner:** • **The morning dose will be initiated at Dose Level 2 (35 µg/kg) and doubled in weekly intervals to a maximum dose of 280 µg/kg , or up to the maximum tolerated dose.** • **Once the morning dose of 280 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO score will be evaluated.** • **Subjects with normal sBA AND ItchRO score <1.5 after morning dose escalation will be maintained at the same dose level and will continue morning dosing only.** • **Subjects with sBA above normal AND/OR ItchRO score ≥1.5 will begin BID dosing (afternoon dose escalation) as outlined above.** **Subjects will continue to receive study drug until they are eligible to enter another LUM001 study or until LUM001 is available commercially, whichever occurs first. The maximum daily dose will be 280 µg/kg BID, i.e. 560 µg/kg/day (maximum 25 mg). If a subject experiences intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician Investigator in consultation with the Sponsor Medical Monitor may lower the dose for the remainder of the study. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose.** **The sBA value used for determination of ADE eligibility will be the most recent available value. The ItchRO score used for ADE eligibility will be derived from the most recent 2-week electronic diary collection period.** ~~Subjects who are eligible to roll over on to 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 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.~~

Section	Description of Change
	~~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 Dose Level 2 (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 maximum tolerated dose.~~ ~~If a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the Sponsor Medical Monitor, may lower the dose to a previously tolerated 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 long-term exposure period.~~ ~~During the long-term exposure period, subjects will return to the clinic at Weeks 24, 36, 44, 48, 60 and 72. 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 Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 48 and 72. At the Week 24 and Week 44 visits, electronic diaries will be issued and AEs and concomitant medications will be assessed and recorded.~~ ~~Subjects/caregivers will receive follow-up phone calls at Weeks 16, 20, 28, 32 and 40. Concomitant medications and any adverse events (AEs) will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.~~ ~~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 Week 44, additional study drug will be supplied at each clinic visit during the long-term exposure period.~~
Section 5.5.2.5, Safety Follow-up 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 AEs noted during this phone call will be recorded. Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in the optional follow-up treatment period under Protocol Amendment 4.** Additional study ~~drug will be supplied at each clinic visit during the follow-up treatment period. Unused~~ Used study drug will be collected at ~~the Week 124~~ **each clinic** visit **and dosing compliance assessed**

Section	Description of Change
Section 5.5.3, Electronic Diary	For subjects who enter the optional follow-up treatment period, **twice daily completion of the electronic diary will occur** during the 2 weeks that follow the Week 84, 96, 108, and 120 **visits, Protocol Amendment 4 DE Week 4, and every clinic visits.visit within each recurring 12-week period**. Electronic diaries will be provided to subjects and caregivers ~~at the Week 24, 44, 84, 96, 108, and 120 visits,~~ and re-training on the use of the diary will occur, as appropriate, at these visits.
Section 5.6, End of Study	**For subjects who did not consent to the optional follow-up treatment period, a subject is considered to have completed treatment if treatment was not permanently discontinued prior to the Week 72 visit. A follow-up phone contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.** **For subjects who consented to the follow-up treatment period, an additional follow-up period disposition is collected in the eCRF. The subject is considered to have completed treatment during the follow-up treatment period if study treatment was not permanently discontinued prior to the subject completing the EOT visit as defined in the most recent consent signed by the subject. A follow-up contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.**
Section 6.2, Enrollment	**Subjects will be enrolled into the optional follow-up treatment period based on the eligibility criteria outlined in Section 7.3.**
Section 8.1.4, 280 µg/kg/day Stable Dosing Treatment Period (Week 9 to Week 13)	At all sites (US, UK, EU and Australia), blood sampling for plasma levels of LUM001 will be collected at Week 13. Blood will be drawn approximately 4 hours post **morning** dosing **for drug level analysis**.
Section 8.1.5, Long-Term Exposure Period (Week 14 to Week 72)	However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator in consultation with the Sponsor Medical Monitor may lower the dose ~~to a previously tolerated dose~~ **for the remainder of the study.** … **Used study drug will be collected at each clinic visit, and dosing compliance will be assessed.** … **At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the optional follow-up treatment period. Following completion of the Week 72 study visit, 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.**
Section 8.1.6, Early Termination for Subjects without Participation in the Optional Follow-up Treatment Period	(new section heading) Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo all procedures specified for the Week 72 study termination visit. In addition the following assessments should be completed; the ItchRO (if prior to the Week 48 visit), the clinician administered pruritus 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 Section 16.1).; **Schedule J**). For safety reasons, efforts must be made to follow subjects for at least 30 days following their last dose of study drug.
Section 8.1.8, 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 J). The following assessments are to be completed at the EOT/ET 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-**

Section	Description of Change
	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. The ItchRO, the clinician administered pruritus scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, and palatability questionnaire also will be completed, as defined for Early Termination (see Section 16.1).
Section 8.1.9, Safety Follow-up 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 AEs noted during this phone call will be recorded. Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in the optional follow-up treatment period.**
Section 8.2, Genetic Testing	**In addition, to better understand the role of genetics in treatment response, an additional blood sample will be taken for exome sequencing. The data analysis will focus initially on genetic variation in candidate genes that may have a role in treatment response, such as ASBT/SLC10A2 and genes in its pathway (ie upstream or downstream of ASBT/SLC10A2) and genes implicated in PFIC (ATP8B1, ABCB11 and ABCB4) with the goal of identifying genetic variation that may discriminate treatment responders from non-responders. Following examination of candidate genes, the data analysis may be expanded to evaluate genetic variation in additional regions of the exome. This genetic analysis is more comprehensive and may provide valuable information beyond the ATP8B1 and ABCB11 genes. The submission of this blood sample is voluntary. The results of this analysis may identify relevant genetic variants, only some of which will be of known clinical benefit. A blood sample for exome sequencing will be drawn once, at the time of consent under Protocol Amendment 4.**
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, Pediatric Quality of Life Inventory (PedsQL); Section 8.5.4, Patient Impression of Change; Section 8.5.5, Caregiver Impression of Change; Section 8.5.6, Caregiver Global Therapeutic Benefit	Edited text to indicate all assessments will be performed as outlined in the Schedule of Procedures in Section 16.1.
Section 8.7.1, 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 screening ~~until the end of the study~~, **throughout the study period and for 30 days following the last dose of the IP.** ~~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.~~

Section	Description of Change
	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 (e.g., 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, e.g., (i) condom (male or female) or (ii) diaphragm, with spermicide; or** **c. Intrauterine device (IUD).** **d. or 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 9.1.1, LUM001	Added new composition of LUM001 1.0 mL Oral Solution and Composition of LUM001 0.5 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.**
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 10.5.2, 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.**
Section 10.6, Adjustment of Dose	**If the subject is on twice daily dosing regimen, dose lowering should first be attempted with the afternoon 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 76 for subjects who do not roll over into the 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 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/assent form and will stop ~~at the end of the subject's follow-up period, which is~~

Section	Description of Change
	~~defined as Week 76 for subjects who do not roll over into the 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 76 or Week 124 visit. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.~~
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 PFIC may have abnormal liver enzyme levels at baseline.**
Section 12.2.3.2, Baseline Data	• **Growth parameters including height and weight at baseline.**
Section 12.2.6.6, Serum Alpha-fetoprotein	**Assessments of serum alpha-fetoprotein (AFP) will be listed for individual subjects and summarized using descriptive statistics by study visit.**

Section 16.1, Schedule of Procedures	Added Overall Scheme and Corresponding Schedule of Procedures
	
	Added Schedule of Procedures E-F: Rollover under Protocol Amendment 4:
	
	Schedule of Procedures E – Extension of Optional Follow-up Treatment Period, for subjects ineligible for ADE, applicable as follows:
	• Subject did not yet complete the optional follow up treatment period as outlined under Protocol Amendment 3 and is able to consent to Protocol Amendment 4 activities without an interruption in LUM001 dosing, OR
	• Subject completed optional follow up treatment period as outlined under PA3 and dosing interruption was <7 days.
	• Subject deemed ineligible for ADE.
	
	Schedule of Procedures F – Extension of Optional Follow-up Treatment Period, for subjects eligible for ADE, applicable as follows:
	• Subject did not yet complete the optional follow up treatment period as outlined under Protocol Amendment 3. (PA3) and is able to consent to Protocol Amendment 4 activities without an interruption in LUM001 dosing OR
	• Subject completed the optional follow up treatment period as outlined under PA3 and dosing interruption was <7 days.
	• Subject deemed eligible for ADE.
	
	Added Schedule of Procedures G-I: Rollover under Protocol Amendment 4:
	
	Schedule of Procedures G – Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, applicable as follows:
	• Subject previously completed (or early terminated from) the optional follow up treatment period as defined under Protocol Amendment 3 and has subsequently experienced an interruption in LUM001 dosing ≥7days
	• Subject is considered eligible for study re-entry under Protocol Amendment 4
	• Subject eligibility will be assessed for afternoon dose escalation at Protocol Amendment 4 DE Week 8 shown in the table below.
	  ○ If subject is found to be ineligible for ADE, subject will move from Schedule G to Schedule H.
	  ○ If subject is found to be eligible for ADE, subject will move from Schedule G to Schedule I.

Section	Description of Change
	Schedule of Procedures H – Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject ineligible for ADE Schedule of Procedures I – Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject eligible for ADE Added Schedule of Procedures J - Study Termination and End of Treatment Procedures
Section 16.2, List of Laboratory Analytes	Added ABC4 under Screening Tests Added alpha-fetoprotein (AFP) under Marker of hepatocellular carcinoma

PROTOCOL AMENDMENT 3

Protocol Number: LUM001-501

Protocol Title: OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Amendment: **3**

Date: **02 November 2015**

The LUM001-501 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 LUM001-501 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.

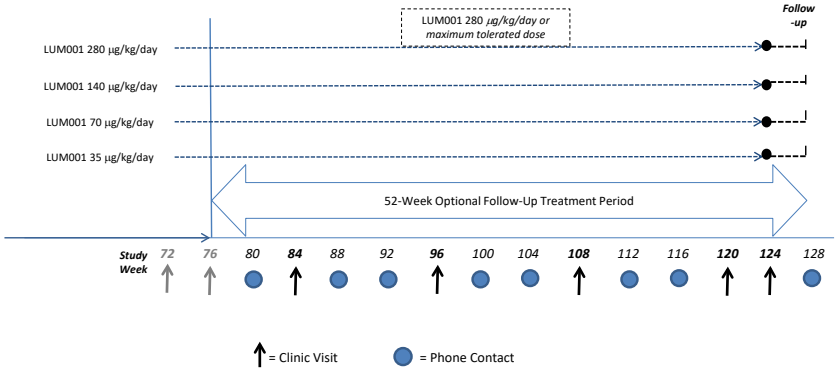
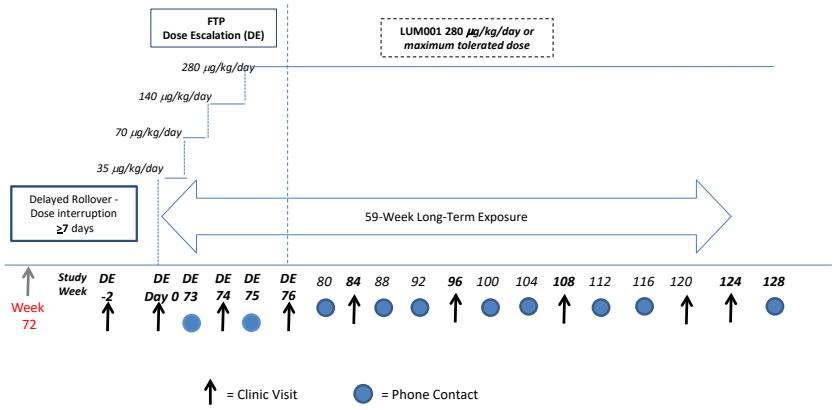
The following changes have been made to the Protocol Amendment 2 (05 November 2014). Note that correction of typos and grammatical errors are not captured in the below table.

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

Section	Description of Change
Title page; Sponsor Contact	**Added:** **Sponsor Medical Monitor:** Susanne Schmidt, MD, PhD Premier Research Office: +1 215 282 5406 Cell: +1 267 838 2380 Email: medmonitorLUM501@premier-research.com
Title page; Sponsor Contact	**Changed "Sponsor Contact" from:** Ciara Kennedy, PhD Lumena Pharmaceuticals, Inc. Phone: +1-858-337-7922 Email: ckennedy@lumenapharma.com **To "Sponsor 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
Synopsis; Objectives Section 3; Objectives	**Changed:** ~~The~~ Objectives of ~~this~~ study ~~are~~: **To:** Objectives of study (Up to and including Week 72):

Section	Description of Change
	Added: Objectives of Optional Follow-up Treatment Period (After Week 72): • To offer eligible subjects in the LUM001-501 study continued study 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.
Synopsis; Objectives Section 3; Objectives Synopsis; Efficacy Evaluations	**Deleted:** • To evaluate the long-term durability of effect of LUM001 in patients with PFIC during 48 weeks of treatment. **Deleted:** ~~Durability of effect~~ from efficacy analyses **Rationale for this change:** The objective evaluating durability of effect of LUM001 was removed. Durability of effect cannot be assessed in this study since it is not placebo controlled and a treatment effect has not yet been established.
Synopsis; Study Design Section5.1; Study Design	**Changed:** The study is divided into 4 parts: a 4-week dose escalation period, a 4-week stable dosing period at 140 µg/kg/day, a 5-week stable dosing period at 280 µg/kg/day, ~~and~~ a 59-week long-term exposure period. **To:** The study is divided into 5 parts: a 4-week dose escalation period, a 4-week stable dosing period at 140 µg/kg/day, a 5-week stable dosing period at 280 µg/kg/day, a 59-week long-term exposure period, and an optional 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 opens to enrollment.
Synopsis; Study Population; Exclusion Criteria Section 7.2; Exclusion Criteria	**Added:** 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 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 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.
Synopsis; Study Drug Dosage and Administration, Rationale for Dose and Schedule Selection Section 10.1 Study Drug Administration	**Changed:** During this period the dose may be adjusted if there is a change of ≥10% in weight since the ~~baseline~~ visit. **To:** During this period the dose may be adjusted if there is a change of ≥10% in weight since the screening visit.

Section	Description of Change
Synopsis; Study Drug Dosage and Administration Section 5.5.2; Treatment Section 5.5.2.1; Dose Escalation Period Section 5.5.2.3; Long-term Exposure Period	**Deleted:** Dosing with LUM001 will continue at a fixed dose in a 59-week long-term exposure period ~~to complete 72 weeks of total drug exposure~~. **Added:** At the investigator's discretion and in consultation with the Sponsor Medical Monitor, subjects… At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll over into the 52-week optional follow-up treatment period. Following the completion of the Week 72 study visit, subjects who choose to participate in the optional follow-up treatment period will enter under one of the following LUM001 dosing scenarios: • 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 dosing 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 Dose Level 2 (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. **Deleted:** ~~The anticipated adverse reaction or intolerance is gastrointestinal in nature (e.g., diarrhea, abdominal pain, cramping, etc.). In the absence intolerance, escalation to the next dose level for an individual subject will occur following a scheduled phone call or visit, see Schedule of Procedures, Section .16.1.~~ **Added:** If a subject experiences intolerance due to gastrointestinal symptoms (eg, diarrhea, abdominal pain, cramping) at any time during the study, the physician …
Synopsis; Rationale for Dose and Schedule Selection	**Added:** To reduce the risk of loose stools, diarrhea and abdominal pain/cramps in this study up to Week 72, the LUM001 dose will be escalated over the first 4 weeks. For subjects in the 52-week optional follow-up treatment period with ≥7 days since the last dose of LUM001, dosing will start at 35 µg/kg/day, and will then be increased over the first 4 weeks up to 280 µg/kg/day or to the maximum tolerated dose starting at Dose Level 2 (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. During the long-term exposure period and the optional follow-up treatment period, the dose may be adjusted… 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.

Section	Description of Change
Synopsis; Study Visit Schedule and Procedures Section 5.5; Overall Study Duration and Follow-up	**Added:** 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. **Follow-up Treatment Scheme** **(no interruption in LUM001 dosing, or interruption <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*** **Follow-up Treatment Scheme** **(interruption in LUM001 dosing ≥7 days):** 
Synopsis; Study Visit Schedule and Procedures	**Added:** Week 72: Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the optional 52-week follow-up treatment period. Eligible subjects must have documented consents in order to continue in the optional follow-up treatment period. … Study drug will be discontinued at this visit if the subject chooses not to participate in the follow-up treatment period.

Synopsis; Study Visit Schedule and Procedures / Follow-up Treatment Period Section 5.5.2.4, Section 8.1.6; Follow-up Period Section 8.1.8 Optional Follow-up Treatment Period	**Added:** Follow-up Treatment Period: For subjects who do not roll over into 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. 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. Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in a follow-up treatment period. Optional Follow-up Treatment Period (post-Week 72 to Week 124): Subjects who are eligible to roll over on to 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 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 maximum tolerated dose starting at Dose Level 2 (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 maximum 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 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, and 124. The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 108, 120, and 124. Subjects/caregivers will receive follow-up phone calls at Weeks 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.

Section	Description of Change
	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 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. 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. Unused study drug will be collected at the Week 124 visit.
Synopsis; Efficacy Evaluations Section 12; Statistical Considerations	**Changed:** The main focus for the analyses of efficacy is the period from Baseline (Day 0) to Week 13. The period from Baseline (Day 0) to Week 48 will be analysed ~~for durability of effect~~ and the period from Weeks 48-72 ~~has~~ been added … **To:** The main focus for the analyses of efficacy is the period from Baseline (Day 0) to Week 13. The period from Baseline (Day 0) to Week 48 will be analysed and the period from Weeks 48-72 and 73-124 have …
Synopsis; Efficacy Evaluations Section 12.2.9.1; Efficacy Variables	**Deleted/Changed:** Pattern of change in serum bile acids from Baseline (Day 0) to Week ~~48~~ 124 will be evaluated ~~to determine the durability of therapeutic effect. The durability of effect criteria~~ and its appropriate analysis methodology… Secondary evaluations ~~for the durability of the therapeutic effect~~ will be… Additional evaluations of safety and ~~durability of therapeutic effect~~ efficacy surrogates will be specified in the Statistical Analysis Plan. **Rationale for this change:** The objective evaluating the 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).
Synopsis; Efficacy Evaluations Section 12.2.9.1; Efficacy Variables; Section 16.7; Patient Impression of Change Section 16.8; Caregiver Impression of Change Section 16.9; Caregiver Global Therapeutic Benefit	**Added:** Additional assessment time points at Week 72, 84, 96, 108, 120, and 124 were added to the efficacy parameters:

Section	Description of Change
	• Change from Baseline (Day 0) in fasting serum bile acid level • Change from Baseline (Day 0) for ALT, and bilirubin (total and direct) • Change from Baseline (Day 0) for other biochemical markers of cholestasis [total cholesterol, low-density lipoprotein cholesterol (LDL-C)] • Change from Baseline (Day 0) in bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)] • Change from Baseline (Day 0) for PedsQL • Change from Baseline (Day 0) for other biochemical markers [autotaxin and lysophosphatidic acid (LPA)] • Change from Baseline (Day 0) for measures of bile acid synthesis (FGF-19 and FGF-21) • Change from Baseline (Day 0) in the Clinician Scratch Scale Additional assessment time points at Week 48, 86, 98, 110, and 122 were added to the efficacy parameters: • Change from Baseline (Day 0) in pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO) • Responder analysis; pruritus response rates as measured by ItchRO (Observer ItchRO/patient ItchRO) Additional assessment time points at Week 108, 120, and 124 were added to the efficacy parameters: • Patient Impression of Change (PIC) • Caregiver Impression of Change (CIC) • Caregiver Global Therapeutic Benefit (CGTB) For subjects entering the 52-week optional treatment period with ≥7 days since last dose of LUM001, any of the above evaluations may also occur at clinic visits during the DE period.
Synopsis; Interim Analyses Section 12.2.7;Interim Analyses	**Deleted:** This analysis will provide an assessment of the long-term safety and ~~durability of effect~~ efficacy of LUM001.
Synopsis; Statistical Considerations	**Added:** Safety measures including AEs, clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively by study phase (Weeks 0-13, 14-48, 49-72, and 73-124) and over the entire study duration (Weeks 0-72, and 0-124).
Section 5.5.2; Treatment	**Deleted:** ~~Dosing will occur over a 13-week treatment period followed by a 59-week long-term exposure period.~~ **Added:** Dosing will occur over a 13-week treatment period (comprised of 4-weeks dose escalation [Dose Level 1-4], 4-weeks stable dosing at 140 µg/kg/day, and 5-weeks stable dosing at 280 µg/kg/day), followed by a 59-week long-term exposure period.

Section	Description of Change
Section 5.5.3; Electronic Diary	**Deleted/Added:** Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects beginning at the screening visit through the end of the Week 13 visit and again during the 4 weeks that follow the Week 24 and Week 44 clinic visits and, for subjects who enter the optional follow-up treatment period, during the 2 weeks that follow the Week 84, 96, 108, and 120 clinic visits. Electronic diaries will be provided to subjects and caregivers at ~~Weeks~~ the Week 24, 44, 84, 96, 108, and 120 visits, and re-training on the use of the diary will occur, as appropriate, at these ~~2~~ visits.
Section 5.5.4; Follow-up	**Changed:** Study drug (LUM001) will be discontinued at Week 72 and subjects will be followed for an additional 4 weeks. A safety follow-up phone call will be made at Week 76. Subjects who complete the study may be eligible for participation in a long-term extension study of LUM001. **To:** Study drug (LUM001) will be discontinued at Week 72 if the subject chooses not to participate in the optional follow-up treatment period and subjects will be followed for an additional 4 weeks. A safety follow-up phone call…
Section 8.1.5; Long-term Exposure Period Section 10.6; Adjustment of Dose	**Added:** At the investigator's discretion and in consultation with the Sponsor Medical Monitor, subjects who were previously down-titrated may be re-challenged.
Section 8.2; Genetic Testing	**Added:** *ATP8B1* or *ABCB11* mutations are predictive of PFIC. For subjects who do not have documentation of an *ATP8B1* or *ABCB11* 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 PFIC including the type of mutation recorded. For those participants for which the type of the mutation cannot be documented, genetic testing may be conducted and the results recorded.
Section 8.3; Physical Examination	**Added:** For subjects who enter into the optional follow-up treatment period, physical examinations will also be conducted at Week 84, Week 96, Week 108, Week 120, and Week 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 Day 0, DE Week 74, and DE Week 76.
Section 8.5.1; Itch Reported Outcome	**Added:** For subjects who enter the optional follow-up treatment period, daily completion of the diary will also be during the 2 weeks following the Week 84, 96, 108, and 120 clinic visits.
Section 8.5.2; Clinician Scratch Scale	**Added:** 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; Pediatric Quality of Life Inventory	**Added:** For subjects who enter the 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.

Section	Description of Change
	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 8.5.4; Patient Impression of Change	**Changed:** The PIC will be completed, by subjects who were 9 years of age or older at the screening visit. It will be completed at the Weeks 13, 48 and 72 visits, see Section 16.7. For subjects who enter the optional follow-up treatment period, the PIC will also be administered at Weeks 108, 120, and 124. **To:** The PIC will be completed by subjects who were 9 years of age or older at the Week 13, Week 48, and Week 72 visits. For subjects who enter the optional follow-up treatment period, the PIC will be completed by subjects who were 9 years of age or older at the Weeks 108, 120, and 124 (see Section 16.7).
Section 8.5.5; Caregiver Impression of Change	**Added:** For subjects who enter the optional follow-up treatment period, the CIC will also be administered at Weeks 108, 120, and 124.
Section 8.5.6; Caregiver Global Therapeutic Benefit	**Added:** For subjects who enter the optional follow-up treatment period, the CGTB will also be administered at Weeks 108, 120, and 124.
Section 10.1; Study Drug Administration	**Added:** During the long-term exposure period (Week 14 to Week 72) of the study, and during the optional follow-up treatment period (Week 76 to Week 124)….
Section 10.3; Concomitant Medications	**Added/Changed:** …administered during participation in the study (the period from the first day of screening through the last contact at Week ~~76~~128).
Section 11.3.1; Serious Adverse Events	**Added/Changed:** 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 ~~72~~76 for subjects who do not roll over into the 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 ~~the~~ prior to the Week ~~72~~ 76 or Week 124 visit.
Section 11.3.2; Non-Serious Adverse Events	**Added/Changed:** 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 76 for subjects who do not roll over into the 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 76 or Week 124 visit.
Section 12; Statistical Considerations	**Added:** Summaries will be provided by study phase (Weeks 0-13, 14-48 and, 49-72, 73-124) and over the entire study duration (Weeks 0-72 and 0-124), by visit…
Section 12.2.6; Safety Analyses	**Added:** Safety data, including AEs, clinical laboratory tests, vital signs, physical examinations, and concomitant medication usage will be summarized descriptively by study phase (Weeks 0-13, 14-48, 49-72, and 73-124) and over the entire study duration (Weeks 0-124).
Section 12.2.9.1; Efficacy Variables	**Added:** For this instrument the caregiver and/or subject indicate the itch severity in the morning and in the evening each day during screening and during the designated study periods

Section	Description of Change
	[Day 0 – 13, Week 24-28, Week 44-48, Week 84-86, Week 96-98, Week 108-110, and Week 120-122]. If a caregiver is not compliant with the ItchRO (Obs) at Weeks 13, 28, 48, 86, 98, 110, and 122, the average daily…
Section 16.1; Schedule of Procedures	**Added:** Two new Schedules of Procedures for the Optional Follow-up Treatment Period (Week 72-Week 124) for 1) subjects with no interruption in LUM001 dosing or interruption <7 days and 2) Subjects with interruption in LUM001 dosing ≥7 days.

PROTOCOL AMENDMENT 2

Protocol Number: LUM001-501

Protocol Title: OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Amendment: **2**

Date: 05 November 2014

The following changes have been made to the Protocol Amendment 1 (US version dated December 10, 2013 and UK/EU version dated May 7, 2014).

The inclusion criterion related to serum bile acid levels is changed from intrahepatic cholestasis manifested by "fasting total serum bile acid to >100 μmol/L" to "total serum bile acid >3x upper limit of normal for age."

The inclusion criterion related to the ability to read and understand English has been expanded to accommodate the following languages: English, Spanish, US Spanish, French, German or Polish.

The exclusion criterion related to a surgical procedure resulting in disruption of the enterohepatic circulation at the time at screening has been clarified to indicate that subjects who have undergone reversal of such surgical procedures and have a permanently restored flow of bile acids from the liver to the terminal ileum may be eligible for the study upon consultation with the Sponsor Medical Monitor.

An exclusion criterion has been added to specify that the administration of sodium phenylbutyrate within 30 days prior to the Baseline / Day 0 visit and during the study is prohibited.

The number of subjects is increased from 12 subjects to approximately 24 evaluable subjects inclusive of the replacement of any subjects who may substantially violate the protocol. A minimum of 8 subjects with FIC1 (ATP8B1 related disease) subjects will be enrolled.

The duration of the treatment period has been increased from 48 weeks to 72 weeks.

The number of clinic visits is increased by 2 (total 12 clinical visits) to accommodate the extended duration of the study. Procedures and assessments for these 2 study visits have been added.

Text has been included to indicate that all assessments completed by the subject and caregiver will be provided as validated translations in the following languages: English, Spanish, US Spanish, French, German or Polish.

The sampling schedules for pharmacokinetic (PK) analysis of LUM001 levels have been clarified to accommodate the requirement for more frequent PK sampling in the US, as was requested by the Food and Drug Administration (FDA), compared to the sampling schedule for the UK, EU and Australia.

An ultrasound at the screening visit will not be required if the results of an ultrasound completed within 6 months are available to the investigator and the clinical status of the subject has not changed significantly since the time of the test.

Revised text was added to indicate that a physical exam will be conducted only at the Screening, and the Weeks 24, 36, 48, 60 and 72 clinic visits.

The frequency of study drug dispensation has been clarified to indicate that study drug will not be dispensed at the Week 44 visit.

The section on Safety Monitoring Rules and Safety Monitoring for Liver Chemistry Tests were clarified to indicate that repeat testing is required within 48 to 72 hours of the availability of the initial report instead of within 48 to 72 hours of the initial collection.

As second interim analysis has been added when all enrolled subjects have reached the 48 week visit.

The Statistical Considerations section has been updated to reflect the increase in the study's duration and the increase in study visits.

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 exposure data from 39 weeks to 76 weeks, inclusive of 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 long term exposure period from 35 weeks to 59 weeks, treatment duration from 48 weeks to 72 weeks and study duration from 52 to 76 weeks, inclusive of 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 Patient & Caregiver Impression of Change evaluation at Week 72.
Synopsis (Section 1), Number of Subjects Number of Subjects (Section 5.4) Statistical Considerations (Section 12)	Increased from 12 to approximately 24 evaluable subjects. At least 8 subjects with FIC1 will be enrolled (increased from 5).
Synopsis (Section 1), Stable Dosing Periods (Section 5.5.5.2)	Text has been clarified to indicate that at Week 8, the dose will be increased to level 5 only for subjects who tolerated dose level 4.
Synopsis (Section 1), Inclusion Criterion #2a (Section 7.1)	Criterion has been modified from "fasting total serum bile acid to >100 µmol/L" to "total serum bile acid >3x upper limit of normal for age".

Section	Description of Change
Synopsis (Section 1), Inclusion Criterion #8 (Section 7.1)	Criterion has been expanded to specify that eligible subjects and caregivers must be able to read and understand the primary language(s) of the country in which the study is being conducted.
Synopsis (Section 1), Exclusion Criterion #2 (Section 7.2)	Criterion clarified to indicate that subjects who have undergone reversal of a prior surgical procedure intended to disrupt enterohepatic circulation and who have a permanently restored flow of bile acids from the liver to the terminal ileum may be eligible for the study upon consultation with the Medical Monitor.
Synopsis (Section 1), Exclusion Criterion #13 (Section 7.2)	Criterion clarified to specify that administration of bile acid or lipid binding resins within 30 days prior to Baseline / Day 0 and throughout the trial is excluded.
Synopsis (Section 1), Exclusion Criterion #14 (Section 7.2)	Criterion added to exclude the administration of sodium phenylbutyrate within 30 days prior to Baseline / Day 0 and throughout the trial. (As a result, the total number of exclusion criteria has increased from 16 to 17.)
Synopsis (Section 1), Drug Level Evaluations, Study Procedures (Section 8), Section 16.1	Added collection of PK samples at Weeks 60 and 72; Clarified sampling schedules.
Number of Study Centers (Section 5.3)	Changed from 3-7 centers to approximately 12 centers.
Synopsis (Section 1), Study Visit Schedule and Procedures Screening Period (Section 8.1.1)	Text inserted to indicate that a screening ultrasound will not be required if the results of an ultrasound completed within 6 months are available, provided the clinical status of the subject has not changed significantly since the time of the test.
Synopsis (Section 1), Statistical Considerations (Section 12)	Statistical considerations revised to reflect an additional interim analysis; updated analyses to reflect the increase in the study's duration and number of visits. Clarified that the main focus for the analyses of efficacy is the period from Baseline (Day 0) to Week 13. The period from Baseline (Day 0) to Week 48 will be analysed for durability of effect and the period from Weeks 48-72 has been added to obtain additional safety data and to monitor biochemical markers of cholestasis. Specified that there will be two analysis populations for efficacy: the Per Protocol population (PP) will consist of all subjects in the MITT population who did not have a major protocol violation, inclusive of violation of entry the criteria. Subjects in this population will be referenced as evaluable.
Physical Examination, Weight, Height, Vital Signs (Section 8.3) Dose Escalation Treatment Period (Day 0 to Week 4) (Synopsis and Section 8.1.2)	Text revised to indicate that a physical examination on each subject should be completed at screening and at the Weeks 24, 36, 48, 60 and 72 clinic visits.
Long-Term Exposure Period (Sections 5.5.2.3 and 8.1.5)	With the exception of the Week 44 and the Study Termination Visit (End of Study), additional study drug will be supplied at each clinic visit during the long-term exposure period.
Long-term Exposure Period (Section 8.1.5)	Added clinic visits at Weeks 60 and 72 and adjusted schedule of procedures as noted in Section 16.1.
Follow-up Period (Week 73 to Week 76) (Section 8.1.6)	Extended follow-up period to Weeks 73-76.

Section	Description of Change
Physical Examination, Weight and Height, Vital Signs (Section 8.3)	Added assessments at Weeks 60 and 72.
Early Termination (Section 8.1.7)	Changed Week 48 to Week 72.
Genetic Testing (Section 8.2)	Clarified that blood samples for genotyping will be collected at the screening visit for subjects who do not have documentation of an *ATP8B1* or *ABCB11* mutation; added text to indicate that genetic counseling will be provided in accordance with local laws.
Pruritus and Quality of Life Assessments (Section 8.5)	Added text to clarify that assessments completed by the subject and caregiver will be provided as validated instruments in the primary language(s) of the country in which the subject and caregiver are participating in the study.
Clinician Scratch Scale (Section 8.5.2)	Added assessments at Weeks 60 and 72.
Pediatric Quality of Life Inventory PedsQL (Section 8.5.3)	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.
Patient Impression of Change (Sections 8.5.4 and 16.7)	Added assessment at Week 72; removed assessment at Screening.
Caregiver Impression of Change (Sections 8.5.5 and 16.8)	Added assessment at Week 72.
Caregiver Global Therapeutic Benefit (Section 8.5.6)	Added assessment at Week 72.
Replacement of Subjects (Section 6.3)	Text has been added to indicate that subjects who substantially violate the protocol may be replaced in order to enroll approximately 24 evaluable subjects.
Safety Monitoring Rules (Section 10.5.2), Safety Monitoring for Liver Chemistry Tests (Section 10.5.2.1)	Text has been modified to specify that confirmation specimen collections should take place within 48 to 72 hours of the availability of the report.
Schedule of Procedures (Section 16.1)	Modified to reflect changes listed above
Liver Disease Diagnoses Excluded from PFIC Definition (Section 16.3)	Clarified criterion #8 to indicate that a confirmed diagnosis of bile acid synthesis defects is excluded; however, testing during screening for bile acid synthesis defects is not a required.
Administrative Changes	To correct typographical errors.

PROTOCOL AMENDMENT 1 (UNITED STATES)

Protocol Number: LUM001-501

Protocol Title: OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Amendment: **1 (US)**

Date: 10 December 2013

The following changes have been made to the original protocol.

In order to limit propylene glycol (PG) exposure to within the recommended limits (WHO acceptable daily intake limits of 25 mg/kg/day), the volume of study drug administered has been reduced from 1 mL to 0.5 mL for subjects who weigh less than 10 kg.

The frequency for the evaluation of LUM001 plasma levels of has been clarified. Blood sampling for LUM001 determination will occur at baseline, and visits at Weeks 2, 4, 8, 13, 24, 36 and 48. To maximize the information generated from sparse sampling, and based on a T_{max} of LUM001 in adults of 2.3 hours, a blood sample for study drug determination will be collected at approximately 2 hours post-dosing at Week 4. At Weeks, 2, 8, 13, 24, 36 and 48, blood samples for study drug determination will be collected at approximately 4 hours post-dosing.

Safety Monitoring Rules and Safety Monitoring for Liver Chemistry Tests will be modified to require repeat testing within 48 to 72 hours.

The section “Further Investigation into Liver Chemistry Elevations” has been modified to include additional evaluations in the event of a confirmed ALT or total bilirubin level.

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

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

Section	Description of Change
Inclusion Criteria (Section 7.1)	Text revised to include upper age limit of 18 years of age.
Treatment (Section 5.5.2), Dose Escalation Period (Section 5.5.2.1), Study Drug Administration (Section 10.1)	Text revised to indicate that subjects who weigh 10 kg or more at screening will receive a 1.0 mL solution containing LUM001. Subjects who weigh less than 10 kg at screening will receive a 0.5 mL solution containing LUM001. The volume administered will not change during the course of the study.
Study Design (Section 5.1)	Blood samples will be collected at baseline and Weeks 2, 4, 8, 13, 24, 36 and 48 for study drug determination. At Week 4, blood will be drawn approximately 2 hours post-dosing for drug level analysis. At Weeks 2, 8, 13, 24, 36 and 48, blood will be drawn approximately 4 hours post dosing for drug level analysis.
Study Drug Description (Section 9.1)	A tabular description of the composition of the LUM001 0.5 mL solution has been included
Safety Monitoring Rules (Section 10.5.2)	Text has been modified to specify that confirmation specimen collections should take place as within 48 to 72 hours of the initial collection.
Safety Monitoring for Liver Chemistry Tests (Section 10.5.2.1)	The section has been modified to require repeat testing within 48 to 72 hours: "If at any time in the study an ALT or total bilirubin result meets the criteria shown in the table below, in relation to the subject's baseline level, the initial measurement(s) should be confirmed within 48 to 72 hours of the initial collection."
Further Investigation into Liver Chemistry Elevations (Section 10.5.2.1)	This section has been modified to include the following evaluations in the event of a confirmed elevation in ALT or total bilirubin level: • Close and frequent monitoring of liver enzyme and serum bilirubin tests as clinically indicated. Frequency of retesting can decrease if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. If the appropriate frequency of monitoring is not feasible study drug administration will be suspended. • Obtain a detailed history of symptoms and prior and concurrent diseases. • Obtain comprehensive history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

Section	Description of Change
	• Obtain a history for exposure to environmental chemical agents and travel. • Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel). • Serology for autoimmune hepatitis [e.g., antinuclear antibody (ANA)]. Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor.
Section 16.6	Addition of the PedsQL quality of life questionnaire of children between the ages of 0-12 months.

PROTOCOL AMENDMENT 1 (UNITED KINGDOM & EUROPE)

Protocol Number: LUM001-501

Protocol Title: OPEN-LABEL STUDY OF THE EFFICACY AND LONG-TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Amendment: **1 (UK and EU)**

Date: 07 May 2014

The following changes have been made to the original protocol.

In order to limit propylene glycol (PG) exposure to within the recommended limits (WHO acceptable daily intake limits of 25 mg/kg/day), the volume of study drug administered has been reduced from 1 mL to 0.5 mL for subjects who weigh less than 10 kg.

Safety Monitoring Rules and Safety Monitoring for Liver Chemistry Tests will be modified to require repeat testing within 48 to 72 hours.

The section "Further Investigation into Liver Chemistry Elevations" has been modified to include additional evaluations in the event of a confirmed ALT or total bilirubin level.

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

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

Section	Description of Change
Inclusion Criteria (Section 7.1)	Text revised to include upper age limit of 18 years of age.

Section	Description of Change
Treatment (Section 5.5.2), Dose Escalation Period (Section 5.5.2.1), Study Drug Administration (Section 10.1)	Text revised to indicate that subjects who weigh 10 kg or more at screening will receive a 1.0 mL solution containing LUM001. Subjects who weigh less than 10 kg at screening will receive a 0.5 mL solution containing LUM001. The volume administered will not change during the course of the study.
Study Drug Description (Section 9.1)	A tabular description of the composition of the LUM001 0.5 mL solution has been included.
Safety Monitoring Rules (Section 10.5.2)	Text has been modified to specify that confirmation specimen collections should take place as within 48 to 72 hours of the initial collection.
Safety Monitoring for Liver Chemistry Tests (Section 10.5.2.1)	The section has been modified to require repeat testing within 48 to 72 hours: "If at any time in the study an ALT or total bilirubin result meets the criteria shown in the table below, in relation to the subject's baseline level, the initial measurement(s) should be confirmed within 48 to 72 hours of the initial collection."
Further Investigation into Liver Chemistry Elevations (Section 10.5.2.1)	This section has been modified to include the following evaluations in the event of a confirmed elevation in ALT or total bilirubin level: • Close and frequent monitoring of liver enzyme and serum bilirubin tests as clinically indicated. Frequency of retesting can decrease if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. If the appropriate frequency of monitoring is not feasible study drug administration will be suspended. • Obtain a detailed history of symptoms and prior and concurrent diseases. • Obtain comprehensive history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets • Obtain a history for exposure to environmental chemical agents and travel. • Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel). • Serology for autoimmune hepatitis [e.g., antinuclear antibody (ANA)]. Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor.

Section	Description of Change
Section 16.6	Addition of the PedsQL quality of life questionnaire of children between the ages of 1-12 months.

1 STUDY SYNOPSIS AND SCHEDULE OF PROCEDURES

Sponsor	Mirum Pharmaceuticals, Inc.
Protocol Number	LUM001-501
Protocol Title	Open Label Study of the Efficacy and Long Term Safety of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis
Study Phase	2
Indication	Treatment of Patients with Progressive Familial Intrahepatic Cholestasis (PFIC)
Objectives	Objectives of Study (Up to and including Week 72): • To evaluate the long-term safety and tolerability of LUM001 in pediatric subjects with PFIC. • To evaluate the effect of LUM001 on serum bile acid levels in pediatric subjects with PFIC at 13 weeks of treatment. • To evaluate the effect of LUM001 on biochemical markers of cholestasis and liver disease at 13 weeks of treatment. • To evaluate the effect of LUM001 on pruritus in pediatric subjects with PFIC at 13 weeks of treatment. Objectives of Optional Follow-up Treatment Period (After Week 72): • To offer eligible subjects in the LUM001-501 study continued study treatment beyond Week 72 until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially. • To obtain safety and efficacy data in subjects treated long-term on LUM001. • To explore a twice a day (BID) dosing regimen and higher daily dosing of LUM001. • To identify genetic indicators of treatment response, including use of exome sequencing. • To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma. • To assess palatability of the LUM001 formulation. Exploratory Objective: • To allow the possibility of analysis of serum markers of treatment response using metabolomic and proteomic analysis on previously collected serum samples.
Study Design	This is an open label study in children with PFIC designed to evaluate the safety and efficacy of LUM001. The study is divided into 5 parts: a 4-week dose escalation period, a 4-week stable dosing period at 140 µg/kg/day, a 5-week stable dosing period at 280 µg/kg/day, a 59-week long-term exposure period, and an optional follow-up treatment period for eligible subjects who choose to stay on treatment with LUM001. During this 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 ongoing efficacy (sBA level and ItchRO score) and safety assessment. Subjects' participation in the optional follow-up treatment period will continue until the first of the following occurs: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.
Number of Subjects	Approximately 24 evaluable subjects will be enrolled in this study. Of the 24 subjects, a minimum of 8 PFIC1 (ATP8B1-related disease) subjects will be enrolled in this study.
Study Population	Inclusion Criteria To participate in this study subjects must meet the following criteria:

	1. Male or female subjects between the ages of 12 months and 18 years inclusive. 2. Diagnosis of PFIC based on: a. Intrahepatic cholestasis manifest by total serum bile acid >3x upper limit of normal (ULN) for age. and, b or c: b. Two documented mutant alleles in ATP8B1, or ABCB11. c. Evidence of chronic liver disease, excluding those listed in (see Section 16.3), with one or more of the following criteria: 1) Duration of biochemical or clinical abnormalities of >6 months, or 2) Pathologic evidence of progressive liver disease, or 3) Sibling of known individual affected by PFIC (predicted to be chronic). 3. GGTP <100 IU/L at screening. 4. Females of childbearing potential must have a negative urine or serum pregnancy test [β human chorionic gonadotropin (β-hCG)] during screening and a negative urine pregnancy test 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 30 days following the last dose of study drug, must agree and use acceptable contraception during the trial. 6. Informed consent and assent (per IRB/EC) as appropriate. 7. Access to phone for scheduled calls from study site. 8. Caregivers and children above the age of assent must have the ability to read and understand one of the following languages: English, Spanish, US Spanish, French, German or Polish. 9. Subjects expected to have a consistent caregiver(s) for the duration of the first 13 weeks of the study. 10. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device as required by the study. To accommodate potential cultural restrictions within the FIC1 affected population a paper version of the ItchRO diary will be made available. 11. Caregivers (and age appropriate subjects) using the eDiary must digitally accept the licensing agreement in the eDiary software at the outset of the study. 12. Caregivers (and age appropriate subjects) must complete at least 10 eDiary reports (morning or evening) during each of two consecutive weeks of the screening period, prior to assignment (maximum possible reports = 14 per week). Subjects using a paper diary must complete the same number of reports within the same timeframe. <u>Exclusion Criteria</u> Subjects will be excluded from the study if they meet any of the following criteria: 1. Chronic diarrhea requiring specific intravenous fluid or nutritional intervention for the diarrhea and/or its sequelae. 2. Surgical disruption of the enterohepatic circulation at the time of screening. Subjects who have undergone reversal of a prior surgical procedure intended to disrupt enterohepatic circulation and who have a permanently restored flow of bile acids from the liver to the terminal ileum may be eligible for the study upon consultation with the Medical Monitor. 3. Liver transplant.

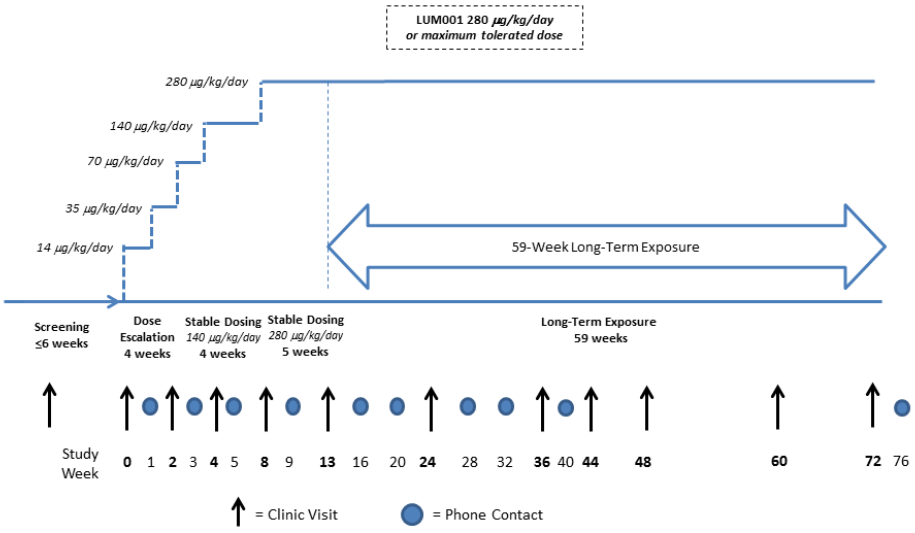
	4. Decompensated cirrhosis [international normalized ratio (INR) > 1.5, albumin < 30 g/L, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy]. 5. ALT >15 × ULN at screening. 6. History or presence of other liver disease (see Section 16.1). 7. History or presence of any other disease or condition known to interfere with the absorption, distribution, metabolism or excretion of drugs, including bile salt metabolism in the intestine (e.g., inflammatory bowel disease). 8. Liver mass on imaging. 9. Known diagnosis of human immunodeficiency virus (HIV) infection. 10. Cancers except for in situ carcinoma, or cancers treated at least 5 years prior to screening with no evidence of recurrence. 11. Any female who is pregnant or lactating or who is planning to become pregnant within 20 weeks of assignment. 12. Any known history of alcohol or substance abuse. 13. Administration of bile acid or lipid binding resins within 30 days prior to Baseline / Day 0 and throughout the trial. 14. Administration of sodium phenylbutyrate within 30 days prior to Baseline / Day 0 and throughout the trial. 15. Investigational drug, biologic, or medical device within 30 days prior to screening, or 5 half-lives of the study agent, whichever is longer. 16. History of non-adherence to medical regimens, unreliability, mental instability or incompetence that could compromise the validity of informed consent or lead to non-adherence with the study protocol based on Investigator judgment. 17. Any other conditions or abnormalities which, in the opinion of the Investigator or Medical Monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study. **Eligible Subjects for Optional Follow-up Treatment Period:** <u>Inclusion Criteria</u> Subjects will be considered eligible for the Optional Follow-up Treatment Period if they meet the following criteria: 1. The subject has either: • completed the protocol through the Week 72 visit with no major safety concerns, OR • discontinued due to safety reasons judged unrelated to the study drug, and blood tests have returned to levels acceptable for this patient population/individual and subject does not meet any of the protocol's stopping rules at re-entry. 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-hCG) at the time of entry into the optional follow-up treatment period. 3. Informed consent and assent (per IRB/EC) as appropriate. <u>Exclusion Criteria</u> Subjects will be excluded from the Optional Follow-up Treatment Period if they meet any of the following criteria: 1. Surgical disruption of the enterohepatic circulation. 2. Investigational drug other than LUM001, biologic, or medical device within 30 days prior to re-entry, or 5 half-lives of the study agent, whichever is longer.

Treatment Groups	This is an open label study. All subjects will receive LUM001, up to 560 µg/kg/day (given as twice-daily doses of 280 µg/kg) or a maximum daily dose of 25 mg BID.
Study Drug Dosage and Administration	Subjects will receive a grape-flavored solution containing LUM001. Each subject dose will be 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 at approximately the same time each day for the duration of the treatment period. **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 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). **Study Drug Dosage** <u>Baseline through Week 72:</u> Initially, the LUM001 dose will be increased weekly over a 4-week period (Dose Levels 1-4). At the end of 4 weeks, subjects will continue dosing for another 4 weeks using the Week 4 dose, or the highest tolerated dose below the Week 4 dose. For those subjects who tolerated Dose Level 4, at the Week 8 visit the dose will be increased to Dose Level 5, and subjects will continue dosing for another 5 weeks (i.e., through Week 13) using the Week 5 dose or the highest tolerated dose below the Week 5 dose. Beginning at Week 14, dosing with LUM001 will continue at a fixed dose in a 59-week long-term exposure period. During this period the dose may be adjusted if there is a change of ≥10% in weight since the screening visit. At the investigator's discretion and in consultation with the Medical Monitor, subjects who were previously down-titrated may be re-challenged during the long-term exposure period (Weeks 14 – Week 72). For the first 72 weeks of the study, each subject will receive either 1.0 mL or 0.5 mL of solution containing LUM001 orally as follows, administered as a daily morning dose: • Dose Level 1: 14 µg/kg/day. • Dose Level 2: 35 µg/kg/day. • Dose Level 3: 70 µg/kg/day. • Dose Level 4: 140 µg/kg/day. • Dose Level 5: 280 µg/kg/day. At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the optional follow-up treatment period. <u>Optional Follow-up Treatment Period (Post-Week 72):</u> Subjects eligible for the optional follow-up treatment period will continue treatment under dosing scenarios based on whether their LUM001 dosing will continue without interruption

	or interruption of <7 continuous days, or with interruption ≥7 days. Eligibility for BID dosing will be determined based on efficacy as measured by sBA level and ItchRO score. Subjects who enter the optional follow-up treatment period without LUM001 dosing interruption or with an interruption of <7 continuous days will be dosed in the following manner: • Subjects with normal sBA level AND ItchRO score <1.5 will be maintained at the same dose level and will continue morning dosing only. • Subjects with sBA level above normal AND/OR ItchRO score ≥1.5 will start BID dosing (afternoon dose escalation; ADE) as follows: – The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated. – The afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled, to a maximum dose of 280 µg/kg (or up to the maximum tolerated dose). – The maximum daily dose will be 280 µg/kg BID, i.e. 560 µg/kg/day(max. 25 mg BID). Subjects who enter the optional follow-up treatment period with a LUM001 dosing interruption of ≥7 days initially will receive morning dosing only and will undergo dose escalation (DE) in the following manner: • The morning dose will be initiated at Dose Level 2 (35 µg/kg) and doubled in weekly intervals to a maximum dose of 280 µg/kg, or up to the maximum tolerated dose. • Once the morning dose of 280 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO score will be evaluated. • Subjects with normal sBA AND ItchRO score <1.5 after morning dose escalation will be maintained at the same dose level and will continue morning dosing only. • Subjects with sBA above normal AND/OR ItchRO score ≥1.5 will begin BID dosing (afternoon dose escalation) as outlined above. Subjects will continue to receive study drug until they are eligible to enter another LUM001 study or until LUM001 is available commercially, whichever occurs first. The maximum daily dose will be 280 µg/kg BID, i.e. 560 µg/kg/day (maximum 25 mg). If a subject experiences intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician Investigator in consultation with the Medical Monitor may lower the dose for the remainder of the study. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose. The sBA value used for determination of ADE eligibility will be the most recent available value. The ItchRO score used for ADE eligibility will be derived from the most recent 2-week electronic diary collection period.
Rationale for Dose and Schedule Selection	The dosage of LUM001 is based upon prior experience with this investigational product in healthy volunteers and adult and pediatric 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 are believed to be related to increased bile acid excretion and a concomitant increase in the concentration of free bile acids in the lower colon. Patients with cholestatic

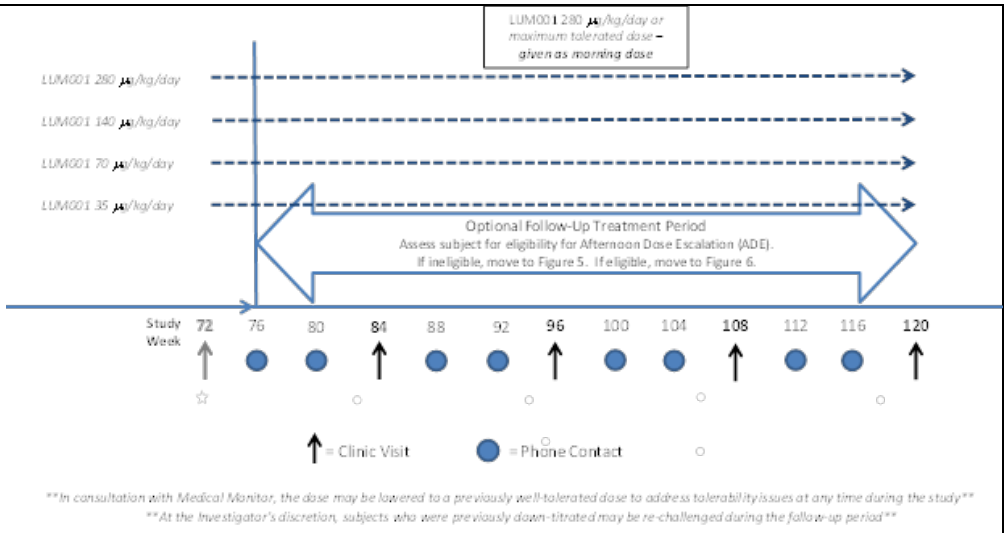
	liver disease have reduced bile flow compared to healthy volunteers and hypercholesterolemic patients and LUM001 is likely to produce a correspondingly smaller increase in free bile acids in the lower colon. There is also evidence in patients with cholestasis to suggest that ASBT expression may be upregulated and higher ASBTi concentrations may be required to achieve the desired target inhibition. Dosing in pediatric subjects will be based on subject weight. The appropriate efficacious dose of LUM001 for the lowering of bile acid concentrations and the reduction of pruritus in cholestatic populations is not known. Earlier studies in healthy volunteers and hypercholesterolemic patients demonstrated that doses of 10 mg to 20 mg daily (equivalent to 140 µg/kg/day to 280 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 weeks of LUM001 dosing and then observed at levels similar to those in the placebo group after 2 or 3 weeks of continuous dosing. In a 4-week dose finding study in healthy volunteers, a dose escalation regimen was evaluated to mitigate the risk of loose stools, diarrhea and abdominal pain/cramps. 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. To reduce the risk of loose stools, diarrhea and abdominal pain/cramps 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 morning dose is initiated and escalated first; the afternoon dose is only initiated and escalated in patients with elevated sBA level and/or ItchRO ≥1.5 on the maximum (or maximum tolerated) morning 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 (i.e. 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (i.e. 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 (PND21 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. During the long-term exposure period and the optional follow-up treatment period, the dose may be adjusted to account for a change of ≥10% in weight since the screening visit (e.g.

	the amount of drug dosed may be increased to reflect the subject's weight increase). 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. If the subject is on a 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 Visit Schedule and Procedures	For an individual subject, the study participation period will consist of a screening period of up to 6 weeks, a 13-week treatment period (including a dose escalation period followed by two stable dose periods), and a 59-week long-term exposure period. Subjects who complete 72 weeks of treatment (Figure 1) may be eligible to receive further treatment during the Optional Follow-up Treatment Period. Study activities will be conducted as described in the Schedule of Procedures (Section 16.1). **Figure 1: Study Design for LUM001-501 (Up to and including Week 72)**  Screening Period (Day -42 to Day -1): After obtaining informed consent (and/or assent when appropriate), demographic data (gender, age, and race) will be collected and subjects will undergo a medical history and physical examination including body weight, height, and vital signs, and determination of concomitant medications. Blood and urine samples will be taken for clinical laboratory testing. An ultrasound will be performed to determine if any mass can be seen in the liver. Note: A screening ultrasound is not required if the results of an ultrasound completed within 6 months are available, provided that the clinical status of the subject has not changed significantly since the time of the test. In the absence of documented ATP8B1 or ABCB11 mutation prior to screening, genetic testing will be performed (refer to Section 8.2). The appropriate genetic counseling will be provided to subjects and their legal caregivers at a study visit following the receipt of results of genetic testing. Results of genetic screen will not impact continued participation in the study, but are done to provide complete and uniform characterization of the subjects' liver disease. The eDiary for assessing pruritus, as measured using an ItchRO instrument, will be dispensed and subjects and caregivers will receive training during the screening visit. The patient/caregiver ItchRO will be administered twice daily. The physician will also provide an assessment of itch severity using the clinician administered scratch scale during screening. Females who are of childbearing potential will have a serum or urine pregnancy test. Enrollment will occur after eligibility criteria have been met, 4-7 days prior to the baseline visit; this will not require a separate visit and will initiate preparation of study drug. Dose Escalation Treatment Period (Day 0 to Week 4): At the baseline visit (Day 0), study eligibility will be confirmed and body weight, height, and vital signs will be evaluated and recorded. Blood and urine samples will be taken for clinical laboratory testing, including fasting lipid panel. Baseline levels of bile acids and other cholestasis biochemical markers

	will be determined from blood and urine; blood will also be collected for determination of baseline fat-soluble vitamins and for a baseline PK sample. Compliance with the ItchRO will be assessed. A clinician administered scratch scale will be determined and the Pediatric Quality of Life Inventory (PedsQL) questionnaire, a measure of quality of life, will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug for Weeks 1 (Dose Level 1) and 2 (Dose Level 2) will be supplied at the baseline visit to eligible subjects. Caregivers and age appropriate subjects will continue twice daily (morning and evening) completion of their eDiary (ItchRO) throughout the dose escalation treatment period. Subjects will return to the clinic at Weeks 2 and 4 and will receive a follow-up phone call at Weeks 1, 3 and 5. On clinic visit days, safety and clinical laboratory evaluations will be performed. Clinician scratch scale will be administered, adherence to study drug will be assessed. At the Week 2 visit study drug and additional dosing instructions for Weeks 3 (Dose Level 3) and 4 (Dose Level 4) will be supplied. ItchRO compliance will be assessed and concomitant medications and any AEs will be recorded at clinic visits and from phone calls. 140 µg/kg/day Stable Dosing Treatment Period (Week 5 to Week 8): Subjects will continue to receive LUM001 for another 4 weeks using Dose Level 4, or the highest tolerated dose below Dose Level 4. Subjects and caregivers will continue daily completion of their eDiary (ItchRO). Subjects will receive a follow-up phone call at Week 5 and return to the clinic at Week 8. At the Week 8 clinic visit, safety and clinical laboratory evaluations will be performed. Clinician scratch scale will be administered, and adherence to study drug will be assessed. For those subjects who tolerated Dose Level 4, at the Week 8 visit the dose will be increased to Dose Level 5. Additional dosing instructions and study drug will be supplied. ItchRO compliance will be assessed and concomitant medications and any AEs will be recorded at clinic visits and from phone calls. 280 µg/kg/day Stable Dosing Treatment Period (Week 9 to Week 13): Subjects will continue to receive LUM001 through Week 13 using Dose Level 5 or the highest tolerated dose below this dose. Subjects and caregivers will continue daily completion of their eDiary (ItchRO). Subjects will receive a follow-up phone call at Week 9 and return to the clinic at Week 13. At this clinic visit, safety and clinical laboratory evaluations will be performed. Clinician scratch scale will be administered, and adherence to study drug will be assessed. The PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments will be administered. The eDiary will be collected. Females who are of childbearing potential will have a urine pregnancy test at Week 13. ItchRO compliance will be assessed and concomitant medications and any AEs will be recorded at clinic visits and from phone calls. Additional dosing instructions and study drug will be supplied for the next phase of the study. Long-Term Exposure Period (Week 14 to Week 72): Subjects will continue to receive study drug for an additional 59 weeks according to the dose achieved during the stable dosing treatment 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. At the Investigator's discretion and in consultation with the Medical Monitor, subjects who were previously down titrated may be re-challenged during the long-term exposure period. During the long-term exposure period, subjects will return to the clinic at Weeks 24, 36, 44, 48, 60 and 72. With the exception of the Week 44 visit, 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 completed at Weeks 24, 48 and 72. The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 48 and 72. At the Week 24 and Week 44 visits, electronic diaries will be issued and AEs and concomitant medications will be assessed and recorded. Subjects/caregivers will

	receive follow-up phone calls at Weeks 16, 20, 28, 32 and 40. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts. Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 4 weeks that follow the Week 24 and Week 44 clinic visits. Electronic diaries will be provided to subjects and caregivers at Weeks 24 and 44, and re-training on the use of the diary will occur, as appropriate, at these 2 visits. 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 44 visit, additional study drug will be supplied at each clinic visit during the long-term exposure dosing period. Week 72: Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the optional follow-up treatment period. Eligible subjects must have documented consents 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 study drug determination. The clinician scratch scale and PedsQL will be administered. Females who are of childbearing potential will have a urine pregnancy test, and concomitant medications and any AEs will be recorded. Study drug compliance will also be assessed and all used and unused study drug and study supplies will be collected. Study drug will be discontinued at this visit if the subject chooses not to participate in the 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 Phone Call: For subjects who do not roll over into the optional follow-up treatment period, a safety follow-up phone call will be made 30 days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and any AEs noted during this phone call will be recorded. Optional Follow-up Treatment Period (post-Week 72): Subjects who are eligible to enter to the follow-up treatment period will continue to receive study drug after Week 72 until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially. Included below are schematics describing the flow of study visits within the optional follow-up treatment period. **Figure 2: Optional Follow-up Treatment Period (<7 days from last LUM001 dose between Protocol Amendment 2 and Amendment 3)** Applies to the following subject population: • Subjects who experienced no interruption in LUM001 dosing, or interruption <7 days between Protocol Amendment 2 and Protocol Amendment 3.

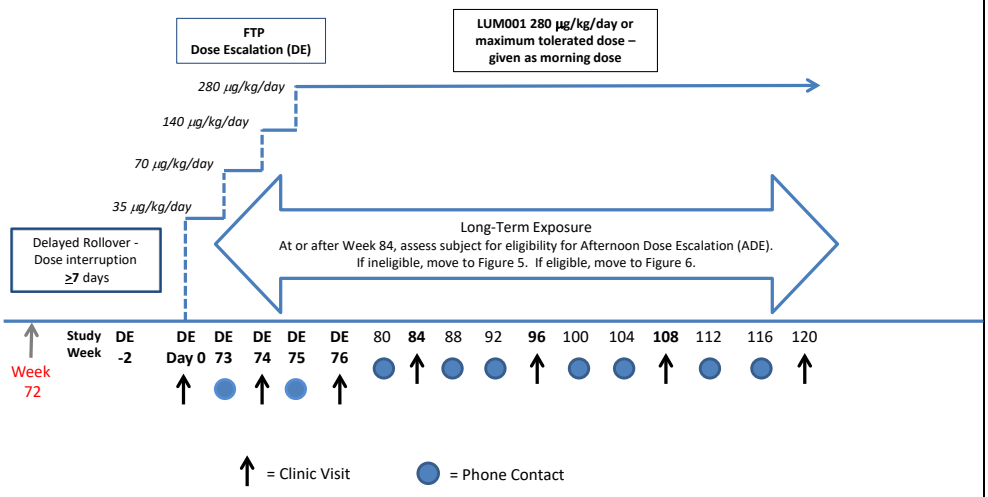


Subjects who are eligible to roll over into the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will initially receive study drug at the dose they were receiving at Week 72. Once Protocol Amendment 4 is implemented at the site, a determination about Afternoon Dose Escalation (ADE) will be made. **The subject then will move to Figure 5 or 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.**

Figure 3: Optional Follow-up Treatment (≥7 days from last LUM001 dose between Protocol Amendment 2 and Protocol Amendment 3)

Applies to the following subject population:

- Subjects who experienced an interruption in LUM001 dosing ≥7 days between Protocol Amendment 2 and Protocol Amendment 3.



Subjects with ≥7 days since last dose of LUM001 (Figure 3) will be dose escalated up to 280 µg/kg/day or to the maximum tolerated dose starting at Dose Level 2 (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:

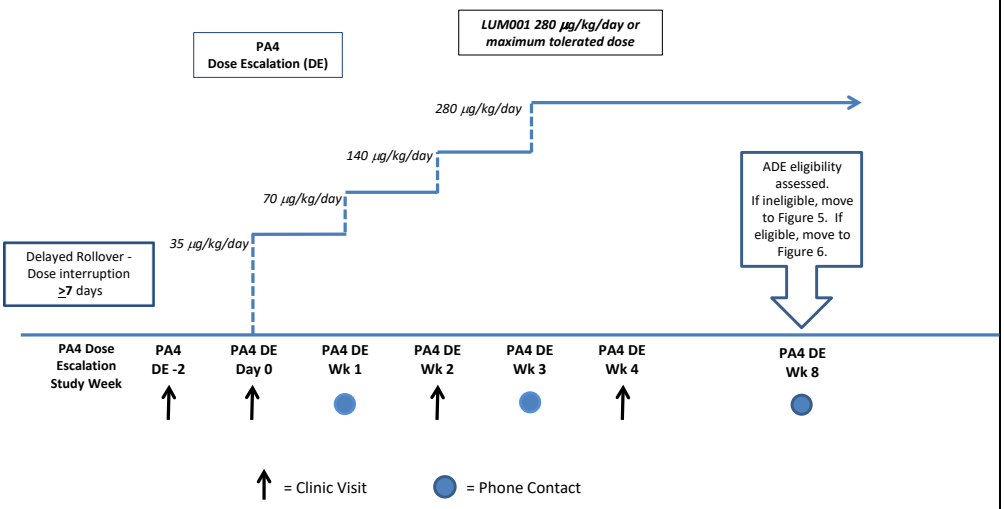
- DE Week -2 Clinic Visit: obtain consent, obtain weight and draw labs.
- DE Day 0 Clinic Visit: Investigator evaluates laboratory results, study drug is dispensed and subject begins at 35 µg/kg/day dose level.
- DE Week 73 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose 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 maximum tolerated dose.

Once Protocol Amendment 4 is implemented at the site, a determination about Afternoon Dose Escalation (ADE) will be made. **The subject then will move to Figure 5 or 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.**

Figure 4: Optional Follow-up Treatment (≥7 days from last LUM001 dose between Protocol Amendment 3 and Protocol Amendment 4)

Applies to the following subject population:

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



Subjects with ≥7 days since last dose of LUM001 prior to site implementation of Protocol Amendment 4 will be dose escalated up to 280 µg/kg/day or to the highest tolerated dose starting at Dose Level 2 (35 µg/kg/day).

The dose escalation (DE) period will proceed as follows:

- Protocol Amendment 4 DE Week -2 Clinic Visit: obtain consent for Protocol Amendment 4, obtain weight and draw labs.
- Protocol Amendment 4 DE Day 0 Clinic Visit: Investigator evaluates laboratory results, study drug is dispensed and subject begins at 35 µg/kg/day dose level.
- Protocol Amendment 4 DE Week 1 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated.

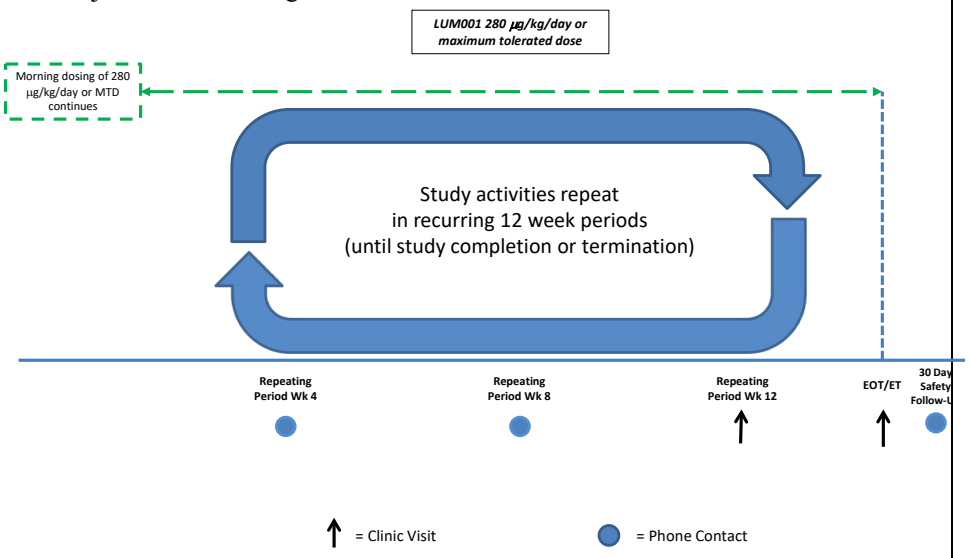
	• Protocol Amendment 4 DE Week 2 Clinic Visit: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated. • Protocol Amendment 4 DE Week 3 Telephone Contact: subject escalates to 280 µg/kg/day dose, if prior dose level was tolerated.

- Protocol Amendment 4 DE Week 4 Clinic Visit: subject continues in follow-up treatment period at 280 µg/kg/day, or maximum tolerated dose.
- At Protocol Amendment 4 DE Week 8 Telephone Contact: eligibility for ADE will be assessed. **The subject then will move to Figure 5 or 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.**

Figure 5: Optional Follow-up Treatment under Protocol Amendment 4, without Afternoon Dose Escalation (ADE)

Applies to the following subject population:

- Subjects deemed ineligible for ADE.



<u>Subjects Deemed Ineligible for ADE:</u>

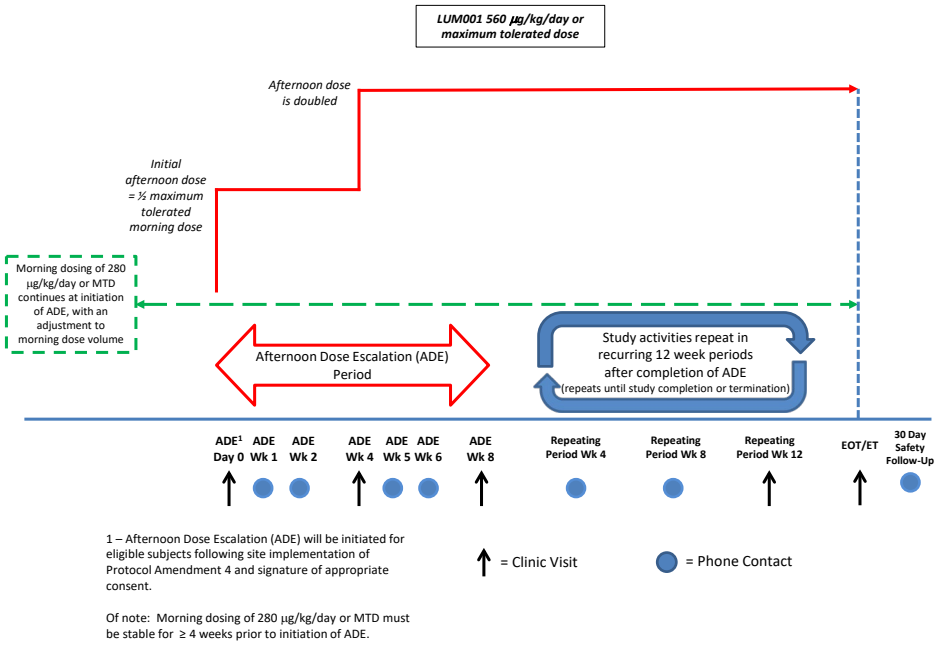
Subjects with normal sBA level AND ItchRO score <1.5 will be deemed ineligible for ADE; such patients will be maintained at the same dose level and will continue morning dosing only. Subjects will have study activities then repeated in recurring 12-week periods as follows, until study completion or termination:

- Recurring Period Week 4 (i.e., beginning Week 88 or 4 weeks after consent to Protocol Amendment 4) Telephone Contact: Collection of concomitant medications and any adverse events.
- Recurring Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.
- Recurring 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 fat-soluble vitamins. Urine samples for clinical laboratory testing will be collected at every visit. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale will be administered, 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 upon completion of other study procedures.

Figure 6: Optional Follow-up Treatment under Protocol Amendment 4, with Afternoon Dose Escalation (ADE)

Applies to the following subject population:

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



Subjects deemed eligible for ADE, i.e., who have sBA level above normal AND/OR ItchRO score ≥1.5, will begin BID dosing (afternoon dose escalation; ADE) as follows:

- On ADE 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 Dosing must have been stable for ≥4 weeks prior to initiation of ADE.
- On ADE 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 (i.e., at ADE Week 4) to a maximum dose of 280 µg/kg (i.e., up to a maximum 560 µg/kg/day or maximum tolerated dose).

The following procedures will occur during the ADE period:

- ADE 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 PK. The clinician scratch 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.
- ADE Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.
- ADE 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 PK. The clinician scratch 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. • ADE Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions. • ADE 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 PK. The clinician scratch 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 5, 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 follow-up treatment period, subjects will return to the clinic every 3 months. 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, every clinic visit within each recurring 12-week period, and at the EOT visit. Additionally, it will be collected at Protocol Amendment 4 DE Day 0, ADE Day 0, ADE Week 4, and ADE Week 8. The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 108, 120, and the EOT visit. Subjects/caregivers will receive follow-up phone calls at Weeks 80, 88, 92, 100, 104, 112, and 116, and twice within each recurring 12-week period, and every 3 months hence for the subsequent visits. 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 clinic visits, at Protocol Amendment 4 DE Week 4, and every clinic visit within each recurring 12-week period. 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 EOT 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 End of Treatment/Early Termination 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 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. The ItchRO, the clinician administered pruritus scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, and palatability questionnaire also will be completed. <u>At completion of the Follow-up Treatment Period or early discontinuation:</u> 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.
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 Data Safety Monitoring Board (DSMB) will review serious AE data, other key subject safety and study data at specified intervals for the duration of the study.

Drug Level Evaluations	**United States:** At sites in the United States, plasma levels of LUM001 will be evaluated at Baseline / Day 0 and Weeks 2, 4, 8, 13, 24, 36, 48, 60 and 72. At Week 4, blood will be drawn approximately 2 hours post-dosing for drug level analysis. At all other blood draws, blood will be drawn approximately 4 hours post morning dosing for drug level analysis. Additionally, for subjects in which afternoon dose escalation is initiated, samples will also be drawn at ADE Day 0, ADE Week 4, ADE Week 8, and at the three scheduled clinic visits following completion of the ADE period. **United Kingdom, Europe and Australia**: At sites in the United Kingdom, Europe and Australia, plasma levels of LUM001 will be evaluated at Baseline / Day 0 and Weeks 4, 13, 24, 36, 48, 60 and 72. Blood will be drawn approximately 4 hours post-morning dosing for drug level analysis. Additionally, for subjects in which afternoon dose escalation is initiated, samples will also be drawn at ADE Day 0, ADE Week 4, ADE Week 8, and at the three scheduled clinic visits following completion of the ADE period.
Safety Evaluations	The following assessments will be used to evaluate safety: • Adverse events (AEs) and serious adverse events (SAEs). • Clinical laboratory results, including alpha-fetoprotein (AFP) as a screening for hepatocellular carcinoma. • Vital signs. • Physical exam findings, including body weight and height. • Concomitant medication usage.
Efficacy Evaluations	The main focus for the analyses of efficacy is the period from Baseline (Day 0) to Week 13. The period from Baseline (Day 0) to EOT will be analyzed. Primary efficacy endpoint: • Fasting serum bile acid level change from Baseline (Day 0) to Week 13. Secondary efficacy endpoints: • Alanine aminotransferase (ALT) and bilirubin (total and direct) change from Baseline (Day 0) to Week 13. • Pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO) change from Baseline (Day 0) to Week 13. (For each subject, the average daily score will be calculated using the 7 days pre-treatment for Baseline / Day 0, and the last 7 days of treatment for Week 13.) Exploratory efficacy endpoints: • Change from Baseline (Day 0) in fasting serum bile acid level at Weeks 4, 8, 24, 36, 48 60, 72, 84, 96, 108, 120, every three months thereafter, and at the End of Treatment (EOT) visit. • Change from Baseline (Day 0) in pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO) at Weeks 4, 8, 28, 48, 86, 98, 110, 122, and every three months thereafter. • Change from Baseline (Day 0) for ALT, and bilirubin (total and direct) at Weeks 4, 8, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit. • Change from Baseline (Day 0) for other biochemical markers of cholestasis [total cholesterol, low-density lipoprotein cholesterol (LDL-C)] at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit. • Responder analysis: pruritus response rates as measured by ItchRO (Observer ItchRO/patient ItchRO) at Weeks 4, 8, 13, 28, 48, 86, 98, 110, 122, and every three months thereafter, up to but not including the EOT visit.

	• Change from Baseline (Day 0) in the Clinician Scratch Scale, at Weeks 2, 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit. • Change from Baseline (Day 0) in bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)] at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit. • Change from Baseline (Day 0) for PedsQL at Weeks 13, 24, 48, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit. • Patient Impression of Change (PIC) at Weeks 13, 48, 72, 108, 120, and the EOT visit. • Caregiver Impression of Change (CIC) at Weeks 13, 48, 72, 108, 120, and the EOT visit. • Caregiver Global Therapeutic Benefit (CGTB) assessment at Weeks 13, 48, 72, 108, 120, and at the EOT visit. • Change from Baseline (Day 0) for other biochemical markers [autotaxin and lysophosphatidic acid (LPA)] at Weeks 4, 8, 13, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit. • Change from Baseline (Day 0) for measures of bile acid synthesis (FGF-19 and FGF-21) at Weeks 4, 8, 13, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit. Additional evaluations of safety and efficacy surrogates will be specified in the Statistical Analysis Plan. For subjects entering the optional follow-up treatment period with ≥7 days since last dose of LUM001, any of the above evaluations may also occur at clinic visits during the DE period.
Interim Analyses	The following interim analyses are planned. The first interim analysis of key safety and efficacy parameters will be performed after the first 12 subjects who meet the Per Protocol population definition have completed the Week 13 study visit. This analysis will provide initial information about the activity of LUM001 in the study population. A second interim analysis will be performed after all enrolled subjects have completed the Week 48 (or Early Termination) study visit. This analysis will provide an assessment of the long-term safety and efficacy of LUM001. A third interim analysis will be performed after all enrolled subjects have completed at least 6 months of treatment under Protocol Amendment 4 (or the Early Termination visit). This analysis will provide an assessment of the long-term safety and efficacy of LUM001. Subsequent interim analyses will be performed in yearly intervals.
Exploratory Genetic Analyses	To better understand the role of genetics in treatment response, an additional blood sample will be taken for exome sequencing. The data analysis will focus initially on genetic variation in candidate genes that may have a role in treatment response, such as ASBT/SLC10A2 and genes in its pathway (ie upstream or downstream of ASBT/SLC10A2) and genes implicated in PFIC (ATP8B1, ABCB11 and ABCB4) with the goal of identifying genetic variation that may discriminate treatment responders from non-responders. Following examination of candidate genes, the data analysis may be expanded to evaluate genetic variation in additional regions of the exome. This genetic analysis is more comprehensive and may provide valuable information beyond the ATP8B1 and ABCB11 genes. The submission of this blood sample is voluntary. The results of this analysis may identify relevant genetic variants, only some of which will be of known clinical benefit.
Exploratory Responder Analyses –	As part of a comprehensive approach to identify serum markers in PFIC patients that respond well to treatment, previously collected serum samples will be analyzed using both metabolomic and proteomic biomarker discovery approaches. Metabolomics addresses the

Metabolomic and Proteomic Investigations	activity of small molecules (<10 kDa) produced by active and living cells during their life cycle. These molecules are not accessible by genomic, transcriptomic or proteomic approaches. Metabolomics monitors the chemical transformations in metabolic cascades and can be used to identify observable differences between patient populations. A targeted mass spectrometry proteomic approach will allow for the identification and quantitation of greater than 150 unique proteins in each serum sample. Serum samples from both responding and non-responding patients will be analyzed in both biomarker discovery platforms and the data will be evaluated for potential markers that can significantly delineate responders from non-responders.
Palatability Data	Palatability data will be collected at each clinic visit in the follow up treatment period, with the exception of the DE and ADE visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age).
Statistical Considerations	Sample Size PFIC is a very rare disease. The planned sample size of approximately 24 evaluable subjects was based on practical considerations, rather than on statistical considerations and desired power for a pre-specified difference. Statistical Analysis Plan A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of the analyses to be performed. Safety All safety analyses will be performed on the Safety Population, defined as all subjects who were assigned and received at least one dose of the study drug. Subjects will be analyzed by the treatment received. Safety measures including AEs, clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively by study phase (Weeks 0-13, 14-48, 49-72, 73-124) and over the entire study duration (Weeks 0-72, 0-EOT Visit). For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation, minimum, and maximum will be given for the values themselves as well as for change from Baseline (Day 0) at each study visit. Qualitative variables will be summarized using counts and percentages at each study visit. Drug Level Analysis Plasma concentrations of LUM001 will be examined descriptively by visit. Efficacy The main population for efficacy will be the modified intention-to-treat population (MITT), defined as all subjects assigned, receiving at least one dose of treatment, and having at least one post-baseline efficacy assessment. Subjects will be analyzed by assigned treatment. The Per Protocol population (PP) will consist of all subjects in the MITT population who did not have a major protocol violation, inclusive of violation of entry criteria. Subjects in this population will be referenced as evaluable. Efficacy endpoints will be displayed by study visit, using summary statistics including the number of observations, the mean, median, standard deviation, minimum, and maximum for continuous measures and counts and percentages for categorical measures. Actual values as well as change from baseline will be presented. For continuous measures the change from baseline will be tested using the paired t-test, or comparable nonparametric measures if appropriate. Examination of potential treatment effects by dose will be done if the sample sizes in the dose groups during the stable dosing phase of the study permit.

	In addition to absolute change from baseline, a responder analysis will be considered. The response definition and its appropriate analysis methodology will be outlined in the SAP for the study. Supportive and exploratory 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
ADE	afternoon dose escalation
AFP	alpha-feto protein
ALGS	Alagille syndrome
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPTT	activated partial thromboplastin time
ASBT	apical sodium-dependent bile acid transporter
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase (SGOT)
ATC	Anatomic Therapeutic Chemical; classification for drugs
ATX	Autotaxin
BA	bile acid
BID	twice a day
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CGTB	caregiver global therapeutic benefit questionnaire
cholesterol 7α-hydroxylase	rate-limiting enzyme in the synthesis of bile acid from cholesterol
CIC	caregiver impression of change questionnaire
CRF	case report form
CS	clinically significant
CV	curriculum vitae
DE	dose escalation
dL	Deciliter

Abbreviation	Definition
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
EOT	End of Treatment
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
FXR	farnesoid X receptor; bile acid receptor
g	Gram
GCP	good clinical practices
GGTP (γGTP)	gamma-glutamyl transpeptidase
GI	Gastrointestinal
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
ITT	intention-to-treat
IU	international unit(s)
IUD	intrauterine device
kDA	kilodalton
kg	Kilogram
L	Litre
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LPA	lysophosphatidic acid
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MITT	modified intention-to-treat
mL	Milliliter
mmol	Millimole
NBD	nasobiliary drainage
NCS	not clinically significant
ng	Nanogram
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
PIC	patient impression of change questionnaire
PND	post-natal day
PRO	patient reported outcome
PSC	primary sclerosing cholangitis

Abbreviation	Definition
Pt	patient
PT	prothrombin time
QD	once daily
q.s.	quantity sufficient
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD-5613	original designation for LUM001
sec	Second
SLC10A2	solute carrier family 10 member 2; gene that encodes ASBT protein
SUSAR	suspected unexpected serious adverse reaction
TG	Triglycerides
TGR5	a G protein-coupled receptor for bile acids
TPN	total parenteral nutrition
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-sub-unit of human chorionic gonadotropin; pregnancy test
µg	Microgram
µM	Micromolar

3 STUDY OBJECTIVES

Objectives of study (Up to and including Week 72):

- To evaluate the long-term safety and tolerability of LUM001 in pediatric subjects with PFIC.
- To evaluate the effect of LUM001 on serum bile acids in pediatric subjects with PFIC at 13 weeks of treatment.
- To evaluate the effect of LUM001 on biochemical markers of cholestasis and liver disease at 13 weeks of treatment.
- To evaluate the effect of LUM001 on pruritus in pediatric subjects with PFIC at 13 weeks of treatment.

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

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

Exploratory Objective:

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

4 BACKGROUND AND RATIONALE

LUM001 (previously known as SD-5613) 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. 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 associated with progressive familial intrahepatic cholestasis (PFIC) and other diseases.

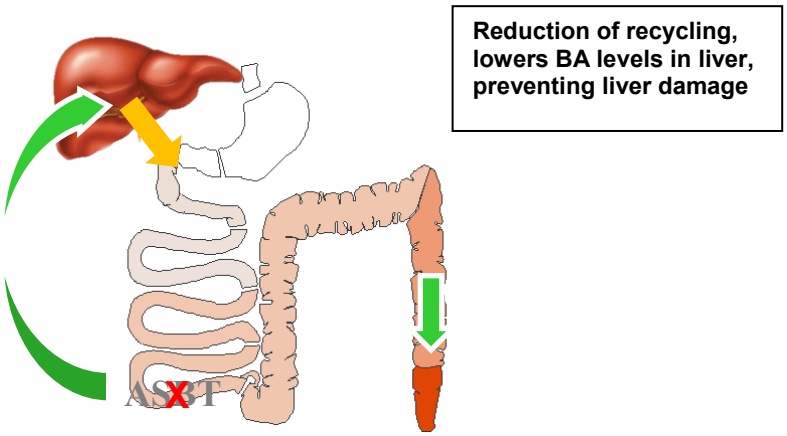
4.1 Therapeutic Rationale

In patients with PFIC, 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 a common symptom associated with cholestasis, it can occur at all stages of cholestatic liver disease, with or without jaundice.

Surgical interruption of the enterohepatic circulation in patients with PFIC 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 for patients with PFIC.

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. Approximately, ninety-five percent of bile acids that enter the gut lumen are recycled to the gallbladder where they are stored for future release to the duodenum.

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

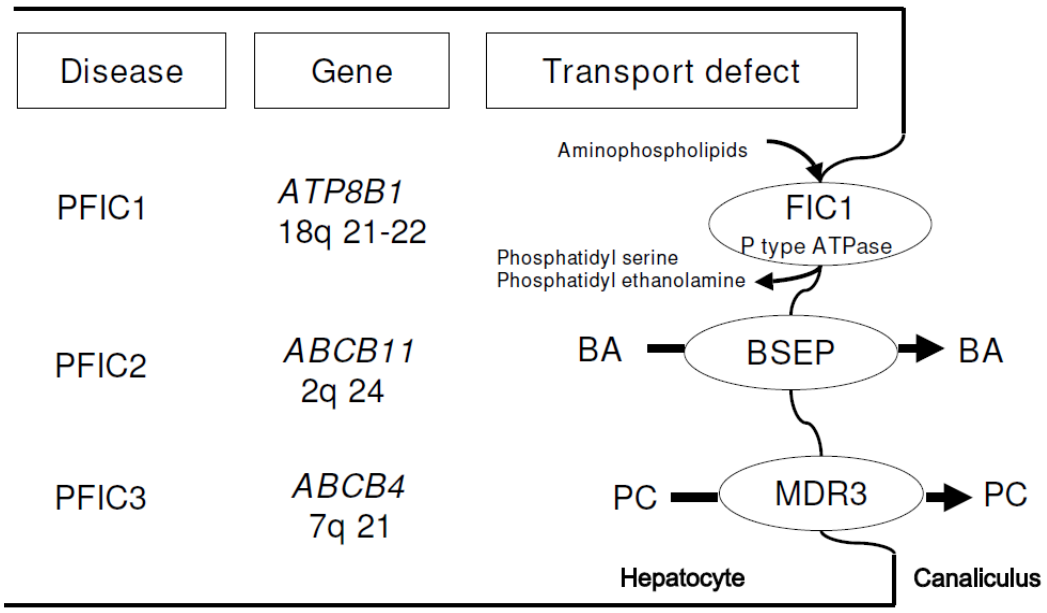


ASBT/IBAT expression is under negative feedback regulation by bile acids; thus in the setting of cholestasis, ASBT/IBAT is maladaptively upregulated (Neimark et al. 2004; Hofmann 2003). Inhibiting the reuptake of bile acids may represent an ideal treatment for cholestatic disease. In cholestasis secondary to defects in FIC1 (ATP8B1) bile acid signaling may be deranged leading to an even more pronounced up-regulation of ASBT, which may be a key part of the pathophysiology of the disease. By blocking 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 study will test this hypothesis.

4.2 Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) refers to a group of autosomal recessive disorders of childhood that disrupt bile formation and present with cholestasis (Alissa et al. 2008). The exact prevalence remains unknown, but the estimated prevalence at birth is between 1/50,000 and 1/100,000. Three types of PFIC have been identified and related to mutations in hepatocellular transport system genes involved in bile formation. Figure 2, taken from Davit-Spraul et al. (2009), shows these three types together with their associated genes and transport defects. This protocol will focus on the PFIC subjects with normal serum gamma-glutamyl transpeptidase (GGTP) activity, namely PFIC1 and PFIC2.

Figure 2: Types of Progressive Familial Intrahepatic Cholestasis



BA: bile acid; PC: phosphatidylcholine.

Progressive familial intrahepatic cholestasis type 1 (FIC1) is thought to comprise ~25-35% of the PFIC population. Cell line based studies and examination of ileal tissue from children with FIC1 disease reveals abnormal homeostatic responses to bile acids (Chen et al. 2004; Frankenberg et al. 2008; Chen et al. 2010; Chen et al. 2013). As such, there is a marked up-regulation of ASBT

in the ileum of individuals with FIC1 disease. Patients with FIC1 usually present with features of neonatal cholestasis. Serum bilirubin is not necessarily increased in FIC1, but elevation in serum bile acids is a nearly uniform feature of the disease. The most prominent and problematic on-going manifestation of FIC1 is pruritus. In the absence of surgical treatment, progression to cirrhosis and end-stage liver disease is expected in the first or second decade of life. Partial external biliary diversion or partial ileal exclusion, can produce rapid and profound improvement in pruritus and biochemical markers of cholestasis, and may slow the progression to cirrhosis (Whitington and Whitington 1988; Emond and Whitington 1995; Hollands et al. 1998; Ng et al. 2000). Liver transplantation in FIC1 disease has been complicated by a number of unique post-transplant problems, including severe diarrhea and progressive steatohepatitis (Lykavieris et al. 2003; Miyagawa-Hayashino et al. 2009).

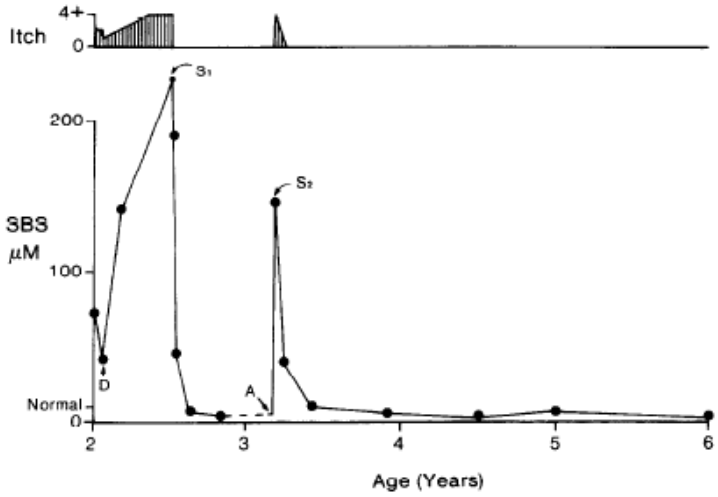
PFIC2 is caused by mutations in the *ABCB11* gene (also designated *BSEP*). This gene encodes the ATP-dependent canalicular bile salt export pump (BSEP) of human liver and is located on human chromosome 2. BSEP protein, expressed at the hepatocyte canalicular membrane, is the major exporter of primary bile acids against extreme concentration gradients. Mutations in this protein are responsible for the decreased biliary bile salt secretion described in affected patients, leading to decreased bile flow and accumulation of bile salts inside the hepatocyte with ongoing severe hepatocellular damage.

Patients with PFIC2, like those with PFIC1, have normal serum gamma-glutamyl transpeptidase (GGTP) activity, normal serum cholesterol level and very high serum bile acid concentration, but PFIC2 patients have higher transaminase and alpha-fetoprotein serum levels at diagnosis. The liver histology is also similar between the two types but the liver architecture is more perturbed in PFIC2, with more pronounced lobular and portal fibrosis and inflammation. Hepatocellular necrosis and giant cell transformation is also much more pronounced and may persist with time. These differences between PFIC1 and PFIC2 likely reflect the severe lobular injury present in PFIC2.

4.3 Pruritus

Intractable and pharmacologically recalcitrant pruritus is one of the major morbidities afflicting children with PFIC. Treatment with anti-pruritics and bile salt binding resins may provide partial relief of itching for children with PFIC, 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 nasobiliary drainage (NBD) substantially reduces pruritus in PFIC (Whitington and Whitington 1988; Emerick and Whitington 2002), and other cholestatic liver diseases including Alagille syndrome and primary biliary cirrhosis. 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 3 extracted from the original description of this procedure by Whitington and Whitington (1988). Rapid lowering of bile acids, bilirubin and ALT has also been observed (Table 1).

Figure 3: Serum Bile Salt Concentration and Degree of Itch



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

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

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

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

A retrospective analysis of PFIC patients following PEBD indicated that normalization of serum bile acids within 1 year of surgery was associated with clinical improvement and an excellent long-term outcome (Schukfeh et al. 2012).

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.

To support the use of LUM001 in young children, a toxicity study in juvenile animals was completed. As expected for a drug intentionally designed to be minimally absorbed, LUM001 exposure was very low and consistent with levels observed in adult rats. No adverse effects were observed on postnatal growth and development of offspring at a dose of 200 mg/kg/day in males and 1000 mg/kg/day in females, the highest doses tested. 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, as evidenced by this and multiple other studies, of particular importance is the age at which the GI tract is considered functionally mature. In humans this occurs by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs during the first three weeks of birth. Therefore this study presented evidence to support the safety of LUM001 in future clinical trials in children 12 months of age and older. These trials have the promise to address a life-threatening clinical need in this patient population.

The higher dosing level implemented with Protocol Amendment 4 is supported by favorable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (PND21 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.

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 absorption, distribution, metabolism, and excretion (ADME) study, a statin co-administration study, a statin interaction study, and a food composition study. Phase 2 studies included two dose-ranging studies in adult subjects, a tolerability study in adolescents and children, and a multiple dose tolerability and efficacy study of three sustained release formulations, compared with the immediate release formulation. More than 1,400 human subjects have been exposed to LUM001 (immediate release) for up to 10 weeks.

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

Administration of LUM001 at doses up to 100 mg once daily over a four-week period was generally safe in healthy volunteers and at does 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. These GI AEs are also observed in subjects who undergo biliary diversion, are believed to be mechanism-based, due to elevated bile acid concentrations in the colon. With the exception of a

single serious adverse event (SAE) of cholecystitis no other SAEs possibly related or related to LUM001 have been reported in the 12 studies conducted to date, (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 cholestatic subjects is 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, i.e. 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 et al.(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 et al. 2002). Their analysis demonstrated that age had a negative and body weight a positive correlation with intestinal length. Taken as a whole, the existing analyses are inconclusive with respect to the dependent variables that predict intestinal length. Consequently, the most reasonable approach is to calculate doses in pediatric subjects from those in adults based using a direct mg/kg scaling. For reference in an average adult subject, weighing 70 kg, a 10 mg daily dose is equivalent to 140 µg/kg/day.

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

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

Sample Daily Exposure (mg/day) in Pediatric Subjects						
Weight (kg)	Dose Level 1 (14µg/kg/day)	Dose Level 2 (35µg/kg/day)	Dose Level 3 (70µg/kg/day)	Dose Level 4 (140µg/kg/day)	Dose Level 5 (280µg/kg/day)	Dose Level 6 (560µg/kg/day)
10	0.14	0.35	0.70	1.40	2.80	5.60
15	0.21	0.53	1.05	2.10	4.20	8.40
20	0.28	0.70	1.40	2.80	5.60	11.20
25	0.35	0.88	1.75	3.50	7.00	14.00
30	0.42	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 <0.25 ng/mL to 1.13 ng/mL) and consistent with a drug that is minimally absorbed. Detection of LUM001 in plasma samples was sporadic, both within and among subjects. In addition there does not appear to be a relationship with either subject age or gender. These data do not differ from the extensive pharmacokinetic data collected in adults to date. Although the bioavailability of LUM001 has not yet been characterized in children younger than 10 years of age, the GI systems are functionally mature in children by about 1 year of age (Walthall et al. 2005; van den Anker et al. 2011). This study will enroll children ages 12 months and older.

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. All subjects completed 14 days of treatment. 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. It is noteworthy that the AEs 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.

In the current study, safety and efficacy of LUM001 will be assessed for the first time in children with PFIC and cholestatic liver disease, 1 year of age and older, starting at a dose of 14 µg/kg/day. The starting dose is equivalent to less than the well tolerated 1 mg dose used in Study 014 (~17 µg/kg, 60 kg body weight), where only two subjects reported moderate or severe GI-associated AEs during 14 days. On a weight basis, 23 subjects received a dose approximately ≥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 subjects in study LUM001-501, the 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). For BID dosing, the morning dose is initiated and escalated first; the afternoon dose is only initiated and escalated in patients with elevated sBA and/or ItchRO ≥1.5 on the maximum (or maximum tolerated) morning 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 (i.e. 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (i.e. 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 (PND21 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 an open label study in children with PFIC (GGTP <100 IU/L) designed to evaluate the safety and efficacy of LUM001. The study is divided into 5 parts: a 4-week dose escalation period, a 4-week stable dosing period at 140 µg/kg/day, a 5-week stable dosing period at 280 µg/kg/day, a 59-week long-term exposure period, and an optional follow-up treatment period for eligible subjects who choose to stay on treatment with LUM001. During the optional follow-up treatment period, subjects may be eligible for BID dosing based on efficacy as measured by sBA level and ItchRO score, and may have their dose of LUM001 increased to a maximum of 560 µg/kg/day (280 µg/kg BID). Subjects' participation in the optional follow-up treatment period will continue until the first of the following occurs: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.

An interim analysis of key safety and efficacy parameters will be performed after the first 12 subjects who meet the Per Protocol population definition have completed the Week 13 study visit. A second interim analysis will be performed after all evaluable subjects have completed the Week 48 (or Early Termination) study visit. A third interim analysis will be performed after all enrolled subjects have completed at least 6 months of treatment under Protocol Amendment 4 (or the Early Termination visit). Subsequent interim analyses will be performed in yearly intervals. See Section 12.2.7 for additional information.

5.2 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will review SAE data, other key subject safety and study data at specified intervals for the duration of the study. The DSMB will be composed of at least 2 members who are otherwise independent from the conduct of the study and one biostatistician. The DSMB's primary responsibility is to review the progress of the study, particularly with regard to safety and risk/benefit, and make recommendations to Sponsor to stop or modify the trial if safety concerns are identified. Further details regarding the structure, function and operation of the DSMB will be detailed in the DSMB charter.

5.3 Number of Study Centers

This will be a multicenter study at approximately 13 clinical centers.

5.4 Number of Subjects

Approximately 24 evaluable subjects are planned for treatment in this study. Of these, a minimum of 8 enrolled will be PFIC1 subjects in light of the potential specific role that ASBT plays in the pathophysiology of FIC1 disease.

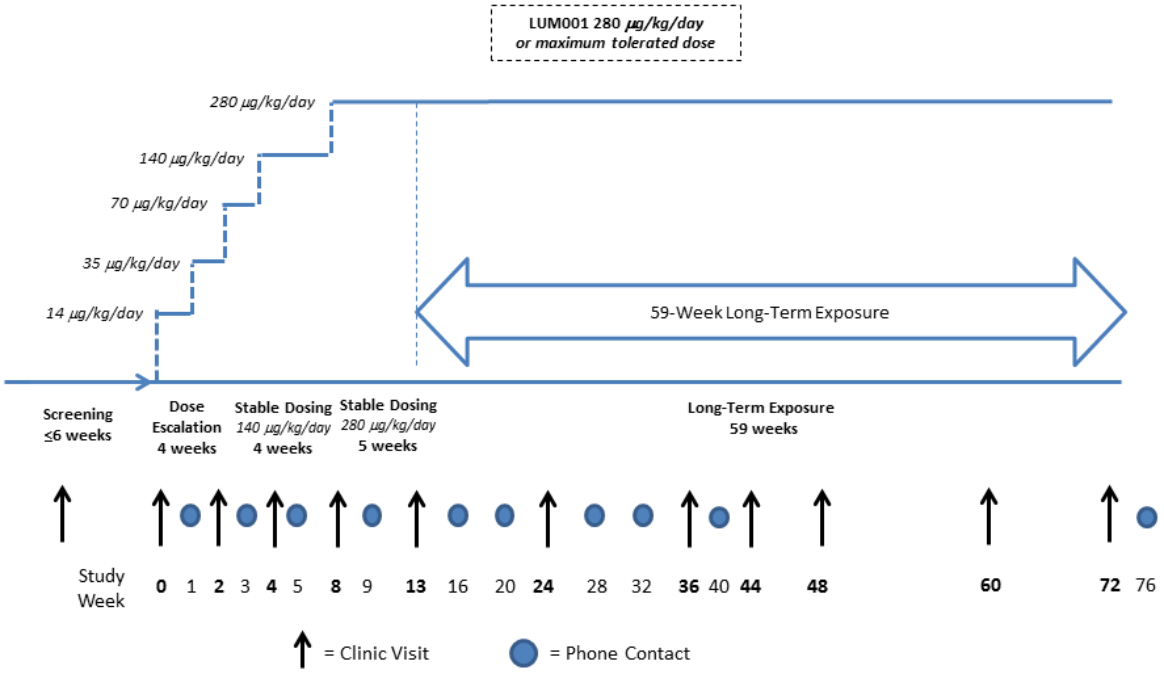
5.5 Overall Study Duration and Follow-up

For an individual subject, the duration of the study, including subject screening, treatment and safety follow-up, is expected to be approximately 76 weeks. Following the screening visit,

subjects who meet all eligibility criteria will return to the clinic for 11 visits and will receive 10 telephone contacts from the study staff (see Figure 4). Subjects who complete 72 weeks of treatment may be eligible to receive further treatment during the optional follow-up treatment period. Eligible subjects may continue study treatment beyond Week 72 until the first of the following occurs: (i) the subject is eligible to enter another LUM001 study or (ii) LUM001 is available commercially.

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

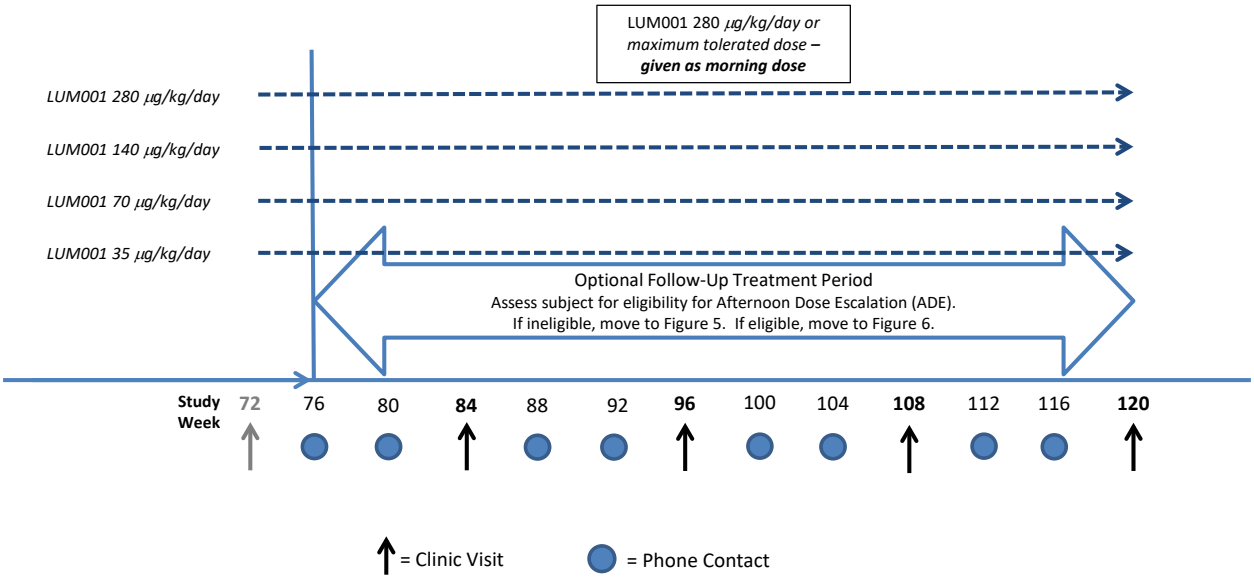
Figure 4: Study Design for LUM001-501 (Up to and including Week 72)



Optional Follow-up Treatment Period (post-Week 72; < 7 days from last LUM001 dose between Protocol Amendment 2 and Protocol Amendment 3)

Applies to the following subject population:

- Subjects who experienced no interruption in LUM001 dosing, or interruption <7 days between Protocol Amendment 2 and Protocol Amendment 3.



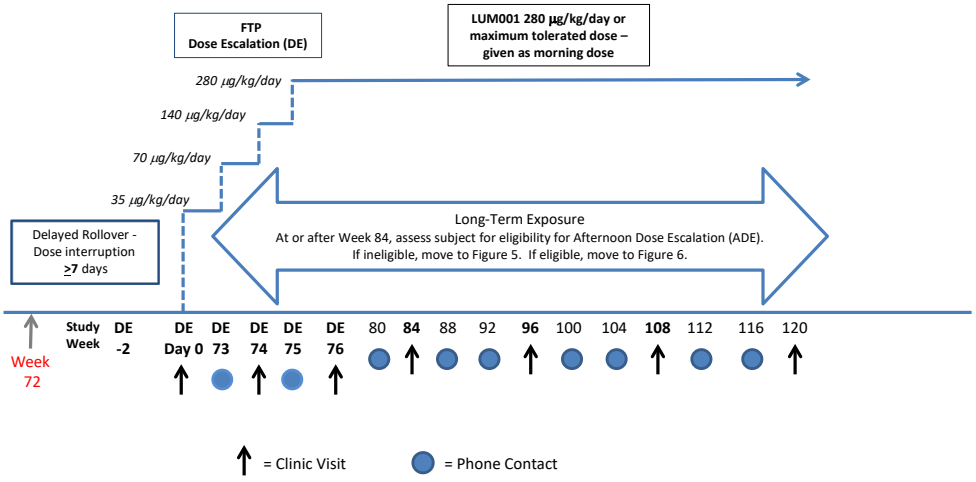
In consultation with Medical Monitor, the dose may be lowered to a previously well-tolerated dose to address tolerability issues at any time during the study

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

Optional Follow-up Treatment Period (post-Week 72; ≥ 7 days from last LUM001 dose between Protocol Amendment 2 and Protocol Amendment 3)

Applies to the following subject population:

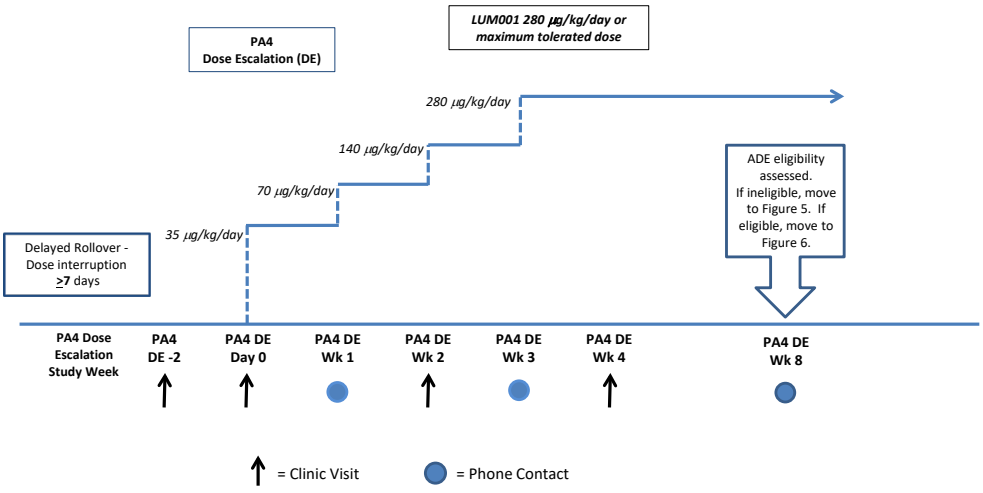
- Subjects who experienced an interruption in LUM001 dosing ≥7 days between Protocol Amendment 2 and Protocol Amendment 3.



Optional Follow-up Treatment Period (post-Week 72; ≥ 7 days from last LUM001 dose between Protocol Amendment 3 and Protocol Amendment 4)

Applies to the following subject population:

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



5.5.1 Screening

Each subject who provides informed consent/assent will complete all screening activities in ≤ 6 weeks.

5.5.2 Treatment

The appropriate amount of study drug will be dispensed at the Study Day 0 visit and daily dosing will begin on Study Day 1.

All subjects will receive LUM001, up to 560 µg/kg/day (given as twice-daily [BID] doses of 280 µg/kg) or up to a maximum daily dose of 25 mg BID. Dosing will occur over a 13-week treatment period (comprised of 4-weeks dose escalation [Dose Level 1-4], 4-weeks stable dosing at 140 µg/kg/day, and 5-weeks stable dosing at 280 µg/kg/day), followed by a 59-week long-term exposure period.

For the first 72 weeks of the study, each subject will receive either 1.0 mL (subjects weighing ≥10 kg) or 0.5 mL (subjects weighing <10 kg) of solution containing LUM001 orally as follows, administered as a daily morning dose:

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

At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll over into the optional follow-up treatment period. Subjects eligible for the optional follow-up treatment period will continue treatment under dosing scenarios based on whether their LUM001 dosing will continue without interruption or interruption of <7 continuous days, or with interruption ≥7 days. Eligibility for BID dosing will be determined based on efficacy as measured by sBA level and ItchRO score.

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

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

5.5.2.1 Dose Escalation Period

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

If a subject experiences intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator in consultation with the Medical Monitor may lower the dose for the remainder of the study. In these circumstances an unscheduled visit will occur and the appropriate replacement study medication will be issued to the subject as quickly as possible.

5.5.2.2 Stable Dosing Period

Following the dose escalation period (Day 0 – 4) subjects will continue LUM001 dosing through Week 8 using Dose Level 4, or the highest tolerated dose below Dose Level 4. For those subjects who tolerated Dose Level 4, at Week 8, the dose will be increased to Dose Level 5 until Week 13.

5.5.2.3 Long-term Exposure Period

Subjects will continue to receive LUM001 during the long-term exposure dosing treatment period according to the highest dose achieved during the stable dosing treatment period. However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator, in consultation with the Medical Monitor, may lower the dose for the remainder of the study. At the investigator's discretion and in consultation with the Medical Monitor, subjects who were previously down-titrated may be re-challenged during the long-term exposure period.

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

During the long-term exposure period, subjects will return to the clinic at Weeks 24, 36, 44, 48, 60 and 72. 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 Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 48 and 72. At the Week 24 and Week 44 visits, electronic diaries will be issued and AEs and concomitant medications will be assessed and recorded.

Subjects/caregivers will receive follow-up phone calls at Weeks 16, 20, 28, 32 and 40. Concomitant medications and any adverse events (AEs) will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.

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 Week 44, additional study drug will be supplied at each clinic visit during the long-term exposure period.

5.5.2.4 Optional Follow-up Treatment Period (Post-Week 72)

Optional Follow-up Treatment Period (Post-Week 72):

Subjects eligible for the optional follow-up treatment period will continue treatment under dosing scenarios based on whether:

-Their LUM001 dosing will continue without interruption or interruption of <7 continuous days,

or

-Their LUM001 dosing will continue with interruption ≥7 days.

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

Subjects who enter the optional follow-up treatment period without LUM001 dosing interruption or with an interruption of <7 continuous days will be dosed in the following manner:

- Subjects with normal sBA level AND ItchRO score <1.5 will be maintained at the same dose level and will continue morning dosing only.

- Subjects with sBA level above normal AND/OR ItchRO score ≥1.5 will start BID dosing (afternoon dose escalation; ADE) as follows:

  - The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated.
  - The afternoon dose will be initiated at half the maximum tolerated morning dose and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be doubled, to a maximum dose of 280 µg/kg (or up to the maximum tolerated dose).
  - The maximum daily dose will be 280 µg/kg BID, i.e. 560 µg/kg/day (max. 25 mg BID).

Subjects who enter the optional follow-up treatment period with a LUM001 dosing interruption of ≥7 days initially will receive morning dosing only and will undergo dose escalation (DE) in the following manner:

- The morning dose will be initiated at Dose Level 2 (35 µg/kg) and doubled in weekly intervals to a maximum dose of 280 µg/kg , or up to the maximum tolerated dose.

- Once the morning dose of 280 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO score will be evaluated.

- Subjects with normal sBA AND ItchRO score <1.5 after morning dose escalation will be maintained at the same dose level and will continue morning dosing only.

- Subjects with sBA above normal AND/OR ItchRO score ≥1.5 will begin BID dosing (afternoon dose escalation) as outlined above.

Subjects will continue to receive study drug until they are eligible to enter another LUM001 study or until LUM001 is available commercially, whichever occurs first.

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

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

5.5.2.5 Safety Follow-up 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 AEs noted during this phone call will be recorded. Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in the optional follow-up treatment period under Protocol Amendment 4.

Additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used study drug will be collected at each clinic visit and dosing compliance assessed.

5.5.3 Electronic Diary

Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects beginning at the screening visit through the end of the Week 13 visit and again during the 4 weeks that follow the Week 24 and Week 44 clinic visits. For subjects who enter the optional follow-up treatment period, twice daily completion of the electronic diary will occur during the 2 weeks that follow the Week 84, 96, 108, and 120 visits, Protocol Amendment 4 DE Week 4, and every clinic visit within each recurring 12-week period~~2~~. Electronic diaries will be provided to subjects and caregivers and re-training on the use of the diary will occur, as appropriate, at these visits.

5.6 End of Study

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

For subjects who consented to the follow-up treatment period, an additional follow-up period disposition is collected in the eCRF. The subject is considered to have completed treatment

during the follow-up treatment period if study treatment was not permanently discontinued prior to the subject completing the EOT visit as defined in the most recent consent signed by the subject. A follow-up contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.

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

6 SUBJECT ENROLLMENT

6.1 Screening

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

Following informed consent/assent, the subject will be entered into the study and will be assigned a unique subject identification number before any study procedures, including screening procedures, are performed. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The Subject identification number must remain constant throughout the entire study. In the event the subject is re-consented and rescreened, the subject must be given a new subject identification number. Subject identification numbers, once assigned, will not be reused.

6.2 Enrollment

Subjects will be enrolled after all screening assessments have been completed and the Investigator has verified that eligibility criteria have been met.

Subjects will be enrolled into the optional follow-up treatment period based on the eligibility criteria outlined in Section 7.3.

6.3 Replacement of Subjects

A subject who withdraws from the study prior to completion of the Week 13 treatment period may be replaced at the discretion of the Sponsor. Subjects who substantially violate the protocol may also be replaced, if required, in order to provide 24 evaluable subjects. Subjects who are determined to be screen failures may be replaced after consultation with the sponsor.

7 SUBJECT ELIGIBILITY

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

7.1 Inclusion Criteria

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

1. Male or female subjects between the ages of 12 months and 18 years inclusive.
2. Diagnosis of PFIC based on:
    a. Intrahepatic cholestasis manifest by total serum bile acid >3x upper limit of normal (ULN) for age.

    and, b or c:

    b. Two documented mutant alleles in ATP8B1, or ABCB11.
    c. Evidence of chronic liver disease, excluding those listed in (see Section 16.3), with one or more of the following criteria:
        1. Duration of biochemical or clinical abnormalities of >6 months, or
        2. Pathologic evidence of progressive liver disease, or
        3. Sibling of known individual affected by PFIC (predicted to be chronic).
3. GGTP <100 IU/L at screening.
4. Females of childbearing potential must have a negative urine or serum pregnancy test [β human chorionic gonadotropin (β-hCG)] during screening and a negative urine pregnancy test at the Baseline (Day 0) 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 30 days following the last dose of study drug, must agree and use acceptable contraception during the trial, as described in Section 8.7.1.
6. Informed consent and assent (per IRB/EC) as appropriate.
7. Access to phone for scheduled calls from study site.
8. Caregivers and children above the age of assent must have the ability to read and understand one of the following languages: English, Spanish, US Spanish, French, German or Polish.
9. Subjects expected to have a consistent caregiver(s) for the duration of the first 13 weeks of the study.
10. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device as required by the study. To accommodate potential cultural restrictions within the FIC1 affected population a paper version of the ItchRO diary will be made available.
11. Caregivers (and age appropriate subjects) using the eDiary must digitally accept the licensing agreement in the eDiary software at the outset of the study.
12. Caregivers (and age appropriate subjects) must complete at least 10 eDiary reports (morning or evening) during each of two consecutive weeks of the screening period, prior to

assignment (maximum possible reports = 14 per week). Subjects using a paper diary must complete the same number of reports within the same timeframe.

7.2 Exclusion Criteria

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

1. Chronic diarrhea requiring specific intravenous fluid or nutritional intervention for the diarrhea and/or its sequelae.
2. Surgical disruption of the enterohepatic circulation at the time at screening. Subjects who have undergone reversal of a prior surgical procedure intended to disrupt enterohepatic circulation and who and have a permanently restored flow of bile acids from the liver to the terminal ileum may be eligible for the study upon consultation with the Medical Monitor.
3. Liver transplant.
4. Decompensated cirrhosis [international normalized ratio (INR) > 1.5, albumin < 30 g/L, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy].
5. ALT >15×ULN at screening.
6. History or presence of other liver disease (see Section 16.3).
7. History or presence of any other disease or condition known to interfere with the absorption, distribution, metabolism or excretion of drugs, including bile salt metabolism in the intestine (e.g., inflammatory bowel disease).
8. Liver mass on imaging.
9. Known diagnosis of human immunodeficiency virus (HIV) infection.
10. Cancers except for in situ carcinoma, or cancers treated at least 5 years prior to screening with no evidence of recurrence.
11. Any female who is pregnant or lactating or who is planning to become pregnant within 20 weeks of assignment.
12. Any known history of alcohol or substance abuse.
13. Administration of bile acid or lipid binding resins within 30 days prior to Baseline / Day 0 and throughout the trial.
14. Administration of sodium phenylbutyrate within 30 days prior to Baseline / Day 0 and throughout the trial.
15. Investigational drug, biologic, or medical device within 30 days prior to screening, or 5 half-lives of the study agent, whichever is longer.
16. History of non-adherence to medical regimens, unreliability, mental instability or incompetence that could compromise the validity of informed consent or lead to non-adherence with the study protocol based on Investigator judgment.
17. Any other conditions or abnormalities which, in the opinion of the Investigator or Medical monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study.

7.3 Eligibility for Optional Follow-up Treatment Period

7.3.1 Inclusion Criteria

To participate in optional follow-up treatment period subjects must meet the following criteria:

1. The subject has either:

- completed the protocol through the Week 72 visit with no major safety concerns.

OR

- discontinued due to safety reasons judged unrelated to the study drug, and blood tests have returned to levels acceptable for this patient population/individual and subject does not meet any of the protocol's stopping rules at re-entry. 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-hCG) at the time of entry into the optional follow-up treatment period.
3. Informed consent and assent (per IRB/EC) as appropriate.

7.3.2 Exclusion Criteria

Subjects will be excluded from the optional follow-up treatment period if they meet the following criteria:

1. Surgical disruption of the enterohepatic circulation.

2. Investigational drug other than LUM001, biologic, or medical device within 30 days prior to re-entry, or 5 half-lives of the study agent, whichever is longer.

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 Screening Period (Day -42 to Day -1)

Screening evaluations will be performed from Day -42 to Day -1. Subjects and caregivers who give written informed consent/assent will provide demographic data (gender, age, and race) and undergo a complete medical history (including ongoing medical conditions and symptoms and assessment of inclusion/exclusion criteria). A physical examination will be conducted including body weight, height, and vital signs, determination of concomitant medications, and blood and urine samples will be taken for clinical laboratory testing. An ultrasound will be performed to determine if any masses are present in the liver. Note: A screening ultrasound is not required if the results of an ultrasound completed within 6 months are available and the clinical status of the subject has not changed significantly since the time of the test.

In the absence of documented *ATP8B1* or *ABCB11* mutation prior to screening, genetic testing will be performed. The appropriate genetic counseling will be provided to subjects and their legal caregivers at a study visit following the receipt of results of genetic testing. Results of genetic screen will not impact continued participation in the study, but are done to provide complete and uniform characterization of the subjects' liver disease.

The eDiary for assessing pruritus, as measured using an Itch Reported Outcome (ItchRO) instrument, will be dispensed and subjects and caregivers will receive training during the screening visit. The patient/caregiver ItchRO will be administered twice daily during the screening period to determine study eligibility and baseline score. The physician will provide an assessment of itch severity using the clinician administered scratch scale during screening.

Females who are of childbearing potential will have a serum pregnancy test. Enrollment will occur after eligibility criteria have been met, 4-7 days prior to the baseline visit.

Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 42-day screening period, consideration may be given to rescreening at a later date. Screening procedures should be repeated at that time.

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

At the baseline visit (Day 0), study eligibility will be confirmed and body weight, height, and vital signs will be evaluated and recorded. Blood and urine samples will be taken for clinical laboratory testing, including fasting lipid panel. Baseline levels of bile acids and other cholestasis biochemical markers will be determined from blood and urine (for a complete list of analytes see Section 16.2). Blood will also be collected for determination of baseline fat-soluble vitamins. Also during the baseline visit, ItchRO compliance will be assessed, the clinician

scratch scale will be administered, and the PedsQL questionnaire, a measure of quality of life will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test at all study visits prior to dispensing study drug. Study drug for Weeks 1 (Dose Level 1) and 2 (Dose Level 2) will be supplied at the baseline visit to eligible subjects. Caregivers and age appropriate subjects will continue twice daily (morning and evening) completion of their eDiary (ItchRO) throughout the dose escalation treatment period.

Subjects will return to the clinic at Weeks 2 and 4 and will receive a follow-up phone call at Weeks 1, 3 and 5. 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. At the Week 2 visit study drug and additional dosing instructions for Weeks 3 (Dose Level 3) and 4 (Dose Level 4) will be supplied. Follow-up phone calls will review dosing instructions for the following week. ItchRO compliance will be assessed and concomitant medications and any AEs will be recorded at clinic visits and from phone calls. Phone contact at Weeks 1 and 3 and clinic visits at Weeks 2 and 4 have a ±2 day window.

Blood sampling for study drug level determination:

- **US:** At sites in the United States, blood sampling for plasma levels of LUM001 will be collected at Baseline (Day 0) and Weeks 2 and 4. At Week 2, blood will be drawn approximately 4 hours post dosing for drug level analysis. At Week 4, blood will be drawn approximately 2 hours post-dosing.
- **UK, EU, and Australia**: At sites in the United Kingdom, Europe and Australia, blood sampling for plasma levels of LUM001 will be collected at Week 4. Blood will be drawn approximately 4 hours post-dosing.

8.1.3 140 µg/kg/day Stable Dosing Treatment Period (Week 5 to Week 8)

Each subject will continue to receive LUM001 during the stable dosing treatment period using Dose Level 4, or the highest tolerated dose below Dose Level 4. Subjects and caregivers will continue daily completion of their eDiary (ItchRO). Subjects/caregivers will receive a follow-up phone call at Week 5 and return to the clinic at Week 8.

At the Week 8 clinic visit, safety and clinical laboratory evaluations as well as blood sampling for study drug determination will be performed, approximately 4 hours post study drug administration. The clinician scratch scale will be administered and adherence to study drug will be assessed. For those subjects who tolerated Dose Level 4, at the Week 8 visit the dose will be increased to Dose Level 5, subjects will continue dosing for another 5 weeks using Dose Level 5 or the highest tolerated dose below this dose. Additional dosing instructions and study drug will be supplied. ItchRO compliance will be assessed and concomitant medications and any AEs will be recorded at clinic visits and from phone calls.

Females who are of childbearing potential will have a urine pregnancy test at all clinic visits. Concomitant medications and any AEs will be recorded at clinic visits and from phone calls. Phone contact at Week 5, and the clinic visit at Week 8 will have a ±5 day window.

Blood sampling for study drug level determination:

- **US:** At sites in the United States, blood sampling for plasma levels of LUM001 will be collected at Week 8. Blood will be drawn approximately 4 hours post morning dosing.
- **UK, EU, and Australia**: At sites in the United Kingdom, Europe and Australia, blood sampling for plasma levels of LUM001 will not be collected between Weeks 5 and 8.

8.1.4 280 µg/kg/day Stable Dosing Treatment Period (Week 9 to Week 13)

Each subject will continue to receive LUM001 during the stable dosing treatment period using Dose Level 5 or the highest tolerated dose below this dose. Subjects and caregivers will continue daily completion of their eDiary (ItchRO). Subjects/caregivers will receive a follow-up phone call at Week 9 and return to the clinic at Week 13.

At the Week 13 clinic visit, safety and clinical laboratory evaluations as well as blood sampling for study drug determination will be performed, approximately 4 hours post study drug administration. The clinician scratch scale will be administered and adherence to study drug will be assessed. Additional dosing instructions and study drug will be supplied at Week 13. At the Week 13 visit, the PedsQL will be administered and the eDiary will be collected.

Females who are of childbearing potential will have a urine pregnancy test at all clinic visits. Additional dosing instructions and study drug will be supplied for the next phase of the study.

Concomitant medications and any AEs will be recorded at clinic visits and from phone calls. Phone contact at Week 9 and the Week 13 clinic visit will have a ±5 day window.

Blood sampling for study drug level determination:

- At all sites (US, UK, EU and Australia), blood sampling for plasma levels of LUM001 will be collected at Week 13. Blood will be drawn approximately 4 hours post morning dosing for drug level analysis.

8.1.5 Long-Term Exposure Period (Week 14 to Week 72)

Subjects will continue to receive LUM001 during the long-term exposure dosing treatment period according to the dose achieved during the stable dosing treatment period. However, if a subject experiences intolerance due to gastrointestinal symptoms, the investigator in consultation with the Medical Monitor may lower the dose for the remainder of the study. At the investigator's discretion and in consultation with the Medical Monitor, subjects who were previously down-titrated may be re-challenged during the long-term exposure period.

During the long-term exposure period, subjects will return to the clinic at Weeks 24, 36 44, 48, 60 and 72. With the exception of Week 44, 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 completed at Weeks 24, 48 and 72, and the Patient and Caregiver Impression of Change (PIC & CIC) and the Caregiver Global Therapeutic Benefit assessments 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 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 4 weeks that follow the Week 24 and Week 44 clinic visits. Electronic diaries will be provided to subjects and caregivers at Weeks 24 and 44, and re-training on the use of the diary will occur, as appropriate, at these 2 visits.

At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the long-term exposure period and will be documented on the appropriate case report form.

With the exception of the Week 44 visit, additional study drug will be supplied at each clinic visit during the long-term exposure period. Used study drug will be collected at each clinic visit, and dosing compliance will be assessed. Clinic visits and telephone contacts during the long-term exposure period have a ±14 day window.

Blood sampling for study drug level determination:

- At all sites (US, UK, EU and Australia), blood sampling for plasma levels of LUM001 will be collected at Weeks 24, 36, 48, 60 and 72. Blood will be drawn approximately 4 hours post dosing.

At Week 72, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the optional follow-up treatment period. Following completion of the Week 72 study visit, 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.

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

Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo all procedures specified for the Week 72 study termination visit. In addition the following assessments should be completed; the ItchRO (if prior to the Week 48 visit), the clinician administered pruritus 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 Section 16.1; Schedule J). 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)

Subjects who are eligible to enter the follow-up treatment period will continue to receive study drug after Week 72 until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.

Included below are schematics describing the flow of study visits within the optional follow-up treatment period.

Subjects who experienced no interruption in LUM001 dosing, or interruption <7 days between Protocol Amendment 2 and Protocol Amendment 3:

Subjects who are eligible to enter the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will initially receive study drug at the dose they were receiving at Week 72. Once Protocol Amendment 4 is implemented at the site, a determination about Afternoon Dose Escalation (ADE) will be made. **The subject then will move to Figure 5 or Figure 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.**

Subjects who experienced an interruption in LUM001 dosing ≥7 days between Protocol Amendment 2 and Protocol Amendment 3:

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 Dose Level 2 (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 maximum tolerated dose.

Once Protocol Amendment 4 is implemented at the site, a determination about Afternoon Dose Escalation (ADE) will be made. **The subject then will move to Figure 5 or Figure 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.**

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

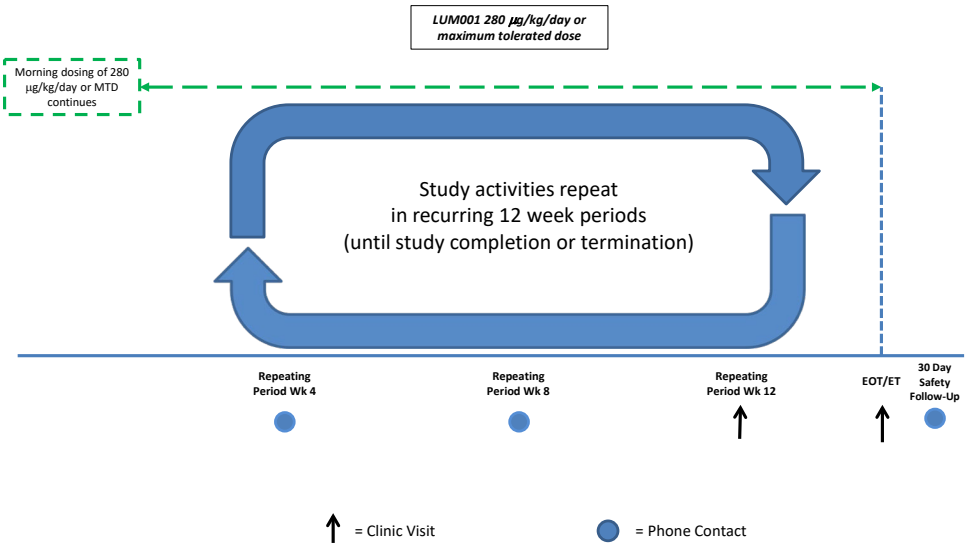
Subjects with ≥7 days since last dose of LUM001 prior to site implementation of Protocol Amendment 4 will be dose escalated up to 280 µg/kg/day or to the highest tolerated dose starting at Dose Level 2 (35 µg/kg/day).
The dose escalation (DE) period will proceed as follows:

- Protocol Amendment 4 DE Week -2 Clinic Visit: obtain consent for Protocol Amendment 4, obtain weight and draw labs.
- Protocol Amendment 4 DE Day 0 Clinic Visit: Investigator evaluates laboratory results, study drug is dispensed and subject begins at 35 µg/kg/day dose level.
- Protocol Amendment 4 DE Week 1 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated.
- Protocol Amendment 4 DE Week 2 Clinic Visit: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated.
- Protocol Amendment 4 DE Week 3 Telephone Contact: subject escalates to 280 µg/kg/day dose, if prior dose level was tolerated.
- Protocol Amendment 4 DE Week 4 Clinic Visit: subject continues in follow-up treatment period at 280 µg/kg/day, or maximum tolerated dose.
- At Protocol Amendment 4 DE Week 8 Telephone Contact: eligibility for ADE will be assessed. The subject will then move to Figure 5 or Figure 6, depending on whether they meet criteria for initiating Afternoon Dose Escalation.

Figure 5: Optional Follow-up Treatment under Protocol Amendment 4, without Afternoon Dose Escalation (ADE)

Applies to the following subject population:

- Subjects deemed ineligible for ADE.



Subjects Deemed Ineligible for ADE:

Subjects with normal sBA level AND ItchRO score <1.5 will be deemed ineligible for ADE; such patients will be maintained at the same dose level and will continue morning dosing only. Subjects will have study activities then repeated in recurring 12-week periods as follows, until study completion or termination:

- Recurring Period Week 4 (i.e., beginning Week 88 or 4 weeks after consent to Protocol Amendment 4) Telephone Contact: Collection of concomitant medications and any adverse events.

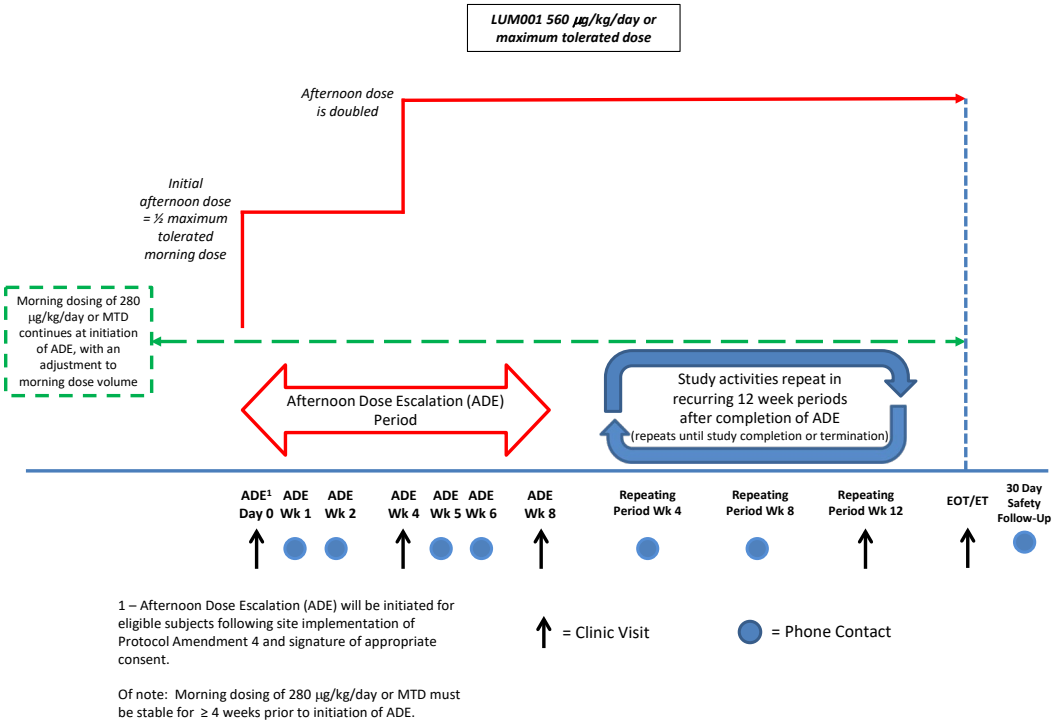
- Recurring Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.

- Recurring 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 fat-soluble vitamins. Urine samples for clinical laboratory testing will be collected at every visit. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale will be administered, 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 upon completion of other study procedures.

Figure 6: Optional Follow-up Treatment under Protocol Amendment 4, with Afternoon Dose Escalation (ADE)

Applies to the following subject population:

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



Subjects deemed eligible for ADE, i.e., who have sBA level above normal AND/OR ItchRO score ≥1.5, will begin BID dosing (afternoon dose escalation; ADE) as follows:

- On ADE 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. Dosing must have been stable for ≥4 weeks prior to initiation of ADE.

- On ADE 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 (i.e., at ADE Week 4) to a maximum dose of 280 µg/kg (i.e., up to a maximum 560 µg/kg/day or maximum tolerated dose).

The following procedures will occur during the ADE period:

- ADE 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 PK. The clinician scratch 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.

- ADE Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.

- ADE 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 PK. The clinician scratch 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.

- ADE Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.

- ADE 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 PK. The clinician scratch 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 5, 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 follow-up treatment period, subjects will return to the clinic every 3 months.

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, every clinic visit within each recurring 12-week period, and at the EOT visit.

Additionally, it will be collected at Protocol Amendment 4 DE Day 0, ADE Day 0, ADE Week 4, and ADE Week 8. The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 108, 120, and the EOT visit. Subjects/caregivers will receive follow-up phone calls at Weeks 80, 88, 92, 100, 104, 112, and 116, and twice within each recurring 12-week period, and every 3 months hence for the subsequent visits. 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 clinic visits, at Protocol Amendment 4 DE Week 4, and every clinic visit (not including the EOT visit) within each recurring 12-week period. 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.

Blood sampling will be performed for study drug level determination as follows:

- **US:** At sites in the United States, for subjects in which afternoon dose escalation is initiated in the optional follow-up treatment period, samples will be drawn at ADE Day 0, ADE Week 4, ADE Week 8, and at the three scheduled clinic visits following completion of the ADE period. Blood will be drawn approximately 4 hours post morning dosing for drug level analysis.
- **UK, EU, and Australia**: At sites in the United Kingdom, Europe and Australia, for subjects in which afternoon dose escalation is initiated in the optional follow-up treatment period, samples will be drawn at ADE Day 0, ADE Week 4, ADE Week 8, and at the three scheduled clinic visits following completion of the ADE period. Blood will be drawn approximately 4 hours post morning dosing for drug level analysis.

With the exception of the EOT 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.

At completion of the 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 terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded.

8.1.8 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 J). The following assessments are to be completed at the EOT/ET 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 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. The ItchRO, the clinician

administered pruritus scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, and palatability questionnaire also will be completed, as defined for Early Termination (see Section 16.1).

8.1.9 Safety Follow-up 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 AEs noted during this phone call will be recorded.

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

8.2 Genetic Testing

ATP8B1 or *ABCB11* mutations are predictive of PFIC. For subjects who do not have documentation of an *ATP8B1* or *ABCB11* 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 PFIC including the type of mutation recorded. For those participants for which the type of the mutation cannot be documented, genetic testing may be conducted and the results recorded.

In addition, to better understand the role of genetics in treatment response, an additional blood sample will be taken for exome sequencing. The data analysis will focus initially on genetic variation in candidate genes that may have a role in treatment response, such as ASBT/SLC10A2 and genes in its pathway (ie upstream or downstream of ASBT/SLC10A2) and genes implicated in PFIC (ATP8B1, ABCB11 and ABCB4) with the goal of identifying genetic variation that may discriminate treatment responders from non-responders. Following examination of candidate genes, the data analysis may be expanded to evaluate genetic variation in additional regions of the exome. This genetic analysis is more comprehensive and may provide valuable information beyond the ATP8B1 and ABCB11 genes. The submission of this blood sample is voluntary. The results of this analysis may identify relevant genetic variants, only some of which will be of known clinical benefit. A blood sample for exome sequencing will be drawn once, at the time of consent under Protocol Amendment 4.

8.3 Physical Examination, Weight and Height, Vital Signs

A physician Investigator (or designee) will conduct a physical examination on each subject at screening and at the Week 24, Week 36, Week 48, Week 60 and Week 72 clinic visits. For subjects who enter into the optional follow-up treatment period, physical examinations will also be conducted at every clinic visit as outlined in the Schedules of Procedures in Section 16.1.

In addition, body weight, height (length), and vital signs, including body temperature, blood pressure, respiration and pulse, will be determined at every study clinic visit.

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 11.4.1 regarding laboratory abnormalities.

8.5 Pruritus and Quality of Life Assessments

All assessments completed by the subject and caregiver will be provided as validated translations in the following languages; English, Spanish, US Spanish, French, German or Polish.

8.5.1 Itch Reported Outcome (ItchRO™)

Pruritus will be assessed using a newly developed Itch caregiver/patient reported outcome measure (ItchRO) administered as a twice daily electronic diary. To accommodate potential cultural restrictions within the FIC1 affected population a paper version of the ItchRO diary will be made available.

Caregivers for all subjects will complete the Observer instrument: ItchRO(Obs)™. Children ≥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 in the use of the electronic (or paper) diary during the screening visit. Beginning with the screening period, pruritus will be assessed and recorded twice daily by caregivers and subjects (ItchRO), as described in Section 16.4.

To be eligible for enrollment, caregivers must complete at least 10 eDiary (or paper) reports (morning and/or evening) during each of two consecutive weeks of the screening period. In addition, subjects ≥9 years of age must complete at least 10 eDiary reports (morning and/or evening) during each of two consecutive weeks of the screening period.

Following enrollment, subjects/caregivers will be required to submit twice daily assessments using the electronic (or paper) diary during Day 0-13 of the study. Electronic diaries will be returned to the study site at the Week 13 clinic visit (or sooner if the subject has withdrawn from the study before then).

During the long-term exposure period, daily completion of the diary will be required by subjects and caregivers only during the 4 consecutive weeks that follow the Week 24 and Week 44 clinic visits. At Week 24 and Week 44, subjects/caregivers will be provided with the electronic diary and re-trained on its use, as needed. At the Week 24 visit, subjects/caregivers will also be

provided with prepaid/pre-labeled mailing supplies that should be used to return the electronic diary to the study center immediately after they have completed the 4 weeks of diary entries. At the Week 44 visit, subjects/caregivers will be instructed to bring their electronic diary with them when they return for the Week 48 clinic visit. For subjects who enter the optional follow-up treatment period, completion of the diary will occur as outlined in the Schedules of Procedures in Section 16.1.

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing very severe itching. The highest score between the morning and evening reports will represent the daily score: a measure of the worst itching over the previous 24-hour period. In the event that either the morning or evening reports are not completed within the allowed reporting window the completed report will represent the daily score. In the event that a subject/caregiver failed to complete both the morning and evening report, the daily score for that day will be treated as missing data. Missing data on the daily ItchRO score will be imputed using the average daily ItchRO score from that study week. When possible the caregiver completing the questions should be a caregiver with whom the child lives with most of the time.

8.5.2 Clinician Scratch Scale

A clinician's assessment of pruritus made by the principal investigator or sub-investigator using the clinician scratch scale (Section 16.5) will be recorded at screening, Day 0 (baseline), Weeks 2, 4, 8, 13, 24, 36, 48, 60, and 72.

For subjects who enter the optional follow-up treatment period, the clinician scratch scale will also be administered at clinic visits as outlined in the Schedules 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 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL™ is a one-page questionnaire that will be administered to subjects and or caregivers at the Day 0 (baseline) and Weeks 13, 24, 48 and 72 visits using the age-appropriate PedsQL module (Section 16.6).

For subjects who enter the optional follow-up treatment period, the PedsQL will also be administered at clinic visits as outlined in the Schedules of Procedures in Section 16.1. 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 adolescents (Varni et al. 2001). In addition to the core generic PedsQL module the multidimensional fatigue and family impact questionnaires will also be administered at the Day 0 (baseline) and Weeks 13, 24, 48 and 72 visits using the age-appropriate module, see Section 16.6.

For subjects who enter the optional follow-up treatment period, the multidimensional fatigue and family impact questionnaires will also be administered at clinic visits as outlined in the Schedules of Procedures in Section 16.1. For subjects with interruptions in LUM001 dosing of ≥7 days, the multidimensional fatigue and family impact questionnaires will also be administered at DE Day 0. Age at the baseline visit will be used as the age for the determination of the appropriate questionnaire to be used throughout the study. This same module will be used for the duration of the study regardless of subsequent birthdays during the study.

8.5.4 Patient Impression of Change

The Patient Impression of Change (PIC) is designed to assess the subject's perception of his/her itching at the end of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The PIC will be completed by subjects who were 9 years of age or older at the Week 13, Week 48, and Week 72 visits, see Section 16.7. For subjects who enter the optional follow-up treatment period, the PIC will be completed by subjects who were 9 years of age or older at clinic visits as outlined in the Schedules of Procedures in Section 16.1.

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 itching at the end of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The CIC will be completed by all caregivers at the Weeks 13, 48, and 72 visits, see Section 16.8. For subjects who enter the optional follow-up treatment period, the CIC will also be administered at will occur at clinic visits as outlined in the Schedules of Procedures in Section 16.1.

8.5.6 Caregiver Global Therapeutic Benefit

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, 48 and 72 visits, see Section 16.9. For subjects who enter the optional follow-up treatment period, the CGTB will also be administered at clinic visits as outlined in the Schedules of Procedures in Section 16.1.

8.5.7 Palatability

A palatability questionnaire (see Section 16.11) will be completed by the subject and/or caregiver (dependent on age) at clinic visits at time points as outlined in the Schedules of Procedures in Section 16.1.

8.6 Metabolomic and Proteomic Investigations

As part of a comprehensive approach to identify serum markers in PFIC patients that respond well to treatment, previously collected serum samples will be analyzed using both metabolomic and proteomic biomarker discovery approaches. Metabolomics addresses the activity of small molecules (<10 kDa) produced by active and living cells during their life cycle. These molecules are not accessible by genomic, transcriptomic or proteomic approaches. Metabolomics monitors the chemical transformations in metabolic cascades and can be used to identify observable

differences between patient populations. A targeted mass spectrometry proteomic approach will allow for the identification and quantitation of greater than 150 unique proteins in each serum sample.

Previously collected serum samples from both responding and non-responding patients will be analyzed in both biomarker discovery platforms and the data will be evaluated for potential markers that can significantly delineate responders from non-responders. No additional sample collection will be required for this exploratory analysis.

8.7 Restriction on the Lifestyle of Subjects

8.7.1 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 screening, throughout the study period and for 30 days following the last dose of the IP.

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 (e.g., 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, e.g., (i) condom (male or female) or (ii) diaphragm, with spermicide; or
c. Intrauterine device (IUD).
d. or 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).

8.7.2 Fasting Requirements

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

9 STUDY DRUG

9.1 Study Drug Description

9.1.1 LUM001

The composition of LUM001 study drug 1.0 mL oral solution is described in Table 4. The composition of LUM001 study drug 0.5 mL oral solution is described in Table 5.

Table 4: 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 5: 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

9.2 Packaging and Labeling

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

9.3 Drug Accountability

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 drug, 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 (LUM001) in this study is based on weight. All subjects will receive LUM001, up to 560 μg/kg/day (given as twice-daily doses of 280 μg/kg) or a maximum daily dose of 25 mg BID. During the long-term exposure period (Week 14 to Week 72) of the study and during the optional follow-up treatment period (Week 76 to EOT), the dose may be adjusted if there is a change of ≥10% in weight since the screening visit (e.g. the amount of drug dosed may be increased to reflect the subject's weight increase). 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) will be prepared by a central pharmacy based on the subject's weight at screening. Diluent will be added by the central pharmacy pharmacist prior to shipping study drug to the site.

Subjects will receive a grape-flavored solution containing LUM001. Each subject dose will be 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 (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.

QD Dosing Regimen

In case of 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

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

For subjects weighing less than 10 kg at study 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).

See Sections 5.5.2, 5.5.2.1, and 5.5.2.2 for information regarding dosing during the dose escalation and stable dosing periods, respectively.

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

10.2 Treatment Compliance

Compliance with treatment dosing will be monitored and recorded by the study center staff. 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).

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 (the period from the first day of screening through the last contact).

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

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.

The dosage and dosing regimen of concomitant drug therapy other than that specified by the protocol should not change during the course of the study, with the exception of weight-based dose adjustments and vitamin supplementation. All modifications to a subject's concomitant drug therapy, including weight-based dose adjustments and vitamin supplementation regimen must be carefully documented in the relevant case report forms. No new medications used to treat pruritus may be added during the period from Baseline (Day 0) until Week 13 (timepoint for primary analysis). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator or Investigator's designee and Sponsor to continue or discontinue the subject.

10.4 Other Protocol-required Drugs

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

10.5 Safety Monitoring Rules

10.5.1 General Monitoring Rules

In the evaluation of AEs and the potential relationship to study drug it is important to note that due to their liver disease many subjects with PFIC will have abnormal liver enzyme levels (e.g. AST, ALT, ALP) and bilirubin at baseline. If an individual subject exhibits a CTCAE Grade 3 treatment emergent toxicity, with the exception of the specific rules outlined below (Section 10.5) dosing will be suspended. Continued dosing with study drug (LUM001) may be considered

following discussion with the Medical Monitor. 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.

To ensure subject safety, dosing up to 140 µg/kg/day or 10 mg maximum dose, will first occur in one subject. If the subject is able to tolerate the 140 µg/kg/day dose, 3 additional subjects will be dosed. If at least 3 of the 4 subjects are able to tolerate the dose then dosing will be open to the rest of the subjects. The same staggered enrollment process will be followed specifically for subjects under 2 years of age.

To ensure subject safety, dosing up to 280 µg/kg/day or 25 mg maximum dose, will first occur in one subject. If the subject is able to tolerate the 280 µg/kg/day dose, 3 additional subjects will be dosed. If at least 3 of the 4 subjects are able to tolerate the dose then dosing will be open to the rest of the subjects. The same staggered enrollment process will be followed specifically for subjects under 2 years of age.

In addition, if 4 or more subjects at a dose level lower, suspend or stop study medication or exhibit treatment emergent toxicity of CTCAE Grade 3 or greater in the same system organ class (SOC), further dosing of subjects at that dose level and any higher dose levels will be halted until a safety assessment is completed. Study visits and completion of the ItchRO diaries, for all assigned subjects, will continue during the assessment period. After review a decision will be made whether to restart dosing at the same dose level, restart dosing at a lower dose level, or discontinue the subjects from the study. The Data and Safety Monitoring Board (DSMB) will be notified of any SAE as specified in the DSMB charter.

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 meeting 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 within 48 to 72 hours of the availability of the initial report. The results from the retest **must be available** prior to the next scheduled clinic visit or phone follow-up.

Stopping Rule Guidance: Subject dosing must be suspended until the retest results are available. If any of the stopping criteria described below (refer to Sections 10.5.2.2 and 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 (LUM001). The subject will be evaluated as outlined below and will be encouraged to complete the early termination study procedures (Week 48 visit). 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.

10.5.2.1 Safety Monitoring for Liver Chemistry Tests

Safety monitoring criteria take into consideration the subject's baseline ALT and total bilirubin levels. The baseline will be defined as the last evaluation before dosing with study drug (Day 0).

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

Baseline ALT	ALT
≤ ULN	> 5 x ULN
> ULN	> 3 x baseline **and** > 5 x ULN

Baseline Total Bilirubin	Total Bilirubin
Total Bilirubin ≤10 mg/dL (or ≤171.04 µmol/L)	3 mg/dl (or 51 µmol/L) increase
Total Bilirubin >10 mg/dL (or >171.04 µmol/L)	5 mg/dl (or 85 µmol/L) increase

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

Further Investigation into Liver Chemistry Elevations: Based on the inclusion criteria for this study the population to be enrolled will have pre-existing baseline liver disease and will be closely monitored by the investigators with experience in the management of pediatric hepatic diseases. For subjects with a confirmed elevation in ALT or total bilirubin level, as described above, the following evaluations should be performed as clinically indicated:

- Close and frequent monitoring of liver enzyme and serum bilirubin tests as clinically indicated. Frequency of retesting can decrease if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. If the appropriate frequency of monitoring is not feasible study drug administration will be suspended.

- Obtain a detailed history of symptoms and prior and concurrent diseases.

- Obtain comprehensive history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Obtain a history for exposure to environmental chemical agents and travel.

- Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel).

- Serology for autoimmune hepatitis [e.g., antinuclear antibody (ANA)].

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

10.5.2.2 Stopping Rules for Liver Chemistry Elevations

In the event of confirmed laboratory results exceeding 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 (LUM001) will be considered if:

Baseline Tests	Change Observed
ALT (any level)	ALT ≥ 20 x ULN
Total Bilirubin ≤10 mg/dL (or ≤171.04 µmol/L)	5 mg/dl (or 85 µmol/L) increase **and** a 2 x increase over baseline level
Total Bilirubin >10 mg/dL (>171.04 µmol/L)	2 x increase over baseline level

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 (LUM001). 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, the Investigator and the Medical Monitor may consider a temporary interruption of study drug (LUM001). 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. If the subject is on 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 will lead to discontinuation of study drug. At the investigator's discretion and in consultation with the Medical Monitor, subjects who were previously down-titrated may be re-challenged during the long-term exposure period.

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 and/or legal guardian who withdraws consent to continued participation 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 caregiver, Investigator or Sponsor before completion of the protocol-specified treatment period, and has received >1 dose of study drug (LUM001), 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 eDiary, unused study drug, and all other study supplies 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 caregiver.
- 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 (e.g., medication or treatment that is prohibited by the protocol).
- At the discretion of the Investigator if deemed not medically acceptable to continue study treatment.

- Noncompliance, including failure to adhere to the study requirements as stated in the study protocol.

- Administrative decision by the Investigator or Sponsor.

11 SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

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

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

11.1 Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of SAEs including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on 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 AEs to allow the Sponsor, or designee, to identify potential study-related, study drug- or dose-related AEs.

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

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

The Sponsor or designee will submit SUSARs to regulatory agencies in according to local law. The Sponsor or designee will submit SUSARs to Investigators.

11.2 Definitions

11.2.1 Adverse Event

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

An AE 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 during the screening period or at the baseline visit.

- Treatment failure or lack of efficacy.

11.2.2 Adverse Reaction and Suspected Adverse Reaction

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

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the 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)

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

- Results in death.

- Is life threatening: that is, poses an immediate risk of death at the time of the event.

- An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE.

- Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization. Admission to the hospital is the criterion that defines "serious", not the duration of hospital stay.

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).

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

11.3 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. 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 center's first knowledge of the event. The collection of SAEs will begin after the subject signs the informed consent/assent form and stop 30 days after the last dose of study drug.

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/assent 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 (e.g., 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 (e.g., 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 16.10). If the CTCAE does not have a grading for a particular AE, the severity of the event should be reported based on the following:

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

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

Please also refer to Section 10.5.2 regarding specific safety monitoring for liver chemistry tests given that subjects with PFIC may have abnormal liver enzyme levels 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 (e.g. medications or procedures) given for the AE should be recorded on the AE eCRF (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

11.3.3.5 Outcome of the Adverse Event

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

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

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

- Ongoing: SAE continuing.

- Persists (as non-serious AE): Subject has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE).

- 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.

11.4.1 Pregnancy Reporting

If a subject becomes pregnant or a pregnancy is suspected 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 (i.e., 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 if the event was accidental or intentional.

Dosing details should be captured on the appropriate eCRF. 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 (e.g., 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 main focus for the analyses of efficacy is the period from Baseline (Day 0) to Week 13. The period from Baseline (Day 0) to EOT will be analyzed and the period from Weeks 48-72 and 73-EOT have been added to obtain additional safety data and to monitor biochemical markers of cholestasis.

Continuous variables will be summarized using descriptive statistics including n, mean, median, standard deviation, and range (i.e., minimum and maximum). Qualitative variables will be summarized using counts and percentages. Summaries will be provided by study phase (Weeks 0-13, 14-48, 49-72, 73-124) and over the entire study duration (Weeks 0-72 and 0-EOT Visit), by visit and by stable dosing dose group (if appropriate). Unless otherwise specified, statistical analyses will be performed using SAS Version 9 or higher. All statistical tests will be conducted at the 0.05 significance level using two-tailed tests and p-values will be reported, if applicable. Given the rare nature of PFIC, the statistical power of any comparison is limited. As such the analysis will be largely descriptive in nature.

12.1 Sample Size Considerations

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

12.2 Populations

12.2.1 Safety Population

The Safety Population is defined as all subjects who were assigned 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 the treatment received.

12.2.2 Efficacy Populations

There will be two analysis populations for efficacy.

The main population for efficacy analysis will use a modified intention-to-treat population (MITT), which will include all subjects who were assigned, received at least one dose of treatment, and have at least one post-baseline efficacy assessment. Subjects will be analyzed by assigned treatment.

The Per Protocol population (PP) will consist of all subjects in the MITT population who did not have a major protocol violation, inclusive of violation of entry the criteria. Subjects in this population will be referenced as evaluable.

12.2.3 Demographic and Baseline Characteristics

12.2.3.1 Subject Disposition

Subject disposition will be summarized descriptively. The number and percentage of subjects assigned, completed, and withdrawing, along with reasons for withdrawal, will be tabulated.

The number and percentage of subjects receiving each study drug dose following the protocol specified dose escalation procedure and stable dosing regimen will be tabulated.

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.

12.2.3.2 Baseline Data

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

- Demographic variables, including age, gender and race/ethnicity.
- Medical history.
- Baseline disease characteristics (e.g., genotyping results, pruritus scores, liver biochemistries).
- Prior medications of interest [e.g., ursodiol (UDCA), rifampicin] and concomitant medications.
- Growth parameters including height and weight at baseline.

Demographic and baseline characteristics will be summarized.

Medical history information will be presented in listings.

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).

12.2.5 Planned Method of Analysis

12.2.6 Safety Analysis

Safety analyses will be performed on the Safety Population. Safety data, including AEs, clinical laboratory tests, vital signs, physical examinations, and concomitant medication usage will be summarized descriptively by study phase (Weeks 0-13, 14-48, 49-72, and 73-120) and over the entire study duration (Weeks 0-EOT Visit). Individual subject listings will be prepared for all safety data.

12.2.6.1 Adverse Events

Frequencies (number and percentage) of subjects with one or more treatment emergent AEs will be summarized, 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 each of the study phases.

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

12.2.6.2 Laboratory Tests

Clinical laboratory (chemistry panel, complete blood count (CBC) with differential, coagulation, lipid panel, cholestasis biomarkers, fat soluble vitamins, and urinalysis parameters) test parameters will be listed for individual subjects and summarized using descriptive statistics by study visit. Change and percent change from baseline for the safety variables will also be presented over time after study drug administration, as appropriate. Percent change from baseline will be added for laboratory values as outlined in the SAP. Baseline for clinical laboratory parameters will be defined as the last evaluation before dosing with study drug (Day 0).

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 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 listed for individual subjects. A separate subject listing presenting shifts in levels of fat soluble vitamins will also be prepared.

12.2.6.3 Physical Exams, Vital Signs and Weight/Height Measurements

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

Vital signs, weight and height (both weight and height are to be measured as an absolute number and as a z-score for age and gender) will be listed for individual subjects and summarized using descriptive statistics by clinical visit. Changes from baseline for all visits after the baseline visit will be included in the summary table. Baseline for vital signs will be defined as the last evaluation before dosing with study drug. In general this will be the Day 0 visit.

12.2.6.4 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized descriptively by Anatomic Therapeutic Chemical (ATC) class, using counts and percentages. Medications started prior to the first dose of study medication will be indicated in the data listing.

12.2.6.5 Study Drug Exposure

Due to poor absorption of LUM001 very low systemic exposure and plasma drug levels are expected. The key measurement will be the pharmacodynamic effect on fasting serum bile acid levels. However, exposure to study drug will be measured approximately 2-4 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.

12.2.6.6 Serum Alpha-fetoprotein

Assessments of serum alpha-fetoprotein (AFP) will be listed for individual subjects and summarized using descriptive statistics by study visit.

12.2.7 Interim Analyses

The following interim analyses are planned. The first interim analysis of key safety and efficacy parameters will be performed after the first 12 subjects who meet the Per Protocol population definition have completed the Week 13 study visit. This analysis will provide initial information about the activity of LUM001 in the study population. A second interim analysis will be performed after all enrolled subjects have completed the Week 48 (or Early Termination) study visit. This analysis will provide an assessment of the long-term safety and efficacy of LUM001. A third interim analysis will be performed after all enrolled subjects have completed at least 6 months of treatment under Protocol Amendment 4 (or the Early Termination visit). This analysis will provide an assessment of the long-term safety and efficacy of LUM001. Subsequent interim analyses will be performed in yearly intervals.

The statistical analysis plan will specify the safety and efficacy parameters to be included in these analyses and describe the procedures for executing the interim analyses.

The results of the interim analyses may lead to changes in the study design. Staff directly involved in the conduct of the trial, including the DSMB, will review the results of the interim

analyses. Interim study information may be shared with trial investigators, investigator staff, study monitors, or sponsor employees or other personnel.

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. Thus, all such analyses will be interpreted cautiously and not used for formal inference.

12.2.9 Efficacy Analyses

The primary analysis population for the efficacy analysis will be the MITT population defined in Section 12.2.2.

12.2.9.1 Efficacy Variables

Primary efficacy endpoint:

- Fasting serum bile acid level change from Baseline (Day 0) to Week 13.

Secondary efficacy endpoints:

- Alanine aminotransferase (ALT) and bilirubin (total and direct) change from Baseline (Day 0) to Week 13.
- Pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO) change from Baseline (Day 0) to Week 13. (For each subject, the average daily score will be calculated using the 7 days pre-treatment for Baseline (Day 0), and the last 7 days of treatment for Week 13.)

Exploratory efficacy endpoints:

- Change from Baseline (Day 0) in fasting serum bile acid level at Weeks 4, 8, 24, 36, 48 60, 72, 84, 96, 108, 120, every three months thereafter, and at the End of Treatment (EOT) visit.
- Change from Baseline (Day 0) in pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO) at Weeks 4, 8, 28, 48, 86, 98, 110, 122, and every three months thereafter.
- Change from Baseline (Day 0) for ALT, and bilirubin (total and direct) at Weeks 4, 8, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit.
- Change from Baseline (Day 0) for other biochemical markers of cholestasis [total cholesterol, low-density lipoprotein cholesterol (LDL-C)] at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit.

- Responder analysis: pruritus response rates as measured by ItchRO (Observer ItchRO/patient ItchRO) at Weeks 4, 8, 13, 28, 48, 86, 98, 110, 122, and every three months thereafter, up to but not including the EOT visit.

- Change from Baseline (Day 0) in the Clinician Scratch Scale, at Weeks 2, 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit.

- Change from Baseline (Day 0) in bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)] at Weeks 4, 8, 13, 24, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit.

- Change from Baseline (Day 0) for PedsQL at Weeks 13, 24, 48, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit.

- Patient Impression of Change (PIC) at Weeks 13, 48, 72, 108, 120, and the EOT visit.

- Caregiver Impression of Change (CIC) at Weeks 13, 48, 72, 108, 120, and the EOT visit.

- Caregiver Global Therapeutic Benefit (CGTB) assessment at Weeks 13, 48, 72, 108, 120, and at the EOT visit.

- Change from Baseline (Day 0) for other biochemical markers [autotaxin and lysophosphatidic acid (LPA)] at Weeks 4, 8, 13, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit.

- Change from Baseline (Day 0) for measures of bile acid synthesis (FGF-19 and FGF-21) at Weeks 4, 8, 13, 36, 48, 60, 72, 84, 96, 108, 120, every three months thereafter, and at the EOT visit.

Pattern of change in serum bile acids from Baseline (Day 0) to EOT will be evaluated and its appropriate analysis methodology will be outlined in the Statistical Analysis Plan (SAP) for the study.

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

- Biochemical markers of cholestasis and liver disease including alanine aminotransferase (ALT), and bilirubin (total and direct).

- Pruritus as measured by the ItchRO instruments (ItchRO(Obs)TM, caregiver instrument/ItchRO(Pt) TM patient instrument).

Additional evaluations of safety and efficacy surrogates will be specified in the Statistical Analysis Plan.

For subjects entering the optional treatment period with ≥7 continuous days since last dose of LUM001, any of the above evaluations may also occur at clinic visits during the DE and

Protocol Amendment 4 DE periods. Additionally, these evaluations may also occur during the ADE period

The primary assessment of pruritus in this study will be composed of the ItchRO assessment from the diary. Given the age range of this population and the small sample size, the primary ItchRO score will be derived from the ItchRO(Obs) instrument. The itch score from the ItchRO(Pt) will be analyzed separately. Subjects 9 years of age or older will complete the ItchRO(Pt) independently. Subjects between the ages of 5 and 8 years of age or where the investigator has expressed concern about the subjects ability to reliably complete the data (e.g. due to developmental delay) will complete the ItchRO(Pt) with the help of the caregiver. There will be no ItchRO(Pt) report for subjects under the age of 5.

For this instrument the caregiver and/or subject indicate the itch severity in the morning and in the evening each day during screening and during the designated study periods [Day 0 – 13, Week 24-28, Week 44-48, Week 84-86, Week 96-98, Week 108-110, Week 120-122, and Week 0-2 of each recurring 12-week period]. The daily score will be assessed as outlined in Section 16.4 and will have a range from 0-4, with the higher score indicating increasing itch severity. The daily score will be taken as the highest score of the morning and evening scores, representing the most severe itch over the 24 hour period. The average daily score will be the average of the daily scores over a defined study week consisting of the 7 days prior to the visit.

For the change from baseline calculation in average daily ItchRO score, baseline is defined as the average daily ItchRO score in the week consisting of the 7 days immediately prior to Day 0. The average daily ItchRO score for each post-baseline study visit (e.g., Weeks 4, 8, 13, 28, 48, 86, 98, 110, and 122) is defined as the average daily ItchRO score in the week consisting of the 7 days immediately prior to the scheduled visit. In addition to change from baseline, a responder analysis will be considered. The response definition and its appropriate analysis methodology will be outlined in the SAP for the study.

The additional questions included in the ItchRO that are not scored, will be tabulated.

If a caregiver is not compliant with the ItchRO (Obs) at Weeks 13, 28, 48, 86, 98, 110, and 122, the average daily score from the most recent, previous compliant week will be used in an LOCF format. On study compliance for the ItchRO will be defined as having at least 4 of the 7 daily ItchRO scores for a 7-day period. Similar methods will be used for the ItchRO (Pt). Missing data imputation will not be done for other efficacy endpoints.

A number of sensitivity analyses will be performed to assess the robustness of the results. Details of these analyses will be outlined in the SAP for the study.

12.2.9.2 Primary Efficacy Analysis

The change from baseline in the serum bile acid levels will be displayed by study visit, using summary statistics including the number of observations, 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 change from baseline will be tested using the paired t-test, or comparable nonparametric measures as appropriate.

Where sample size allows, treatment effects over time will be examined using methods appropriate for repeated observations. Examination of potential dose effects will be done if the sample sizes in the dose groups during the stable dosing phase of the study permit.

12.2.9.3 Secondary, Exploratory and Other Efficacy Analyses

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

Exploratory efficacy measures that are categorical will be summarized by frequencies and percents. P-values from the secondary and exploratory efficacy analyses will be considered nominal.

The sensitivity of the results for pruritus to missing data assumptions will be explored as outlined in the SAP for the study. The sensitivity analyses may include analyses using observed cases as well as various assumptions for missing data from subjects who terminate from the study early.

Additional exploratory analyses may be performed and will be defined and outlined in the SAP for the study. Inferential statistics may be used as part of the data summary.

12.2.10 Exploratory Genetic Analyses

To identify genetic indicators of treatment response using exome sequencing, an additional blood sample will be taken. The data analysis will focus initially on genetic variation in candidate genes that may have a role in treatment response, such as ASBT/SLC10A2 and genes in its pathway (ie upstream or downstream of ASBT/SLC10A2) and genes implicated in PFIC (ATP8B1, ABCB11 and ABCB4) with the goal of identifying genetic variation that may discriminate treatment responders from non-responders. Following examination of candidate genes, the data analysis may be expanded to evaluate genetic variation in additional regions of the exome. This genetic analysis is more comprehensive and may provide valuable information beyond the ATP8B1 and ABCB11 genes. The submission of this blood sample is voluntary. The results of this analysis may identify relevant genetic variants, only some of which will be of known clinical benefit.

12.2.11 Exploratory Responder Analyses (Metabolomic and Proteomic Investigations)

As part of a comprehensive approach to identify serum markers in PFIC patients that respond well to treatment, previously collected serum samples will be analyzed using both metabolomic and proteomic analysis. Metabolomics addresses the activity of small molecules (<10 kDa) produced by active and living cells during their life cycle. These molecules are not accessible by genomic, transcriptomic or proteomic approaches. Metabolomics monitors the chemical transformations in metabolic cascades and can be used to identify observable differences between patient populations. A targeted mass spectrometry proteomic approach will allow for the identification and quantitation of greater than 150 unique proteins in each serum sample. Serum samples from both responding and non-responding patients will be analyzed in both biomarker discovery platforms and the data will be evaluated for potential markers that can significantly delineate responders from non-responders.

12.2.12 Palatability Analyses

Palatability data will be collected at each clinic visit in the follow-up treatment period, with the exception of the DE and ADE visits. A palatability questionnaire will be completed by the subject and/or caregiver, dependent on age (see Section 16.11). Data will be listed for individual subjects and summarized using descriptive statistics by study visit. Change over time will also be presented over time, as appropriate. Baseline will be defined as the first recorded evaluation.

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, based 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 screening 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/assent form (ICF/IAF) summarizing the discussion at screening. 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 (e.g., due to protocol amendment or significant new safety information). The resulting IEC-approved ICF/IAF will be used for all subjects subsequently entering the study or those already enrolled and still actively participating in the trial.

13.2 Ethical Conduct of the Study

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

13.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent/assent forms, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor or designee before recruitment of subjects into the study and shipment

of study drug. A copy of the written approval of any other items/materials that must be approved by the study center or IEC/IRB must also be received by the Sponsor or designee before recruitment of subjects into the study and shipment of study drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. 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 SAEs occurring at the study center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

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

13.4 Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the 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 (e.g., 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 by Mirum Pharmaceuticals, Inc., as they deem necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal regulations, the Investigator is obliged to furnish Mirum Pharmaceuticals, Inc., with the complete test results and all data compiled in this study.

14 ADMINISTRATIVE AND LEGAL OBLIGATIONS

14.1 Study Personnel

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

14.2 Pre-study Documentation Required

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

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

In addition, in advance of enrollment of subjects, study staff are required to complete all required training.

14.3 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of

all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The Investigator must send a copy of the approval letter from the IEC/IRB to the Sponsor or designee. Amendments to the protocol will not be implemented until written IEC/IRB approval has been received.

14.4 Study Termination

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

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

14.5 Study Documentation and Storage

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

- Subject files containing completed 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 center, documentation for proof of receipt, study drug accountability records, return of study drug for destruction, final study drug product reconciliation statement, and all drug-related correspondence.

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

14.6 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting

the various records of the trial (e.g., 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.

14.7 Language

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

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

14.8 Compensation for Injury

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

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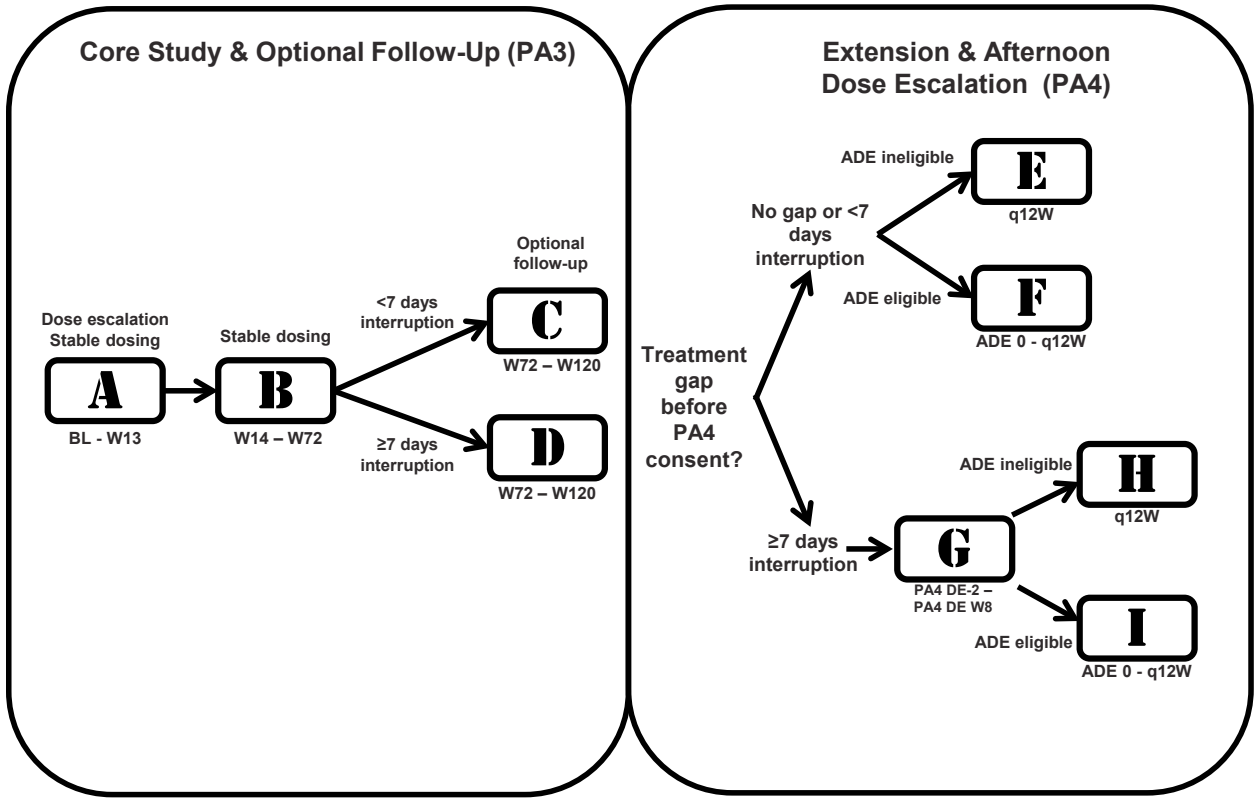
16 APPENDICES

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 – I).
Study Termination and End of Treatment Procedures are outlined in Schedule J.



16.1.1 Schedule of Procedures A-D: Study Entry – Week 120

Schedule of Procedures A (Baseline – Week 13)

Study Period	Screening	Treatment Period								
			Dose Escalation				Stable Dosing Period			
Study Week			1	2	3	4	5	8	9	13
Study Day	Day -42	Day 0	7	14	21	28	35	56	63	91
Window (in days)			(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)
Informed Consent/Assent	X									
Eligibility Assessment (Inclusion/Exclusion)	X									
Demographics	X									
Medical History	X									
Physical Exam	X									
Body Weight & Height	X	X		X		X		X		X
Vital Signs [1]	X	X		X		X		X		X
Liver imaging (ultrasound) [2]	X									
Serum or Urine Pregnancy Test (if indicated)[3]	X	X		X		X		X		X
CBC with Differential [4]	X	X		X		X		X		X
Coagulation[4]	X	X		X		X		X		X
Chemistry Panel [4]	X	X		X		X		X		X
Lipid Panel [4,5,]		X		X		X		X		X
Cholestasis Biomarkers [4,5]	X	X		X		X		X		X
Fat Soluble Vitamins [4,5,6]		X						X		X
Plasma Sample for LUM001: US		X[a]		X[a]		X[a]		X[a]		X[a]
Plasma Sample for LUM001: UK, EU, Australia		X[b]				X[b]				X[b]
PFIC Genotyping[7]	X									
Urinalysis [4]	X	X[c]		X[c]		X		X		X
Caregiver ItchRO/Patient ItchRO	X	X	X	X	X	X	X	X	X	X
Clinician Scratch Scale	X	X		X		X		X		X
PedsQL		X								X
Patient/ Caregiver Impression of Change										X
Caregiver Global Therapeutic Benefit										X
Enrollment	X									
Study Drug Supplied		X		X		X		X		X
Review Study Diaries & Assess Compliance		X		X		X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Phone Contact			X		X		X		X	

Schedule of Procedures A (Baseline – Week 13)

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

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

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


Clinic Visit
Phone Contact

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

Study Period	Treatment Period (continued)										Study Termination	Safety Follow Up
	59 Week Long-term exposure											
Study Week	16	20	24	28	32	36	40	44	48	60	Week 72 (or Early Term[7])	30 days after final dose
Study Day	112	140	168	196	224	252	280	308	336	420	504	
Window (in days)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±5)
Physical Exam			X			X			X	X	X	
Body Weight & Height			X			X			X	X	X	
Vital Signs[1]			X			X			X	X	X	
CBC with Differential[2]			X			X			X	X	X	
Coagulation[2]			X			X			X	X	X	
Chemistry Panel[2]			X			X			X	X	X	
Lipid Panel[2,3]			X			X			X	X	X	
Cholestasis Biomarkers[2,3]			X			X			X	X	X	
Fat Soluble Vitamins[2,3,4]			X			X			X	X	X	
Plasma Sample for LUM001: All			X[a]			X[a]			X[a]	X[a]	X[a]	
Urinalysis[2]			X			X			X[b]	X	X[b]	
Urine Pregnancy Test [5]			X			X			X	X	X	
Clinician Scratch Scale			X			X			X	X	X	
Caregiver ItchRO/Patient ItchRO			X[c]	X[c] to Week 28				X[c]	X to Week 48			
PedsQL			X						X		X	
Patient/Caregiver Impression of Change									X		X	
Caregiver Global Therapeutic Benefit									X		X	
Study Drug Supplied			X			X			X	X	X[d]	
Assess Compliance			X			X		X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[6]	X	X		X	X		X					X

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

Study Period	Treatment Period (continued)										Study Termination	Safety Follow Up
	59 Week Long-term exposure											
Study Week	16	20	24	28	32	36	40	44	48	60	Week 72 (or Early Term[7])	30 days after final dose
Study Day	112	140	168	196	224	252	280	308	336	420	504	
Window (in days)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±14)	(±5)

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.

2 See Section 16.2 for detailed list of laboratory analytes.

3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.

4 Blood samples must be drawn before administration of vitamin supplementation.

5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.

6 Subjects must be available to receive a phone call from study staff.

7 Subjects who withdraw early should complete all evaluations at this visit.

a At Weeks 24, 36, 48, 60 and 72 blood will be drawn approximately 4 hours post dosing for drug level analysis.

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

c During the long-term exposure period, daily completion of the study diary for 4 consecutive weeks will be required following the Week 24 & Week 44 clinic visits.

d For subjects entering optional Follow-up Treatment Period, once corresponding consent is signed.

Clinic Visit

Phone Contact

Schedule of Procedures C – Optional Follow-Up Treatment Period: Week 72- Week 120 For Subjects With No Interruption in LUM001 Dosing or Interruption <7 Days. Includes Evaluation of Eligibility for BID Dosing Regimen.

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

Schedule of Procedures C – Optional Follow-Up Treatment Period: Week 72- Week 120 For Subjects With No Interruption in LUM001 Dosing or Interruption <7 Days. Includes Evaluation of Eligibility for BID Dosing Regimen.

Study Period	Treatment Period (continued)											
	Follow-up Treatment Period											
FTP Study Week	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**
Study Day	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**784**	**812**	**840**
Window (in days)	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Assess Study Drug Compliance			X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[7]	X	X		X	X		X	X		X	X	

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.

2 See Section 16.2 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Genotyping sample will be drawn at Week 84 or at the time of re-consent for the optional follow-up treatment period; sample will be used to provide a full characterization and documentation of the mutation type in support of the diagnosis of PFIC.
6 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
7 Subjects must be available to receive a phone call from study staff.
8 Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent patient for Protocol Amendment 4 at next clinic visit.
9 Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent has been signed, site will assess patient eligibility for Protocol Amendment 4. Depending on outcome of ADE eligibility assessment, patient will move into either Schedule of Procedures E or F. **Of note: It is possible that subject will not necessarily complete up through Week 120 before they move to Schedule of Procedures E or F.**
10 Sample will require consenting under PA4 and will be drawn once, at the time of such re-consent.

a At indicated visits during treatment period, oxalate will be part of the UA.
b During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 84, Week 96, Week 108, and Week 120 visits.

Clinic Visit
Phone Contact

Schedule of Procedures D – Optional Follow-Up Treatment Period: Week 72-Week 120 for Subjects With Interruption in LUM001 Dosing ≥7days. Includes Evaluation of Eligibility for BID Dosing Regimen.

Study Period	Treatment Period (continued)																
	Follow-up Treatment Period Dose Escalation (DE)						Continuation of Follow-up Treatment										
FTP Study Week	**DE -2**	**DE Day 0**	**DE 73**	**DE 74**	**DE 75**	**DE 76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**
Study Day	**-14**	**0**	**511***	**518***	**525***	**532***	**560***	**588***	**616***	**644***	**672***	**700***	**728***	**756***	**784***	**812***	**840***
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Informed Consent/Assent for study re-entry under PA3[11]	X																
Assess Eligibility for study re-entry	X	X															
Informed Consent/Assent for PA4								X			X			X			X
Afternoon dose escalation (ADE) eligibility assessment followed by shift in visit schedule[9]								X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Physical Exam	X	X		X		X		X			X			X			X
Body Weight & Height	X	X		X		X		X			X			X			X
Vital Signs[1]	X	X		X		X		X			X			X			X
CBC with Differential[2]	X	X		X		X		X			X			X			X
Coagulation[2]	X	X		X		X		X			X			X			X
Chemistry Panel[2]	X	X		X		X		X			X			X			X
Lipid Panel[2,3]	X	X		X		X		X			X			X			X
Cholestasis Biomarkers[2,3]	X	X		X		X		X			X			X			X
Fat Soluble Vitamins[2,3,4]	X	X		X		X		X			X			X			X
Optional Genotyping[5]	X																
Urinalysis[2]	X	X		X		X		X			X			X[a]			X[a]
Exome Sequencing Sample[10]								X[10]			X[10]			X[10]			X[10]

Schedule of Procedures D – Optional Follow-Up Treatment Period: Week 72-Week 120 for Subjects With Interruption in LUM001 Dosing ≥7days. Includes Evaluation of Eligibility for BID Dosing Regimen.

Study Period	Treatment Period (continued)																
	Follow-up Treatment Period Dose Escalation (DE)						Continuation of Follow-up Treatment										
FTP Study Week	**DE -2**	**DE Day 0**	**DE 73**	**DE 74**	**DE 75**	**DE 76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**
Study Day	**-14**	**0**	**511***	**518***	**525***	**532***	**560***	**588***	**616***	**644***	**672***	**700***	**728***	**756***	**784***	**812***	**840***
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Serum or Urine Pregnancy Test (if indicated)[6]	X	X		X		X		X			X			X			X
Clinician Scratch Scale	X	X		X		X		X			X			X			X
Caregiver ItchRO/ Patient ItchRO								X[b]	X[b] to Week 86		X[b]	X[b] to Week 98		X[b]	X[b] to Week 110		X[b]
PedsQL		X						X			X			X			X
Patient/Caregiver Impression of Change														X			X
Caregiver Global Therapeutic Benefit														X			X
Study Drug Supplied		X		X		X		X			X			X			
Assess Compliance				X		X		X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[7]			X		X		X		X	X		X	X		X	X	

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.

2 See Section 16.2 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation type in support of the diagnosis of PFIC.
6 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
7 Subjects must be available to receive a phone call from study staff.
8 Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent patient for Protocol Amendment 4 at next clinic visit.

Schedule of Procedures D – Optional Follow-Up Treatment Period: Week 72-Week 120 for Subjects With Interruption in LUM001 Dosing ≥7days. Includes Evaluation of Eligibility for BID Dosing Regimen.

Study Period	Treatment Period (continued)																
	Follow-up Treatment Period Dose Escalation (DE)						Continuation of Follow-up Treatment										
FTP Study Week	DE -2	DE Day 0	DE 73	DE 74	DE 75	DE 76	80	84	88	92	96	100	104	108	112	116	120
Study Day	-14	0	511*	518*	525*	532*	560*	588*	616*	644*	672*	700*	728*	756*	784*	812*	840*
Window (in days)	(±14)	(±2)	(±2)	(±2)	(±2)	(±2)	(±14)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)	(±7)	(±7)	(±14)

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

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

11 For participants re-entering under Protocol Amendment 3, Baseline laboratory values are considered those collected at re-entry visit DE-2 weeksCalculation of Study Day includes subject's participation through the first 72 weeks.

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

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

Clinic Visit
Phone Contact

16.1.2 Schedule of Procedures E-F: Rollover under Protocol Amendment 4

Schedule of Procedures E – Extension of Optional Follow-Up Treatment Period, for subjects ineligible for ADE, applicable as follows:

- **Subject did not yet complete the optional follow up treatment period as outlined under Protocol Amendment 3 and is able to consent to Protocol Amendment 4 activities without an interruption in LUM001 dosing, OR**
- **Subject completed optional follow up treatment period as outlined under PA3 and dosing interruption was <7 days.**
- **Subject deemed ineligible for ADE.**

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

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

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.

2 See Section 16.2 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.
8 Sample will be drawn at every other clinic visit.

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

Clinic Visit
Phone Contact

Schedule of Procedures F – Extension of Optional Follow-Up Treatment Period, for subjects eligible for ADE, applicable as follows:

- **Subject did not yet complete the optional follow up treatment period as outlined under Protocol Amendment 3 (PA3) and is able to consent to Protocol Amendment 4 activities without an interruption in LUM001 dosing OR**
- **Subject completed the optional follow up treatment period as outlined under PA3 and dosing interruption was <7 days.**
- **Subject deemed <u>eligible</u> for ADE.**

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeat in recurring 12 week periods after completion of the ADE period7		
Study Week	**ADE Day 0**	**ADE Week 1**	**ADE Week 2**	**ADE Week 4**	**ADE Week 5**	**ADE Week 6**	**ADE Week 8**	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**To be scheduled as soon as ADE eligibility is confirmed and materials are on-site**							**The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.**		
Window (in days)	**N/A – see above**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±7)**	**(±7)**	**(±14)**
Physical Exam	X			X			X			X
Body Weight & Height	X			X			X			X
Vital Signs[1]	X			X			X			X
CBC with Differential[2]	X			X			X			X
Coagulation[2]	X			X			X			X
Chemistry Panel[2]	X			X			X			X
Lipid Panel[2,3]	X			X			X			X
Cholestasis Biomarkers[2,3]	X			X			X			X
Fat Soluble Vitamins[2,3,4]	X			X			X			X
Urinalysis[2]	X			X			X			X[a]
AFP Sample										X[8]
Plasma Sample for LUM001[9]	X			X			X			X[9]

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeat in recurring 12 week periods after completion of the ADE period7		
Study Week	**ADE Day 0**	**ADE Week 1**	**ADE Week 2**	**ADE Week 4**	**ADE Week 5**	**ADE Week 6**	**ADE Week 8**	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**To be scheduled as soon as ADE eligibility is confirmed and materials are on-site**							**The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.**		
Window (in days)	**N/A – see above**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±7)**	**(±7)**	**(±14)**
Serum or Urine Pregnancy Test (if indicated)[5]	X			X			X			X
Clinician Scratch Scale	X			X			X			X
Caregiver ItchRO/ Patient ItchRO										X (collected for 2 week period following this visit)
PedsQL	X			X			X			X
Palatability Questionnaire										X
Study Drug Supplied	X			X			X			X
Assess Compliance	X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Follow-up Phone Contact[6]		X	X		X	X		X	X	

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

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.
8 Sample will be drawn at every other clinic visit.
9 PK sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose escalation period.

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

Clinic Visit
Phone Contact

16.1.3 Schedule of Procedures G-I: Subject Re-Entry under Protocol Amendment 4

Schedule of Procedures G – Optional Follow-Up Treatment Period: Re-Entry Under Protocol Amendment 4 applicable as follows:

- **Subject previously completed (or early terminated from) the optional follow up treatment period as defined under Protocol Amendment 3 and has subsequently experienced an interruption in LUM001 dosing ≥7days**
- **Subject is considered eligible for study re-entry under Protocol Amendment 4**
- **Subject eligibility will be assessed for afternoon dose escalation at Protocol Amendment 4 DE Week 8 shown in the table below.**
  - **If subject is found to be ineligible for ADE, subject will move from Schedule G to Schedule H.**
  - **If subject is found to be eligible for ADE, subject will move from Schedule G to Schedule I.**

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

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

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

Clinic Visit
Phone Contact

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

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

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

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

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.

2 See Section 16.2 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.
8 Sample will be drawn at every other clinic visit.

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

Clinic Visit
Phone Contact

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

Study Period	Follow-up Treatment Period Afternoon Dose Escalation (ADE)							Study activities repeating in recurring 12 week periods after completion of the ADE period[7]		
FTP Study Week	**ADE Day 0**	**ADE Week 1**	**ADE Week 2**	**ADE Week 4**	**ADE Week 5**	**ADE Week 6**	**ADE Week 8**	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**To be scheduled as soon as ADE eligibility is confirmed and materials are on-site**							**The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.**		
Window (in days)	**N/A – see above**	**(±2)**	**(±2)**	**(±2)**		**(±2)**	**(±2)**	**(±7)**	**(±7)**	**(±14)**
Physical Exam	X			X			X			X
Body Weight & Height	X			X			X			X
Vital Signs[1]	X			X			X			X
CBC with Differential[2]	X			X			X			X
Coagulation[2]	X			X			X			X
Chemistry Panel[2]	X			X			X			X
Lipid Panel[2,3]	X			X			X			X
Cholestasis Biomarkers[2,3]	X			X			X			X
Fat Soluble Vitamins[2,3,4]	X			X			X			X
Urinalysis[2]	X			X			X			X[a]
AFP Sample										X[8]
Plasma Sample for LUM001[9]	X			X			X			X[9]
Serum or Urine Pregnancy Test (if indicated)[5]	X			X			X			X
Clinician Scratch Scale	X			X			X			X

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

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

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

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

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.
2 See Section 16.2 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential, result must be reviewed prior to dispensing study drug.
6 Subjects must be available to receive a phone call from study staff.
7 Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.
8 Sample will be drawn at every other clinic visit.
9 PK sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose escalation period.

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

Clinic Visit
Phone Contact

16.1.4 Schedule of Procedures J – Study Termination and End of Treatment Procedures

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

	EOT / ET	Safety Follow Up
Scheduling Considerations	**To take place upon completion of study[7] or at the time of early withdrawal**	**Minimum of 30 days after final dose**
Physical Exam	X	
Body Weight & Height	X	
Vital Signs[1]	X	
CBC with Differential[2]	X	
Coagulation[2]	X	
Chemistry Panel[2]	X	
Lipid Panel[2,3]	X	
Cholestasis Biomarkers[2,3]	X	
Fat Soluble Vitamins[2,3,4]	X	
Urinalysis[2]	X[a]	
AFP Sample	X	
Serum or Urine Pregnancy Test (if indicated)[5]	X	
Clinician Scratch Scale	X	
PedsQL	X	
Patient/Caregiver Impression of Change	X	
Caregiver Global Therapeutic Benefit	X	
Palatability Questionnaire	X	
Assess Compliance	X	
Concomitant Medications	X	X
Adverse Events	X	X
Follow-up Phone Contact[6]		X

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

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

1 Blood pressure (BP), heart rate (HR), temperature, respiration rate.

2 See Section 16.2 for detailed list of laboratory analytes.
3 Subjects are required to fast at least 4 hr (only water permitted) prior to collection.
4 Blood samples must be drawn before administration of vitamin supplementation.
5 Females of childbearing potential.
6 Subjects must be available to receive a phone call from study staff.
7 Will take place when the first of the following occur: (i) subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially.

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

Clinic Visit
Phone Contact

16.2 List of Laboratory Analytes

Screening Tests

Genotyping (if indicated)

ATP8B1/

ABCB11

ABCB4

Serum βhCG (if indicated)

CBC with Differential

Red blood cells

Hemoglobin

Hematocrit

MCV, MCH, MCHC

Platelets

White blood cells

WBC Differential (% and absolute)

- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Clinical Chemistry

Sodium

Potassium

Chloride

Bicarbonate

Total protein

Albumin

Calcium

Phosphate

Glucose

Blood urea nitrogen (BUN)

Creatinine

Uric Acid

Total bilirubin

Direct bilirubin

Alkaline phosphatase (ALP)

AST (SGOT)

ALT (SGPT)

GGTP

Lipid Panel[1]

Total cholesterol

LDL-C (direct)

HDL-C

Triglycerides (TG)

Cholestasis Biomarkers[1]

Serum bile acids

7α hydroxy-4-colesten-3-one (C4)

Fat Soluble Vitamins[1]

25-hydroxy vitamin D

Retinol

Retinol binding protein

Tocopherol (α)

Marker of hepatocellular carcinoma

alpha-fetoprotein (AFP)

Urinalysis

pH

Specific gravity

Protein

Glucose

Ketones

Bilirubin

Occult blood and cells

Nitrite

Urobilinogen

Leukocyte esterase

Microscopic examination[2]

Oxalate[3]

LUM001 Drug Levels

LUM001 in plasma

Coagulation

Activated partial thromboplastin time (aPTT) (sec)

Prothrombin time (PT) (sec)

INR

1 Other biomarkers [e.g., autotaxin, lysophosphatidic acid (LPA), FGF-19, FGF-21] may be measured.

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 Liver Disease Diagnoses Excluded from PFIC Definition

1. Confirmed diagnosis of other chronic cholestatic liver disease, such as biliary atresia, cystic fibrosis, autoimmune liver disease, extrahepatic biliary obstruction/disease, autosomal recessive polycystic kidney disease, hepatic venoocclusive disease, chronic allograft rejection, bile acid synthesis defect, alpha-1-antitrypsin deficiency, Alagille syndrome, mitochondrial defect, large duct primary sclerosing cholangitis (PSC), or PSC in the setting of inflammatory bowel disease or immunodeficiency.
2. Short bowel syndrome/TPN related disease.
3. Chronic known infectious hepatitis (e.g. Hepatitis C, Hepatitis B, etc.).
4. Chronic known or strongly suspected drug toxicity (e.g. Augmentin related cholestasis).
5. Acquired immunodeficiency syndrome.
6. Acute liver failure.
7. Extrahepatic portal vein obstruction, congenital hepatic fibrosis or congenital portosystemic shunt.
8. Confirmed diagnosis of bile acid synthesis defect.

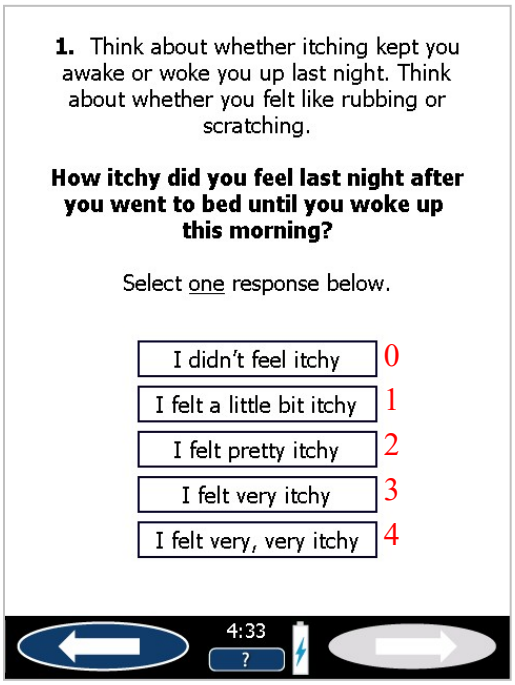
16.4 Itch Reported Outcome Instrument (ItchRO™)

Many of the PFIC subjects in this study are expected to be between 12 months and 5 years of age, 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 (PRO) 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 PRO and ObsRO.

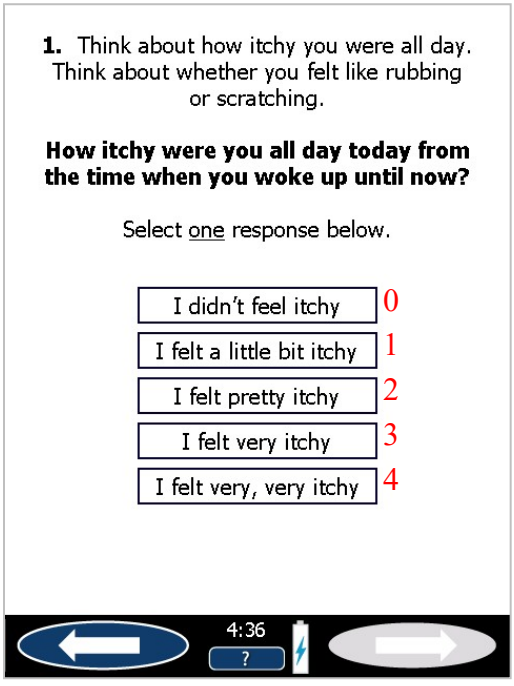
16.4.1 Patient Itch Reported Outcome Instrument, ItchRO(Pt)™

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.

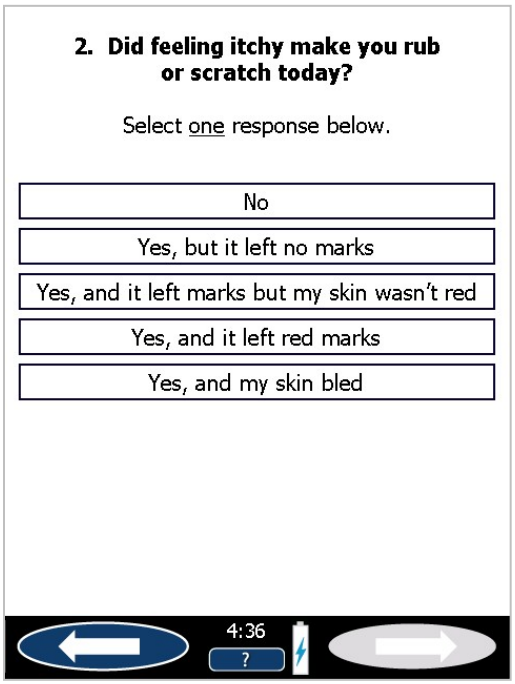


If the patient selects "I didn't feel itchy at all" the diary is complete, if not the following screens will be shown on the eDiary:

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.

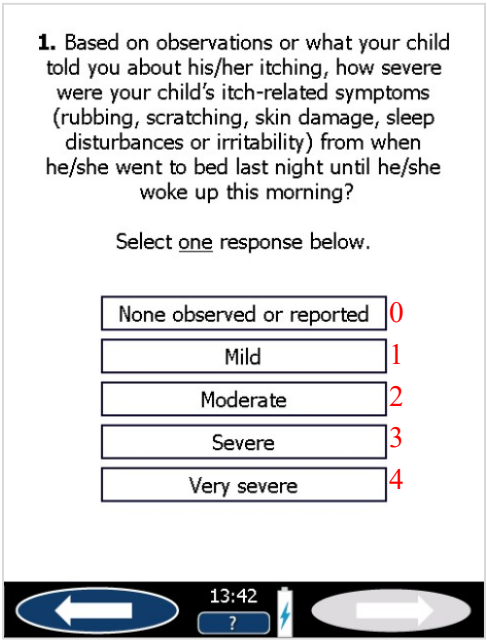


If the patient selects "I didn't feel itchy" the diary is complete, if not the following screen will be shown on the eDiary:

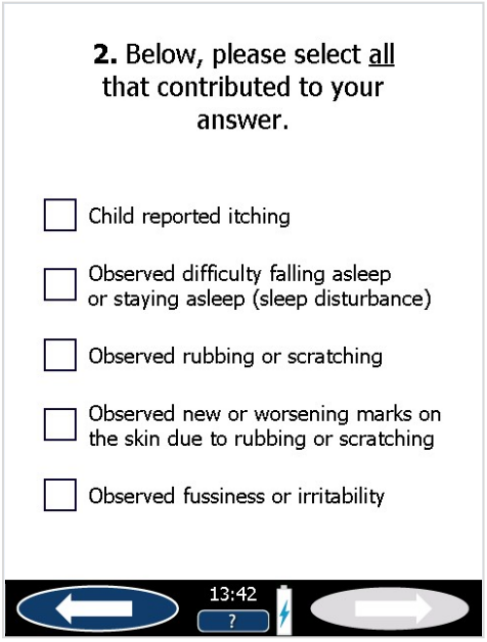


16.4.2 Observer Itch Reported Outcome Instrument, ItchRO(Obs)™

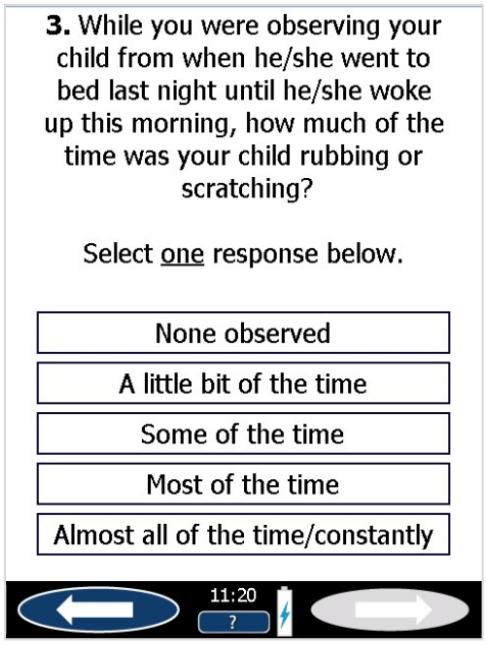
A screen shot from the ItchRO(Obs) **morning report** is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) morning report score is 0 and the maximum score is 4.



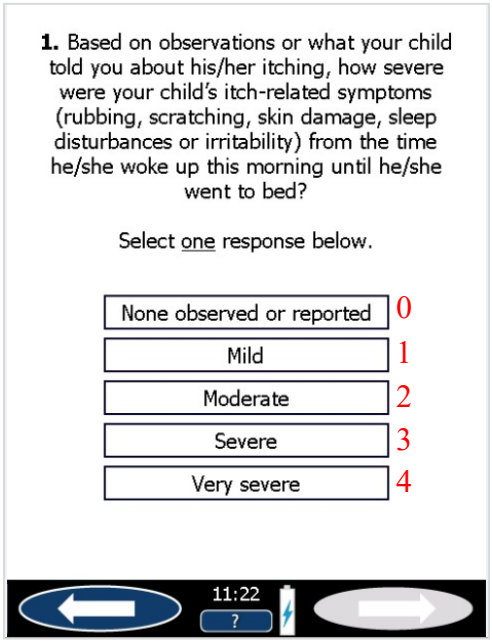
If the caregiver selects "None observed or reported" the diary is complete, if not the following screen will be shown on the eDiary:



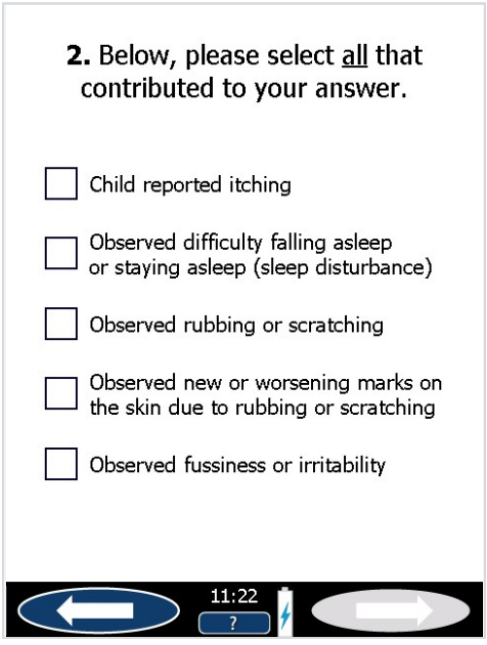
All caregivers will also be required to answer the following question on the ItchRO(Obs) **morning report**:



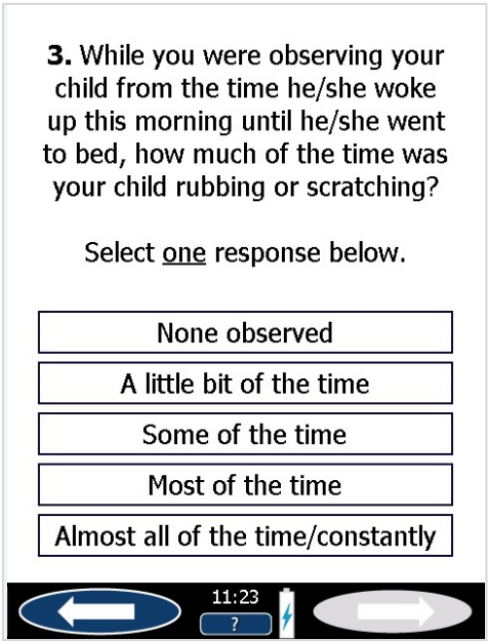
The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) evening report score is 0 and the maximum score is 4. A screen shot from the ItchRO(Obs) **evening report** is shown below:



If the caregiver selects "None observed or reported" the 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:**


3. While you were observing your child from the time he/she woke up this morning until he/she went to bed, how much of the time was your child rubbing or scratching?
Select one response below.
None observed
A little bit of the time
Some of the time
Most of the time
Almost all of the time/constantly
11:23
?

16.5 Clinician Scratch Scale

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

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

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

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 and 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 2-18 years.

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 1-12 months)

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

PedsQL 3

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 13-24 months)

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

PedsQL 3

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

Please complete this section if your child attends school or daycare

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

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

ID#_____

Date:_____

PedsQL™
Pediatric Quality of Life Inventory

Version 4.0

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

Instructions for interviewer:

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

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

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

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

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

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

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

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

PedsQL 2

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

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

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

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

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

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

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

PedsQL 3

How much of a problem is this for you?

Not at all

Sometimes

A lot

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID# _____

Date: _____

PedsQL™
Multidimensional Fatigue Scale

Standard Version

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

Instructions for interviewer:

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

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

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

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

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

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

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

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

PedsQL 2

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

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

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

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

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

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

PedsQL 3

How much of a problem is this for you?

Not at all

Sometimes

A lot

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

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

ID# _____

Date: _____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID# _____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

16.6.17 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 Patient Impression of Change (PIC)

The Patient Impression of Change (PIC) is designed to assess the subject's perception of his/her itching at the end of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The PIC will be completed, by subjects who were 9 years of age or older at the Week 13, Week 48, Week 72, Week 108, Week 120, and EOT visits.

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

PIC

How much has your itching changed, if at all, since you started this study?

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

16.8 Caregiver Impression of Change (CIC)

The Caregiver Impression of Change (CIC) is designed to assess the caregiver's perception of the subject's itching at the end of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The CIC will be completed by all caregivers at the Week 13, Week 48, Week 72, Week 108, Week 120, and EOT visits.

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

CIC

How would you rate the change in your child's itch related symptoms (rubbing, scratching, skin damage, sleep disturbances or irritability) 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)

16.9 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, Week 48, Week 72, Week 108, Week 120, and EOT visits.

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 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)].

16.11 Palatability Questionnaire

LUM001 501 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 501 Palatability Questionnaire

Child Only or Child and Caregiver

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

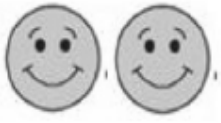
Questionnaire to be completed by:

- 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