CLINICAL PROTOCOL

PROTOCOL NUMBER: LUM001-301

ITCH STUDY

THE EVALUATION OF THE **I**NTESTINAL BILE ACID **T**RANSPORT (IBAT) INHIBITOR LUM001 IN THE REDUCTION OF PRURITUS IN ALAGILLE SYNDROME, A **CH**OLESTATIC LIVER DISEASE

Developed in Collaboration with ChiLDReN

THE CHILDHOOD LIVER DISEASE RESEARCH NETWORK

Protocol Amendment 3: February 11, 2015

Protocol History:
Original Protocol: October 22, 2013
Protocol Amendment 1: December 10, 2013
Protocol Amendment 2: January 28, 2015

Lumena Pharmaceuticals LLC
12531 High Bluff Drive, Suite 110
San Diego, CA 92130
USA

SPONSOR SIGNATURE PAGE

LUM001-301

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Sponsor:
Lumena Pharmaceuticals LLC
12531 High Bluff Drive, Suite 110
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_____
Ciara Kennedy, PhD, MBA
Vice President

TITLE PAGE

Study Drug:	LUM001
Protocol Number:	LUM001-301
Amendment Number:	3
Date:	February 11, 2015
Study Phase:	Phase 2
Protocol Title:	The Evaluation of the Intestinal Bile Acid Transport (IBAT) Inhibitor LUM001 in the Reduction of Pruritus in Alagille Syndrome, a Cholestatic Liver Disease
Sponsor:	Lumena Pharmaceuticals LLC 12531 High Bluff Drive, Suite 110 San Diego, CA 92130 USA
Sponsor Contact:	Ciara Kennedy, PhD Lumena Pharmaceuticals LLC Phone: 858-337-7922 Email: ckennedy@lumenapharma.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

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:

THE EVALUATION OF THE INTESTINAL BILE ACID TRANSPORT (IBAT) INHIBITOR LUM001 IN THE REDUCTION OF PRURITUS IN ALAGILLE SYNDROME, A CHOLESTATIC LIVER DISEASE

Protocol Number:	LUM001-301
Amendment Number:	3
Date:	February 11, 2015
Sponsor:	Lumena Pharmaceuticals LLC 12531 High Bluff Drive, Suite 110 San Diego, CA 92130

As Agreed:

_____ _____

Investigator's Signature Date

_____

Investigator's Name (Please print)

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Protocol Number: LUM001-301

Protocol Title: THE EVALUATION OF THE INTESTINAL BILE ACID TRANSPORT (IBAT) INHIBITOR LUM001 IN THE REDUCTION OF PRURITUS IN ALAGILLE SYNDROME, A CHOLESTATIC LIVER DISEASE

Amendment: 1

Date: December 10, 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 has been clarified. PK blood sampling will occur at baseline, and at Weeks 2, 4, 8 and 13. 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 will be collected for study drug determination at approximately 2 hours post-dosing at Week 4. At Weeks, 2, 8, and 13 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 elevation in 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
Treatment (Section 5.5.2), Dose Escalation Period (Section 5.5.2.1), Study Drug Administration (Section 10.1)	Text has been revised to indicate that subjects who weigh 10 kg or more at screening will receive a 1.0 mL solution containing LUM001 or placebo. Subjects who weigh less than 10 kg at screening will receive a 0.5 mL solution containing LUM001 or placebo. The volume administered will not change during the course of the study.

Section	Description of Change
Study Procedures (Section 8.0)	Blood samples will be collected at baseline and Weeks 2, 4, 8, and 13 for study drug determination. At Week 4, blood will be drawn approximately 2 hours post-dosing for drug level analysis. At Weeks 2, 8, and 13 blood will be drawn approximately 4 hours post dosing for drug level analysis.
Follow-up (Section 5.5.3), Follow-up Period (Weeks 14 -17) (Section 8.1.5)	The procedures for follow-up have been clarified to indicate that subjects who enrolled in an extension study will be followed at Week 17 under the extension protocol.
Study Drug Description (Section 9.1)	Tabular descriptions of the composition of the LUM001 0.5 mL solution and the 0.5 mL placebo solution have been included.
Safety Monitoring Rules (Section 10.5.2)	Text has been modified to specify that confirmation specimen collections should take place 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 nonprescription medications, herbal and dietary supplement preparations), alcohol

Section	Description of Change
	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.
Schedule of Procedures (section 16.1)	The table has been corrected to reflect that testing of cholestasis biomarkers is not required at the Screening Visit.

PROTOCOL AMENDMENT 2

Protocol Number: LUM001-301

Protocol Title: THE EVALUATION OF THE INTESTINAL BILE ACID TRANSPORT (IBAT) INHIBITOR LUM001 IN THE REDUCTION OF PRURITUS IN ALAGILLE SYNDROME, A CHOLESTATIC LIVER DISEASE

Amendment: 2

Date: January 28, 2015

The following changes have been made to Protocol Amendment 1:

- Lowered age of eligibility from 2 years to 12 months; upper age (18 years inclusive) remains unchanged
- An additional treatment arm ("high dose" 280 µg/kg/day) has been added. Subjects will be randomized to one of 4 treatment groups as follows: 70 µg/kg/day (n=8), 140 µg/kg/day (n=8), 280 µg/kg/day (n=8) or placebo (n=12). The randomization ratio, 2:1, between placebo and LUM001 treatment remains unchanged
- The sample size was increased by 12 to a total of 36 evaluable subjects. Eight (8) subjects will be enrolled in the 280 µg/kg/day treatment arm; 12 subjects will be enrolled in the placebo arm (increased by 4).
- A Phone Contact Visit was added at Week 5
- An exclusion criterion has been added to specify that the administration of sodium phenylbutyrate within 28 days prior to the Baseline / Day 0 visit and during the study is prohibited
- An inclusion criterion has been added which requires eligible subjects to be able to adhere to local Ethics Committee or Institutional Review Board (IRB) blood volume limits for laboratory testing.
- Added an inclusion criterion indicating that Spanish-speaking patients and/or caregivers are eligible
- The protocol's statistical considerations have been modified and/or clarified as follows:
    - For efficacy analyses, the first statistical test performed for each primary and secondary outcome measure will be the comparison between the active and placebo groups. The active group will consist of the two highest tolerated active dose groups combined.
    - A Per Protocol analysis population has been specified that will consist of all subjects in the MITT population who did not have a major protocol violation, inclusive of a violation of entry criteria. Subjects in this population will be referenced as evaluable.
    - Language was added to address the randomization and statistical management of data generated from siblings enrolled in the study.

- Clarification was added to explain that the p-values from the secondary and exploratory analyses will be interpreted as hypothesis generating and not definitive.

- 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
Treatment (Section 5.5.2), Dose Escalation Period (Section 5.5.2.1), Randomization (Section 6.2), Study Drug Administration (Section 10.1), Statistical Considerations (Section 12)	Added treatment group of 280 µg/kg/day
Number of Subjects (Synopsis, Section 5.4), Statistical Considerations (Section 12)	Added 12 subjects for total of 36 subjects to be randomized to one of 4 treatment groups as follows: 70 µg/kg/day (n=8), 140 µg/kg/day (n=8), 280 µg/kg/day (n=8) or placebo (n=12). The randomization ratio, 2:1, between placebo and LUM001 treatment remains unchanged.
Inclusion Criteria (Synopsis, Section 7.1)	Lower age of eligibility from 2 years to 12 months; upper age (18 years inclusive) remains unchanged
Inclusion Criteria (Synopsis, Section 7.1)	Added ability of eligible subjects to adhere to local Ethics Committee or Institutional Review Board (IRB) blood volume limits for laboratory testing
Inclusion Criteria (Synopsis, Section 7.1)	Added ability to read and understand Spanish (caregivers and children above the age of assent) in eligibility criteria
Synopsis (Section 1), Exclusion Criterion #14 (Section 7.2)	Criterion clarified to specify that administration of bile acid or lipid binding resins within **28** days prior to Baseline / Day 0 and throughout the trial is excluded
Synopsis (Section 1), Exclusion Criterion #15 (Section 7.2)	Criterion added to exclude the administration of sodium phenylbutyrate within 28 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.)
Fasting Requirements (Section 8.6.2)	Clarified fasting requirements for Week 4. *Note: The FDA requested that at least one PK blood sample be collected around expected Tmax (e.g. 2 hours post-dosing based on median Tmax of 2.3 hr. in adults). As a result, a sampling time point at 2-hours post-dose was included at Week 4. Samples for LUM001 levels at all other visits will be collected at ~4 hours post-dose. All samples will be obtained*

Section	Description of Change
	under fasting conditions.
Synopsis (Section 1), Study Visit Schedule and Procedures, Study Design (Section 5.1)	Added a Phone Contact Visit at Week 5
Synopsis, Treatment (Section 5.5.2), Randomization (Section 6.2), Screening Period (Section 8.8.1),	Clarified that subjects will be randomized in the study approximately 7 days prior to the Baseline / Day 0 Visit.
Itch Reported Outcome (Section 8.5.1)	Clarified that age at the screening visit will be used as the age for the determination of the appropriate use of the electronic diary for the duration of the study, regardless of subsequent birthdays during the study.
Pediatric Quality of Life Inventory PedsQL (Section 8.5.4)	Clarified that age at the 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.
Fasting Requirements (Section 8.6.2)	Clarification was added to specify that at the Week 4 visit, subjects are required to fast for at least 2 hours (versus 4 hours for all other visits)
LUM001 (Section 9.1.1)	Tables 5 and 6 have been updated to reflect quantity of LUM001 per 1.0 mL and 0.5 mL oral solutions
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 initial report.
Synopsis, Statistical Considerations (Section 12)	Statistical considerations revised to reflect the addition of a 4th dosing arm and the increase in the study's sample size and number of visits. Specified 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.
Synopsis, Statistical Considerations (Section 12.2.3)	Language was added to address the randomization and statistical management of data generated from siblings enrolled in the study.
Synopsis, Statistical Considerations (Section 12.2.5.3)	Clarified that the p-values from the secondary and exploratory analyses will be interpreted as hypothesis generating and not definitive.
All Sections	Minor changes have been made to the text to improve the clarity of the protocol and/or correct minor inconsistencies.

PROTOCOL AMENDMENT 3

Protocol Number: LUM001-301

Protocol Title: THE EVALUATION OF THE INTESTINAL BILE ACID TRANSPORT (IBAT) INHIBITOR LUM001 IN THE REDUCTION OF PRURITUS IN ALAGILLE SYNDROME, A CHOLESTATIC LIVER DISEASE

Amendment: **3**

Date: **February 11, 2015**

The following changes have been made to Protocol Amendment 2:

- The date of the document has been changed throughout to February 11, 2015.
- A typographical error in the tabular description of the changes made in Protocol Amendment 2 was corrected to state that language was added to the statistical section of the protocol to address the randomization and statistical management of data generated from siblings.
- The logo on the protocol's cover page was updated to reflect the Childhood Liver Disease Research Network's (ChiLDReN) current design.

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

Section	Description of Change
Header	Date changed to February 11, 2015
Cover Page	Date changed to February 11, 2015 ChiLDReN's logo updated
Sponsor Signature Page	Date changed to February 11, 2015
Title Page	Date changed to February 11, 2015
Protocol Signature Page	Date changed to February 11, 2015
Protocol Amendment 2 Tabular Summary of Changes (Page 15, line #9)	Language was added to address the randomization and statistical management of data generated from siblings enrolled in the study.

1 STUDY SYNOPSIS AND SCHEDULE OF PROCEDURES

Sponsor	Lumena Pharmaceuticals LLC
Protocol Number	LUM001-301
Protocol Title	The Evaluation of the Intestinal Bile Acid Transport (IBAT) Inhibitor LUM001 in the Reduction of Pruritus in Alagille Syndrome, a Cholestatic Liver Disease
Study Phase	2
Indication	Reduction in pruritus in patients with Alagille Syndrome (ALGS)
Objectives	In pediatric patients with Alagille Syndrome: • To evaluate the effect of LUM001 versus placebo on pruritus as measured by the Itch Reported Outcome (ItchRO) instrument • To evaluate the safety and tolerability of LUM001 • To evaluate the effect of LUM001 versus placebo on serum bile acids • To explore the effect of LUM001 versus placebo on other biochemical markers of cholestasis and liver disease
Study Design	Randomized, double-blind, placebo-controlled, parallel group, multi-center study with 13 weeks of treatment in children with ALGS.
Number of Subjects	Approximately 36 evaluable subjects with ALGS. Eligible subjects will be randomized to one of 4 treatment groups as follows: 70 µg/kg/day (n=8), 140 µg/kg/day (n=8), 280 µg/kg/day (n=8) or placebo (n=12). There is a 2:1 randomization ratio between LUM001 and placebo.
Study Population	**Study Eligibility Criteria:** Inclusion Criteria To participate in this study subjects must meet all of the following criteria: 1. Male or female subjects between the ages of 12 months and 18 years inclusive 2. Diagnosis of ALGS based on the diagnostic criteria outlined in Section 16.3 3. Evidence of cholestasis (one or more of the following): a. Fasting total serum bile acid > 3x ULN for age b. Direct bilirubin > 1 mg/dL c. Fat soluble vitamin deficiency otherwise unexplainable d. GGT > 3x ULN for age e. Intractable pruritus explainable only by liver disease 4. Average daily score ≥ 2 on the Itch Reported Outcome (ItchRO™) questionnaire (maximum possible daily score of 4) for two consecutive weeks in the screening period, prior to randomization. A daily score is the higher of the scores for the morning and evening ItchRO. The average daily score is the sum of all daily scores divided by the number of days the ItchRO was completed. 5. Females of childbearing potential must have a negative serum pregnancy test [β human chorionic gonadotropin (β-hCG)] during Screening 6. Sexually active females must be prepared to use an effective method (≤ 1% failure rate) of contraception during the trial. Effective methods of contraception are considered to be: a. Hormonal (e.g., contraceptive pill, patch, intramuscular implant or injection); or b. Double barrier method, i.e., (a) condom (male or female) or (b) diaphragm, with spermicide; or

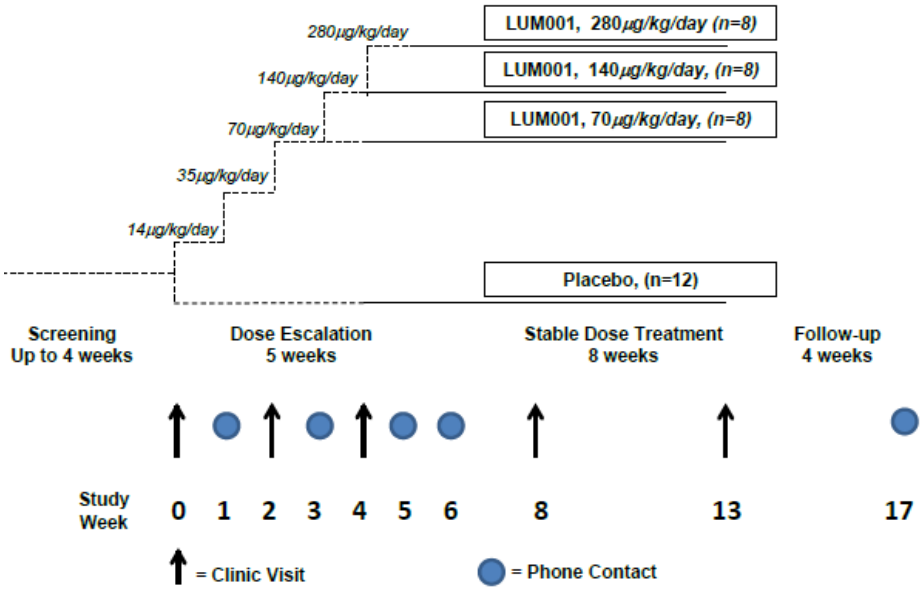
	c. Intrauterine device (IUD) 7. The ability to read and understand English or Spanish (caregivers and children above the age of assent) 8. Subjects expected to have a consistent caregiver(s) for the duration of the study 9. Informed consent and assent (per IRB/EC) as appropriate 10. Access to phone for scheduled calls from study site 11. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device daily for the duration of the study 12. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the eDiary software at the outset of the study 13. 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 randomization (maximum possible reports = 14 per week) 14. Eligible subjects must be able to adhere to local Ethics Committee or Institutional Review Board (IRB) blood volume limits for laboratory testing <u>Exclusion Criteria</u> Subjects will be excluded from the study if they meet any of the following criteria: 1. Chronic diarrhea requiring ongoing specific intravenous fluid or nutritional intervention for the diarrhea and/or its sequelae 2. Surgical interruption of the enterohepatic circulation 3. Liver transplant 4. ALT >15 x ULN 5. Decompensated cirrhosis [INR $\geq$ 1.5 (unresponsive to vitamin K therapy), albumin < 3.0 gm/dL, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy] 6. History or presence of other concomitant liver disease 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. Known diagnosis of human immunodeficiency virus (HIV) infection 9. Cancers except for in situ carcinoma, or cancers treated at least 5 years prior to Screening with no evidence of recurrence 10. Any subject whose recent medical history, or current status suggests that, in the opinion of the Investigator or Medical Monitor, the subject may be unable to complete this study without interruption for intercurrent medical problems 11. The anticipated need for a surgical procedure within 20 weeks from randomization 12. Any female who is pregnant or lactating or who is planning to become pregnant within 20 weeks of randomization 13. Any known history of alcohol or substance abuse 14. Administration of bile acid or lipid binding resins within 28 days prior to randomization and throughout the trial 15. Administration of sodium phenylbutyrate within 28 days prior to randomization and throughout the trial 16. Receipt of an investigational drug, biologic, or medical device within 30 days prior to Screening, or 5 half-lives of the study agent, whichever is longer 17. 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

<table>
<tr><td></td><td>18. 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</td></tr>
<tr><td>Treatment Groups</td><td>There will be four treatment groups:
LUM001 low dose: 70 µg/kg/day (maximum daily dose of 5 mg/day)
LUM001 mid dose: 140 µg/kg/day (maximum daily dose of 10 mg/day)
LUM001 high dose: 280 µg/kg/day (maximum daily dose of 20 mg/day)
Placebo
Eligible subjects will be randomized to one of the 4 treatment groups as follows: 70µg/kg/day (n=8), 140µg/kg/day (n=8), 280µg/kg/day (n=8) or placebo (n=12).</td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>Study drug 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. Study drug will be dispensed to subjects/caregivers at the study site. The appropriate amount of study drug will be dispensed at the Study Day 0 visit and daily dosing will begin on Study Day 1. Subjects who weigh 10 kg or more at screening will receive 1.0 mL grape flavored solution containing LUM001 or placebo. Subjects who weigh less than 10 kg at screening will receive 0.5 mL grape flavored solution containing LUM001 or placebo. The volume administered, either 1.0 mL or 0.5 mL, will not change during the course of the study. Dosing will occur over a 13-week treatment period. Each daily dose will be administered in the morning at least 30 minutes before breakfast (qAM, ac). Study drug should be administered approximately at the same time every day.

<u>Dose Escalation Period</u>
Subjects will be blinded to the dose escalation schedule. For subjects randomized to LUM001, there will be a dose escalation period to acclimate the subject to drug. For subjects randomized to LUM001 low dose (70 µg/kg/day), the dose for each subject will be increased weekly over a 3-week period. During week 4, subjects will receive the same dose as in week 3 (Dose Level 1-3). At the end of three weeks, subjects will continue dosing for another 10 weeks using the Week 3 dose, or the highest tolerated dose below the Week 3 dose. For subjects randomized to LUM001 mid dose (140 µg/kg/day), the dose for each subject will be increased weekly over a 4-week period (Dose Level 1-4). At the end of four weeks, subjects will continue dosing for another 9 weeks using the Week 4 dose, or the highest tolerated dose below the Week 4 dose. For subjects randomized to LUM001 high dose (280 µg/kg/day), the dose for each subject will be increased weekly over a 5-week period (Dose Level 1-5). At the end of five weeks, subjects will continue dosing for another 8 weeks using the Week 5 dose, or the highest tolerated dose below the Week 5 dose. Subjects randomized to placebo will continue dosing during the 5-week period. Each subject will receive LUM001 orally as follows:

<table>
<tr><th rowspan="2">Dose Escalation Period</th><th rowspan="2">Dose Level</th><th colspan="4">Assigned Treatment Group (µg/kg/day)</th><th rowspan="2">Dosing Duration</th></tr>
<tr><th rowspan="2">Placebo</th><th>Low Dose</th><th>Mid Dose</th><th>High Dose</th></tr>
<tr><th>LUM001 70 µg/kg/day</th><th>LUM001 140 µg/kg/day</th><th>LUM001 280 µg/kg/day</th></tr>
<tr><td>Week 1</td><td>1</td><td>0</td><td>14</td><td>14</td><td>14</td><td>7 days</td></tr>
<tr><td>Week 2</td><td>2</td><td>0</td><td>35</td><td>35</td><td>35</td><td>7 days</td></tr>
<tr><td>Week 3</td><td>3</td><td>0</td><td>70[1]</td><td>70</td><td>70</td><td>7 days</td></tr>
<tr><td>Week 4</td><td>4</td><td>0</td><td>70</td><td>140[2]</td><td>140</td><td>7 days</td></tr>
<tr><td>Week 5</td><td>5</td><td>0</td><td>70</td><td>140</td><td>280[3]</td><td>7 days</td></tr>
</table></td></tr>
</table>

	[1] Subjects randomized to LUM001 (70 µg/kg/day) will be dosed up to a maximum daily dose of 5 mg/day, or the highest tolerated dose below the Week 3 dose. [2] Subjects randomized to LUM001 (140 µg/kg/day) will be dosed up to a maximum daily dose of 10 mg/day, or the highest tolerated dose below the Week 4 dose. [3] Subjects randomized to LUM001 (280 µg/kg/day) will be dosed up to a maximum daily dose of 20 mg/day, or the highest tolerated dose below the Week 5 dose. The anticipated adverse reaction or intolerance is gastrointestinal in nature (e.g., diarrhea, abdominal pain, cramping). In the absence of 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. If a subject experiences intolerance due to gastrointestinal symptoms, 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. <u>Stable Dosing Period</u> At the end of the dose escalation period, subjects will continue dosing through Study Week 13 using the highest tolerated dose in the dose escalation period. Dosing will be stopped after Week 13 and subjects will be followed for an additional 4 weeks. See Section 10.5 for safety monitoring rules.
Rationale for Dose and Schedule Selection	The dosage of LUM001 in pediatric subjects with Alagille Syndrome is based upon prior experience with this investigational product in healthy volunteers and adult and pediatric patients 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 increases 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 therefore higher ASBTi concentrations may be required to achieve the desired target inhibition of bile acid transport in the terminal ileum. 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 daily (equivalent to 140 µg/kg/day for a 70 kg subject) led to a decrease in serum bile acids by >50% following 2 weeks of treatment. In previous studies with LUM001, GI AEs were generally recorded in the first weeks of LUM001 dosing and then observed at levels similar to those in the placebo group after 2-3 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 and diarrhea during the first few weeks of therapy. 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 and diarrhea in subjects, the LUM001 dose will be escalated over a 3-5 week period. Dosing will start at 14 µg/kg/day, and will then be increased at 7 day intervals up to 280 µg/kg/day (equivalent to approximately 20 mg daily dose in a 70 kg subject).
Study Visit Schedule and Procedures	For an individual subject, the study participation period will consist of a screening period of up to 4 weeks, a 13-week treatment period (including a 3-5 week dose escalation period followed by an up to 8-10 week period at a stable dose, depending on dose group), and a follow-up period of up to 4 weeks. Study activities will be conducted as described in the Schedule of Procedures (Section 16.1). No increases in dose levels of pre-study medications are permitted during the course of the study. No new medications used to treat pruritus may be added during the course of the study. Study Scheme (as described below):  <u>Screening Period (Day -28 to Day -1)</u>: After obtaining inform consent (and 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, a 12-lead electrocardiogram (ECG), determination of concomitant medications, and have blood and urine samples taken for clinical laboratory testing. For ALGS subjects who meet clinical diagnostic criteria for ALGS but do not have documentation of a JAGGED-1 mutation, a blood sample will be obtained for genotyping to confirm the clinical diagnosis (results available post-randomization). 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 ItchROs 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 reported outcome (ClinRO) scratch score during Screening. Females who are of childbearing potential will have a serum pregnancy test. Randomization will occur after eligibility criteria have been met, approximately 7 days prior to the Baseline Visit (see below).

	Dose Escalation Treatment Period (Day 0 to Week 5): At the Baseline Visit (Day 0), subjects will be assessed to confirm study eligibility and undergo a physical examination including body weight, height, and vital signs, and have blood and urine samples taken for clinical laboratory testing, including fasting lipid panel. Baseline levels of bile acids and other cholestasis biochemical markers will also be determined from blood and urine. Blood will also be collected for determination of baseline fat soluble vitamins and plasma drug level. Also during the Baseline Visit, ItchRO compliance will be assessed, the clinician scratch score will be determined, the degree and severity of xanthomatosis will be evaluated using the clinician xanthoma scale, 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 prior to dispensing study medication. Study medication for Weeks 1 and 2 will be supplied at the Baseline Visit to eligible subjects. Subjects and caregivers will continue daily completion of their 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 as well as blood sampling for study drug determination will be performed during the Dose Escalation Period. Clinician scratch score will be determined, and adherence to study medication will be assessed. Additional study drug will be supplied at clinic visits at Weeks 2 and 4. ItchRO compliance will be assessed and concomitant medications and any adverse events will be recorded at clinic visits and from phone calls. Stable Dosing Treatment Period (Week 6 to Week 13): Each subject will continue dosing with study drug during the 8-week Stable Dosing Treatment Period using the Week 5 dose, or the highest tolerated dose below the Week 5 dose. Subjects and caregivers will continue daily completion of their ItchRO. Subjects will receive a follow-up phone call at Week 6 and return to the clinic at Weeks 8 and 13. At these visits, safety and clinical laboratory evaluations as well as blood sampling for study drug determination will be performed. Clinician scratch score will be determined and adherence to study medication will be assessed at visits at Weeks 8 and 13. Additional study drug will be supplied at Week 8. At the Week 13 visit, an ECG will be performed, xanthomatosis will be evaluated using the clinician xanthoma scale, and the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments will be administered. Females who are of childbearing potential will have a urine pregnancy test at Week 13. All study drugs (active and placebo) will be discontinued at the Week 13 Visit. ItchRO compliance will be assessed and concomitant medications and any adverse events will be recorded at clinic visits and from phone calls. 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 safety and clinical laboratory evaluations, including determination of serum bile acids, other cholestasis biochemical markers, fat soluble vitamins, and plasma drug level. In addition the following assessments should be completed: the ItchRO, the clinician scratch score, the clinician xanthoma scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, as defined for Early Termination (see Schedule of Procedures, Section 16.1). Efforts must be made to follow subjects for at least 28 days following their last dose of study drug.

	Follow-up Period (Week 14 to Week 17): A safety follow-up phone call will be made at Week 17. For any subject who terminates prior to Week 13 a safety follow-up phone call will be made 4 weeks after the last dose of study drug. Concomitant medications and any adverse events will be recorded. Subjects who complete the Week 13 study visit will be eligible for participation in an extension study of LUM001.
Safety and Tolerability Evaluations	The safety and tolerability of LUM001 will be assessed by determining the incidence, severity, and relationship to study drug of treatment-emergent AEs, withdrawals due to AEs, changes in vital signs, laboratory and other safety parameters. Safety results in subjects dosed with LUM001 will be compared with those from subjects dosed with placebo and between LUM001 dose levels. An independent Data and Safety Monitoring Board (DSMB) will review serious adverse event data, other key subject safety and study data at specified intervals for the duration of the study.
Drug Level Evaluations	LUM001 was designed to be a non-absorbed drug. In previous clinical and preclinical settings the bioavailability of LUM001 was <1%. Plasma levels of LUM001 will be evaluated at baseline and Weeks 2, 4, 8 and 13. At Weeks 2, 8 and 13, blood samples for LUM001 determination will be collected approximately 4 hours after dosing. At Week 4, the blood sample for LUM001 determination will be collected approximately 2 hours after dosing.
Efficacy Evaluations	The primary efficacy evaluation will be compared to placebo as mean change from baseline to Week 13 in: • Pruritus as measured by the average daily score for the ItchRO(Obs). The average daily score will be calculated using the 7 days pre-treatment for baseline, and the last 7 days of treatment for Week 13. The following secondary evaluations will be compared to placebo as mean change from baseline to Week 13 in: • Fasting serum bile acid level • Serum enzymes alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT), and bilirubin (total and direct) The following exploratory evaluations will be compared to placebo: • Mean change from baseline in fasting serum bile acid level at Weeks 4 and 8 • Mean change from baseline in liver enzymes (ALT, ALP, GGT) at Weeks 4 and 8 • Mean change from baseline in pruritus as measured by the average daily ItchRO(Obs) at Weeks 5, and 8. The average daily score will be calculated using the 7 days prior to each visit. • Mean change from baseline in pruritus as measured by the average daily ItchRO(Pt) at Weeks 5, 8, and 13. The average daily score will be calculated using the 7 days prior to each visit. • Mean change from baseline for other biochemical markers of cholestasis [total and direct bilirubin, total cholesterol, low-density lipoprotein cholesterol (LDL-C)] at Weeks 4, 8 and 13 • Responder analysis: pruritus response rates as measured by ItchRO

	(Observer ItchRO and patient ItchRO) at Weeks 5, 8 and 13 • Mean change from baseline in the clinician administered pruritus scale, at Weeks 2, 4, 8 and 13 • Mean change from baseline in bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)] at Weeks 4, 8 and 13 Change from baseline to Week 13 in: • PedsQL • Patient Impression of Change (PIC) • Caregiver Impression of Change (CIC) • Caregiver Global Therapeutic Benefit (CGTB) assessment • Xanthoma severity as measured by clinician xanthoma scale
Statistical Considerations	Sample Size Alagille syndrome is a rare disease. The planned sample size of 36 evaluable Alagille subjects is based on practical considerations, rather than a desired power for a pre-specified difference. With the proposed sample of 28 subjects for the primary endpoint (16 LUM001, from the two highest tolerated dose arms, and 12 placebo), there would be 80% power to detect an effect size of 1.12 or greater. Safety All safety analyses will be performed on the Safety Population, defined as all subjects who were randomized 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, ECG, physical exams, and concomitant medication usage will be summarized descriptively. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation and range will be given for the values themselves as well as for change from baseline by treatment group at each study visit. Qualitative variables will be summarized using counts and percentages by treatment group 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 randomized, receiving at least one dose of treatment, and having at least one post-baseline efficacy assessment. Subjects will be analyzed by assigned treatment. No adjustment for multiplicity will be made. For efficacy analyses, the first statistical test performed for each primary and secondary outcome measure will be the comparison between the active and placebo groups. For the purposes of these analyses, the active groups will be the two highest tolerated active dose groups, that is the data from these groups will be combined. In addition, all doses will be pooled and compared to placebo, as well as individually compared to placebo. A dose will be considered "not-tolerated" if more than 50% of subjects in that dose cohort do not tolerate the treatment. A lack of tolerability on a subject level is defined as a subject who lowers, suspends, or stops dosing due to gastrointestinal tolerability related to LUM001. 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.

	The change from baseline in pruritus as measured by the ItchRO(Obs) will be summarized for each treatment group by study visit. Differences from baseline will be calculated and summarized as above, with a 95% confidence interval for the mean. The difference between treatment groups in change from baseline to Week 13 in the average daily ItchRO(Obs) scores will be evaluated using an ANCOVA model with treatment and average daily ItchRO(Obs) score as a covariate. Where sample size allows, treatment effects over time will be examined using methods appropriate for repeated observations. 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 analyzed using the chi-square test. They will be summarized by frequencies and percents, overall, and by treatment group. P-values from the secondary and exploratory efficacy analyses will be interpreted as hypothesis generating and not definitive. 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. Examination of treatment effects over time may be examined using methods appropriate for repeated observations depending on sample sizes. Additional exploratory analyses may be performed and will be defined and outlined in the SAP for the study. <u>Siblings</u> Siblings enrolled in the study will be assigned in a blinded manner to the same treatment arm. The data from all enrolled participants (including siblings) will be used for the safety analysis. For the efficacy analysis, data from only one of the siblings will be used. The choice of which subject's data to use in the efficacy analysis will be done in a random fashion before the study is unblinded. Additionally, a sensitivity analysis will be conducted using the data from the siblings that were not randomly chosen in order to assess the potential impact on the results. Additional methodological detail will be included in the protocol's Statistical Analysis Plan. 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
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibody
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ASBT	apical sodium-dependent bile acid transporter
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase (SGOT)
ATC	Anatomic Therapeutic Chemical; classification for drugs
ATX	autotaxin
BA	bile acid
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
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
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
dL	deciliter

DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
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
FXR	farnesoid X receptor; bile acid receptor
g	gram
GCP	good clinical practices
GGT	gamma-glutamyltransferase
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 Harmonization
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board

ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Itch Reported Outcome observer instrument
ItchRO(Pt)™	Itch Reported Outcome patient instrument
ITT	intention-to-treat
IU	international unit(s)
IUD	intrauterine device
kg	kilogram
L	liter
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LPA	lysophosphatidic acid
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MITT	modified intention-to-treat
mL	milliliter
mmol	millimole
NBD	nasal biliary drainage
NCS	not clinically significant
ng	nanogram
ObsRO	observer reported outcome
PBC	primary biliary cirrhosis
PBO	placebo
PEBD	partial external biliary diversion
PedsQL	Pediatric Quality of Life Inventory
PFIC	progressive familial intrahepatic cholestasis
PI	principal investigator
PK	pharmacokinetic
PROM	patient reported outcome measure
PSC	primary sclerosing cholangitis

Pt	patient
PT	prothrombin time
q.s.	quantity sufficient
qAM	every morning
SAE	serious adverse event
SAP	statistical analysis plan
SD-5613	original designation for LUM001
sec	second
SLC10A2	solute carrier family 10 member 2; gene that encodes IBAT protein
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TG	triglycerides
TGR5	a G protein-coupled receptor for bile acids
UDCA	ursodeoxycholic acid, ursodiol
ULN	upper limit of normal
US, USA	United States of America
WBC	white blood cell
WHO	World Health Organization
WMA	World Medical Association
yr(s)	year(s)
β-hCG	beta-sub-unit of human chorionic gonadotropin; pregnancy test
µg	microgram
µM	micromolar

3 STUDY OBJECTIVES

In pediatric patients with Alagille syndrome, the objectives of the study are:

- To evaluate the effect of LUM001 versus placebo on pruritus as measured by the Itch Reported Outcome (ItchRO) instrument
- To evaluate the safety and tolerability of LUM001
- To evaluate the effect of LUM001 versus placebo on serum bile acids
- To explore the effect of LUM001 versus placebo on other biochemical markers of cholestasis and liver disease

4 BACKGROUND AND RATIONALE

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

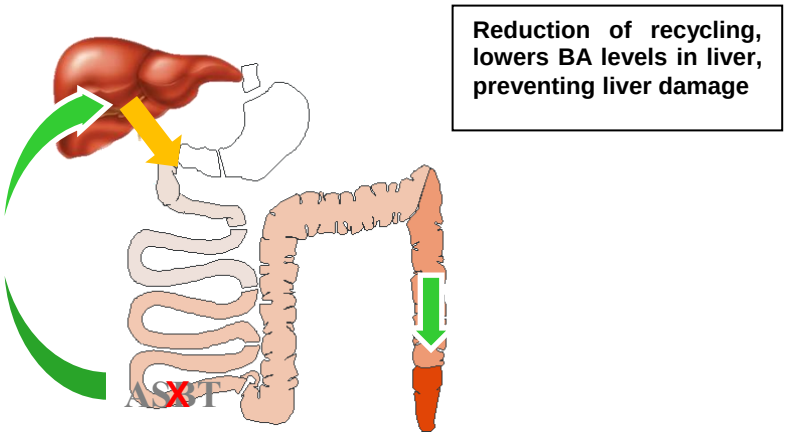
4.1 Therapeutic Rationale

In patients with Alagille syndrome, 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. Present in most patients with Alagille Syndrome, Itch is the archetypal symptom of cholestasis, occurring at all stages of cholestatic liver disease, with or without jaundice.

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

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

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



ASBT/IBAT expression is under negative feedback regulation by bile acids; thus in the setting of cholestasis, ASBT/IBAT is maladaptively upregulated (Neimark, Chen, Li, & Shneider, 2004) (Hofmann, 2003). Therefore, inhibiting the reuptake of bile acids may represent an ideal treatment for cholestatic disease. In the current study, ALGS will serve as a model for generalized cholestasis. By inhibiting the intestinal reabsorption of bile acids, LUM001 could interrupt the enterohepatic circulation and mimic the effects of partial external biliary diversion or ileal exclusion (Figure 1).

4.2 Alagille Syndrome

Alagille syndrome (ALGS) is an autosomal dominant with variable penetration genetic multisystem disorder. The clinical diagnosis is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities and characteristic facial features. Fewer than 200 patients with ALGS are born each year in the United States. The estimated prevalence in the United States is 3 per 100,000. Elevations of serum bilirubin up to 30 times normal and serum bile salts up to 100 times normal are common. Levels of markers of bile duct damage, including gamma-glutamyltransferase (GGTP or GGT) and alkaline phosphatase (ALP), usually are significantly elevated. Cholesterol levels may also be elevated. Multiple xanthomas are common sequelae of severe cholestasis. The pruritus seen in patients with this condition is among the most severe of any chronic liver disease and it is present in most children by the third year of life. Although surgical interruption of the enterohepatic circulation has been successfully employed in the treatment of cholestasis and hypercholesterolemia in ALGS (Emerick & Whitington, 2002) (Modi, Suh, Jonas, Lillehei, & Kim, 2007), the management of cholestasis in ALGS remains largely supportive at this time. As cholestasis tends to improve over the first 5 to 10 years of life, therapies that ameliorate the complications of cholestasis, without a

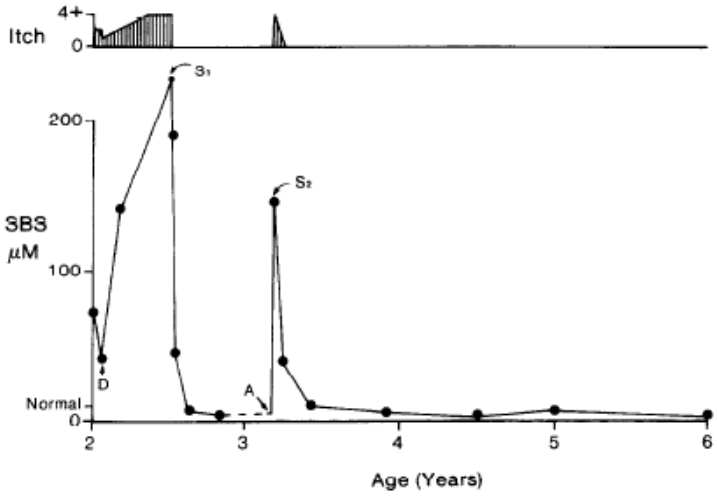
commitment to liver transplantation, are highly desirable (Emerick, Rand, Goldmuntz, Krantz, Spinner, & Piccoli, 1999).

4.3 Pruritus

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

Intractable and pharmacologically recalcitrant pruritus is one of the major morbidities afflicting children with ALGS. Treatment with anti-pruritics and bile salt resins may provide partial relief of itching for children with ALGS, but currently available pharmacologic approaches are of limited value. It has been shown that removing bile with surgical procedures such as partial external biliary diversion (PEBD) and nasal biliary drainage (NBD) substantially reduces pruritus in ALGS (Emerick & Whitington, 2002), progressive familial intrahepatic cholestasis (PFIC) and PBC. Almost complete resolution of pruritus has been observed in children with PFIC disease in a period of as little as two to four weeks following the procedure. The rapid resolution of itch in response to therapy can be seen in Figure 2 extracted from the original description of this procedure by Whitington and Whitington (1988). Rapid lowering of bile acids, bilirubin and ALT has also been observed (Table 1).

Figure 2: Serum Bile Salt Concentration and Degree of Itch



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

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

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

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

4.4 LUM001

4.4.1 Nonclinical Studies

4.4.1.1 Pharmacology

LUM001 is a minimally-absorbed, 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 much 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. The results from this study were very favorable; 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 that were previously determined in several oral gavage studies with 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.

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 patients, a tolerability study in adolescents and children, and a multiple dose tolerability and efficacy study of three sustained release formulations, compared with the immediate release formulation. More than 1,400 human subjects have been exposed to LUM001 (immediate release) for up to 10 weeks.

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

Administration of LUM001 at doses up to 100 mg once daily over a four-week period was generally safe in healthy volunteers and at doses up to 40 mg once daily for up to 10 weeks in patients 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 patients 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 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 that LUM001 will produce a correspondingly smaller increase in free bile acids in the lower colon, and could potentially lead to the drug being better tolerated at the same dose level.

Ideally, dosing in pediatric subjects should be scaled from that in adults based on intestinal length, 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, Austin, & Cole (1991) provided data indicating that the average length of the small intestine increases with age from birth through 20 years; this relationship followed a curve that is similar to the height and weight growth curves. However, a plateau had not been reached at the maximum age examined (20 years), precluding predictions of intestinal length for older adults and thus scaling to infants and children based on estimated intestinal length. An analysis of intestinal length as a function of age, weight, and height in adult cadavers was conducted by (Hounnou, Destrieux, Desme, Bertrand, & Velut, 2001). Their analysis demonstrated that age had a negative correlation 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.

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

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

Weight (kg)	LUM001 70 µg/kg/day	LUM001 140 µg/kg/day	LUM001 280 µg/kg/day
10	0.7	1.4	2.8
15	1.1	2.1	4.2
20	1.4	2.8	5.6
25	1.8	3.5	7.0
30	2.1	4.2	8.4

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

In Study 014 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. A total of 49 of 50 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

	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)
GI Adverse Events					
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% following 2 weeks of treatment. 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.

There are 5 ongoing pediatric studies of LUM001 that are currently enrolling patients with cholestatic liver disease, including 4 studies in subjects with Alagille syndrome and 1 open-label study in subjects with PFIC. As of October 31, 2014, a total of 33 pediatric subjects ranging in age from 12 months to 17 years have been exposed to LUM001 at doses up to 280 µg/kg/day. Of these 33 subjects, at least 6 are between 12-24 months old. In the open-label study in subjects with PFIC, 3 subjects between 12-24 months old have been exposed to LUM001 at the 280 µg/kg/day dose level with ongoing dosing durations ranging from 3 weeks 16 weeks.

The most commonly reported adverse reactions in the ongoing pediatric studies of LUM001 are diarrhea and abdominal pain. The majority of adverse events as of October 31, 2014 were mild or moderate in severity. Three serious adverse events have been reported. Of the 3 serious adverse events reported, none were judged to be related to study drug by the investigators. No studies have been completed to date, and consequently no finalized study reports are available.

In the current study, safety and efficacy of LUM001 will be assessed in children with Alagille syndrome and cholestatic liver disease, 12 months to 18 years inclusive,

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 LUM001-301, the LUM001 dose will be escalated over an up to 5-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 group.

5 INVESTIGATIONAL PLAN

5.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel group, multi-center study in children with ALGS. The study is designed to investigate the effects of LUM001, compared to placebo, on pruritus, serum bile acids, liver enzymes, and other biochemical markers associated with cholestatic liver disease, following daily dosing over a 13-week period.

There will be four treatment groups:

- LUM001 low dose: 70 µg/kg/day (maximum daily dose of 5 mg/day)
- LUM001 mid dose: 140 µg/kg/day (maximum daily dose of 10 mg/day)
- LUM001 high dose: 280 µg/kg/day (maximum daily dose of 20 mg/day)
- Placebo

Eligible subjects will be randomized to one of the 4 treatment groups as follows: 70µg/kg/day (n=8), 140µg/kg/day (n=8), 280µg/kg/day (n=8) or placebo (n=12). There is a 2:1 randomization ratio between LUM001 and placebo.

5.2 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will review serious adverse event data, other key subject safety and study data at specified intervals for the duration of the study. The DSMB will be composed of several members who are otherwise independent from the conduct of the study: one or more physicians 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 NIDDK 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 multi-center study in approximately 12 clinical sites.

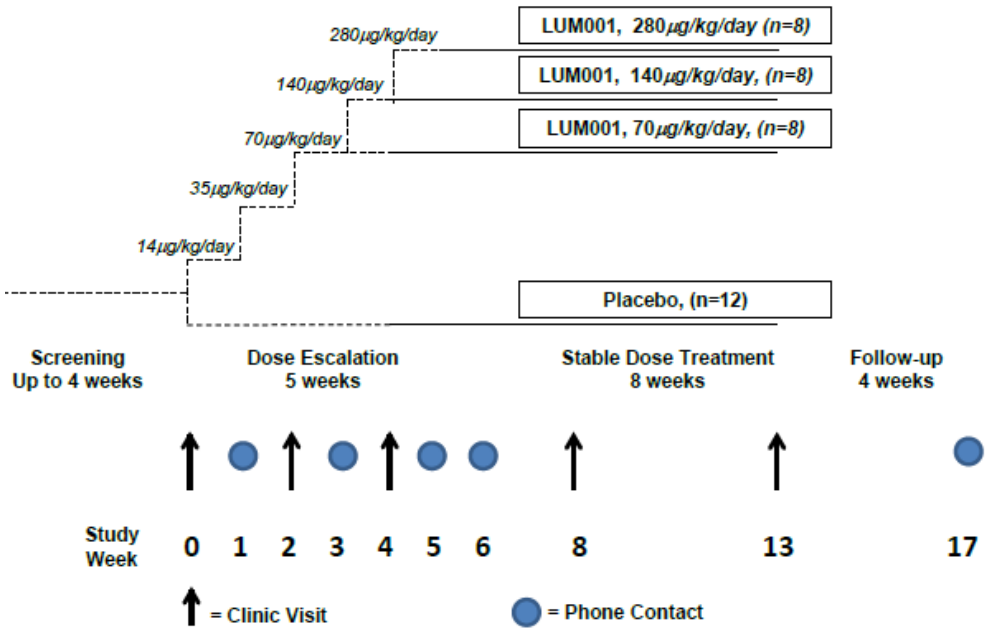
5.4 Number of Subjects

Approximately 36 evaluable subjects with ALGS will be enrolled in the study.

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 17 weeks. Following screening, subjects who meet all eligibility criteria will return to the clinic for 5 visits and will receive 5 telephone contacts from the study staff (see Figure 3). Study activities will be conducted as described in the Schedule of Procedures (Section 16.1).

Figure 3: Study Design for LUM001-301



5.5.1 Screening

Each subject who provides informed consent/assent will complete all screening activities in ≤ 4 weeks.

5.5.2 Treatment

Eligible subjects will be randomized during the screening period, approximately 7 days prior to Study Day 0 (baseline visit). Study drug will be prepared for each individual subject 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. Study drug will be dispensed to subjects/caregivers at the study site. The appropriate amount of study drug will be dispensed at the Study Day 0 visit and daily dosing will begin on Study Day 1. Subjects who weigh 10 kg or more at screening will receive a 1.0 mL grape-flavored solution containing LUM001 or placebo. Subjects who weigh less than 10 kg at screening will receive a 0.5 mL grape-flavored solution containing LUM001 or placebo. The volume administered will not change during the course of the study. Dosing will occur over a 13-week treatment period. Each daily dose will be administered in the morning at least 30 minutes before breakfast (qAM, ac). Study drug should be administered approximately at the same time every day.

5.5.2.1 Dose Escalation Period

Subjects will be blinded to the dose escalation schedule. For subjects randomized to LUM001, there will be a dose escalation period to acclimate the subject to drug.

For subjects randomized to LUM001 low dose (70 µg/kg/day), the dose for each subject will be increased weekly over a 3-week period (Dose Level 1-3). During week

4, subjects will receive the same dose as in week 3. At the end of three weeks, subjects will continue dosing for another 10 weeks using the Week 3 dose, or the highest tolerated dose below the Week 3 dose.

For subjects randomized to LUM001 mid dose (140 µg/kg/day), the dose for each subject will be increased weekly over a 4-week period (Dose Level 1-4). At the end of four weeks, subjects will continue dosing for another 9 weeks using the Week 4 dose, or the highest tolerated dose below the Week 4 dose.

For subjects randomized to LUM001 high dose (280 µg/kg/day), the dose for each subject will be increased weekly over a 5-week period (Dose Level 1-5). At the end of five weeks, subjects will continue dosing for another 8 weeks using the Week 5 dose, or the highest tolerated dose below the Week 5 dose.

Subjects randomized to placebo will continue dosing during the 5-week period.

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

Table 4: Dose Escalation Regimens

Dose Escalation Period	Dose Level	Assigned Treatment Group (µg/kg/day)				Dosing Duration
		Placebo	Low Dose	Mid Dose	High Dose	
			LUM001 70 µg/kg/day	LUM001 140 µg/kg/day	LUM001 280 µg/kg/day	
Week 1	1	0	14	14	14	7 days
Week 2	2	0	35	35	35	7 days
Week 3	3	0	70[1]	70	70	7 days
Week 4	4	0	70	140[2]	140	7 days
Week 5	5	0	70	140	280[3]	7 days

[1] Subjects randomized to LUM001 low dose (70 µg/kg/day) will be dosed up to a maximum daily dose of 5 mg/day, or the highest tolerated dose below the Week 3 dose.
[2] Subjects randomized to LUM001 mid dose (140 µg/kg/day) will be dosed up to a maximum daily dose of 10 mg/day, or the highest tolerated dose below the Week 4 dose.
[3] Subjects randomized to LUM001 high dose (280 µg/kg/day) will be dosed up to a maximum daily dose of 20 mg/day, or the highest tolerated dose below the Week 5 dose.

The anticipated adverse reaction or intolerance is gastrointestinal in nature (e.g., diarrhea, abdominal pain, cramping, etc.). In the absence of 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).

If a subject experiences intolerance due to gastrointestinal symptoms, 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. 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

At the end of the dose escalation period, subjects will continue dosing through Study Week 13 using the highest tolerated dose.

5.5.3 Follow-up

All study drug (LUM001 or placebo) will be discontinued at Week 13 and subjects will be followed for an additional 4 weeks. A safety follow-up phone call will be made at Week 17. Subjects who complete the Week 13 study visit will be eligible for participation in a long-term extension study of LUM001. Subjects who enroll in an extension study will be followed at Week 17 under the extension study's protocol.

5.6 End of Study

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 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 considered enrolled 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 Randomization

Subjects will be randomized after all screening assessments have been completed and the Investigator has verified that eligibility criteria have been met. At the time of randomization, subjects will be assigned a unique randomization number. Subjects will be randomized approximately 7 days prior to the baseline visit (Day 0). No subject may begin treatment prior to randomization. Eligible subjects will be randomized to one of 4 treatment groups as follows: 70 µg/kg/day (n=8), 140 µg/kg/day (n=8), 280 µg/kg/day (n=8) or placebo (n=12). There will be a 2:1 randomization ratio between combined LUM001 treatment groups and placebo.

The Sponsor (or designee) will prepare the randomization list; the pharmacist at a central pharmacy will be unblinded to treatment group. The study staff including the local site pharmacist (or qualified delegate) will remain blinded to the treatment assignment.

6.3 Replacement of Subjects

A subject who withdraws from the study prior to completion of the treatment period (Week 13) may be replaced at the discretion of the Sponsor. A subject who at Study Day 0 is determined to be ineligible after receiving a randomization number but before dosing will be discontinued and will be replaced.

6.4 Unblinding of Treatment Assignment

The Sponsor (or designee) will prepare the randomization list. All subjects, monitors, and study center personnel related to the study, except for the pharmacist (or qualified designee) who prepares the study drug and the pharmacy monitor who monitors the pharmacy records and procedures, will be blinded to study treatment throughout the

study. A designated statistician will securely maintain an unblinded randomization schema.

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

Although all subjects will receive LUM001 or placebo during this study, breaking of the blind should not occur except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or when causality must be determined prior to submitting a regulatory safety report for a serious adverse event (SAE) (as defined in Section 11.2.3).

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

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

7 SUBJECT ELIGIBILITY

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

7.1 Inclusion Criteria

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

1. Male or female subjects between the ages of 12 months and 18 years inclusive
2. Diagnosis of ALGS based on the diagnostic criteria outlined in Section 16.3
3. Evidence of cholestasis (one or more of the following):
    a. Fasting total serum bile acid > 3x ULN for age
    b. Direct bilirubin > 1 mg/dL
    c. Fat soluble vitamin deficiency otherwise unexplainable
    d. GGT > 3x ULN for age
    e. Intractable pruritus explainable only by liver disease
4. Average daily score ≥ 2 on the Observer Itch Reported Outcome (ItchRO(Obs)™) questionnaire (maximum possible daily score of 4) for two consecutive weeks in the screening period, prior to randomization. A daily score is the higher of the scores for the morning and evening ItchRO. The average daily score is the sum of all daily scores divided by the number of days the ItchRO(Obs) was completed.
5. Females of childbearing potential must have a negative serum pregnancy test [β human chorionic gonadotropin (β-hCG)] during Screening
6. Sexually active females must be prepared to use an effective method (≤ 1% failure rate) of contraception during the trial. Effective methods of contraception are considered to be:
    a. Hormonal (e.g., contraceptive pill, patch, intramuscular implant or injection); or
    b. Double barrier method, i.e., (a) condom (male or female) or (b) diaphragm, with spermicide; or
    c. Intrauterine device (IUD)
7. The ability to read and understand English or Spanish (caregivers and children above the age of assent)
8. Subjects expected to have a consistent caregiver(s) for the duration of the study
9. Informed consent and assent (per IRB/EC) as appropriate
10. Access to phone for scheduled calls from study site

11. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device daily for the duration of the study
12. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the eDiary software at the outset of the study
13. 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 randomization (maximum possible reports = 14 per week)
14. Eligible subjects must be able to adhere to local Ethics Committee or Institutional Review Board (IRB) blood volume limits for laboratory testing

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 interruption of the enterohepatic circulation
3. Liver transplant
4. ALT >15 x ULN
5. Decompensated cirrhosis [INR $\geq$ 1.5 (not due to vitamin K deficiency), albumin < 3.0 gm/dL, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy]
6. History or presence of other concomitant liver disease
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. Known diagnosis of human immunodeficiency virus (HIV) infection
9. Cancers except for in situ carcinoma, or cancers treated at least 5 years prior to Screening with no evidence of recurrence
10. Any subject whose recent medical history, or current status suggests that, in the opinion of the Investigator or Medical Monitor, the subject may be unable to complete this study without interruption for intercurrent medical problems
11. The anticipated need for a surgical procedure within 20 weeks from randomization
12. Any female who is pregnant or lactating or who is planning to become pregnant within 20 weeks of randomization
13. Any known history of alcohol or substance abuse
14. Administration of bile acid or lipid binding resins within 28 days prior to randomization and throughout the trial

15. Administration of sodium phenylbutyrate within 28 days prior to randomization and throughout the trial
16. Receipt of an investigational drug, biologic, or medical device within 30 days prior to Screening, or 5 half-lives of the study agent, whichever is longer
17. 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
18. 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

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 -28 to Day -1)

Screening evaluations will be performed from Day -28 to Day -1. In the absence of documented JAGGED1 or NOTCH2 mutation prior to screening, genetic testing will be performed for JAGGED1 (Spinner, Hutchinson, Krantz, & Kamath, 2000). 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.

Subjects and caregivers who give written informed consent/assent will provide demographic data (gender, age, and race), undergo a medical history (including current medical problems and symptoms and assessment of inclusion/exclusion criteria) and physical examination including body weight, height, and vital signs, a 12-lead electrocardiogram (ECG), determination of concomitant medications, and have blood and urine samples taken for clinical laboratory testing. 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 and/or 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 clinican scratch scale during screening. Females who are of childbearing potential will have a serum pregnancy test. Randomization will occur after eligibility criteria have been met, approximately 7 days prior to the baseline visit.

Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 28-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 5)

At the baseline visit (Day 0), subjects will be assessed to confirm study eligibility and undergo a physical examination including body weight, height, and vital signs, and have blood and urine samples taken for clinical laboratory testing, including fasting lipid panel, baseline levels of bile acids, other cholestasis biochemical markers, fat soluble vitamins and plasma drug level. Also during the baseline visit, ItchRO compliance will be assessed, the clinician scratch scale will be administered, the degree and severity of xanthomatosis will be evaluated using the clinician xanthoma scale, 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. Dosing instructions and study drug for Weeks 1 and 2 will be supplied at the baseline visit to eligible subjects.

Subjects and caregivers will continue daily completion of their morning and evening eDiary (ItchRO) throughout the dose escalation treatment period. Subjects will return to the clinic at the end of Weeks 2 and 4 and will receive a follow-up phone call at the end of Weeks 1, 3 and 5. On clinic visit days, safety and clinical laboratory evaluations as well as blood sampling for study drug determination will be performed. At Week 2, blood sampling for study drug determination will occur approximately 4 hours after dosing. At Week 4, blood sampling for study drug determination will occur approximately 2 hours after dosing. The clinician scratch scale will be administered, adherence to study drug will be assessed and additional dosing instructions and study drug will be supplied at clinic visits at the end of Weeks 2 and 4. Follow-up phone calls will review dosing instructions for the next week. ItchRO compliance will be assessed and concomitant medications and any adverse events will be recorded at clinic visits and from phone calls. Phone contact at Weeks 1, 3 and 5 and clinic visits at Weeks 2 and 4 have a ±2 day window.

8.1.3 Stable Dosing Treatment Period (Week 6 to Week 13)

Each subject will continue dosing with study drug during the stable dosing treatment period using the highest tolerated dose in the dose escalation period. Subjects and caregivers will continue daily completion of their eDiary (ItchRO). Subjects/caregivers will receive a follow-up phone call at Week 6 and return to the clinic at Weeks 8 and 13.

At these clinic visits, safety and clinical laboratory evaluations as well as blood sampling for study drug determination will be performed, approximately 4 hours post study drug administration and following a 4-hour fasting period. The clinician scratch scale will be administered and adherence to study drug will be assessed at visits at Weeks 8 and 13. Additional dosing instructions and study drug will be supplied at Week 8. At the Week 13 visit, an ECG will be performed, xanthomatosis will be evaluated using the clinician xanthoma scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments 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. All study drugs (active and placebo) will be discontinued at Week 13. Concomitant medications and any adverse events will be recorded at clinic visits and from phone calls. Clinic visits at Weeks 8 and 13 have a ±5 day window.

8.1.4 Early Termination

Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo safety and clinical laboratory evaluations for bile acids, other cholestasis biochemical markers, fat soluble vitamins, drug level. In addition the following assessments should be completed; the ItchRO, the clinician scratch scale, the clinician xanthoma scale, the PedsQL, the Patient Impression of Change, the Caregiver

Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, as defined for Early Termination (see Schedule of Procedures, Section 16.1). For safety reasons, efforts must be made to follow subjects for at least 28 days following their last dose of study drug.

8.1.5 Follow-up Period (Week 14 to Week 17)

A safety follow-up phone call will be made at 17 weeks. For any subject who terminates prior to Week 13 a safety follow-up phone call will be made 4 weeks after the last dose of study drug. Concomitant medications and any adverse events will be recorded. Phone contact at Week 17 has a ±5 day window.

Subjects who complete the study at Week 13 may be eligible for participation in an extension study of LUM001.

8.2 Genetic Testing

JAGGED1 mutations are predictive of ALGS. For ALGS subjects who meet clinical diagnostic criteria for ALGS (see Section 16.3) but do not have documentation of a JAGGED1, the clinical diagnosis of ALGS will be confirmed by genotyping (results may be available post-randomization). The appropriate genetic counseling will be provided to subjects and their legal caregivers.

8.3 Physical Examination, Weight and Height, Vital Signs

A physician Investigator will conduct a physical examination on each subject at screening and at every study clinic visit. In addition, body weight, height, 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 11.4.3 regarding laboratory abnormalities.

8.5 Pruritus and Quality of Life Assessments

8.5.1 Itch Reported Outcome (ItchRO™)

Pruritus will be assessed using newly developed Itch caregiver and patient reported outcome measures (ItchRO) administered as a twice daily electronic diary. 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). The primary measure of pruritus will be made using the ItchRO(Obs).

Subjects and caregivers will be trained in the use of the electronic 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 randomization, caregivers must complete at least 10 eDiary reports (morning and/or evening) during each of two consecutive weeks of the screening period and have an average daily score of ≥ 2.0 for each of 2 consecutive weeks prior to randomization. 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 randomization, ALGS subjects/caregivers will be required to submit twice daily assessments using the electronic diary for the duration 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 the Week 13 visit).

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more 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.

The electronic diary should be completed in a consistent manner throughout the study. Subjects who turn 5 years old during the study will not be issued an electronic diary and subjects who turn 9 years old should not begin completing the electronic diary on their own. The manner in which the electronic diary is completed during the study is determined at Screening and is not changed during the study.

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, and 13.

The clinician's assessment of the subject's pruritus is focused on scratching and visible damage to the skin as a result of scratching as observed by the physician. The clinician scratch scale uses a 5-point scale, in which 0 designates no evidence of scratching and 4 designates cutaneous mutilation with bleeding, hemorrhage and scarring. Whenever possible, the same individual should make the assessments for a subject visits.

8.5.3 Clinician Xanthoma Scale

A clinician's assessment of xanthomatosis will be made by the principal investigator or sub-investigator using the clinician xanthoma Scale (Section 16.6). This assessment will be completed at Baseline (Day 0) and at Week 13.

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

8.5.4 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL™ is a one-page questionnaire that will be administered to subjects and or caregivers at the Day 0 (baseline) and Week 13 visits using the age-appropriate PedsQL module (Section 16.7) The PedsQL is a validated, modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescents (Varni, Seid, & Kurtin, 2001). In addition to the core generic PedsQL module the multidimensional fatigue and family impact questionnaires will also be administered at the Week 0 (baseline) and Week 13 visits using the age-appropriate module, see Section 16.7. Age at the baseline visit will be used as the age for the determination of the appropriate questionnaire to be used during the study. This same module will be used for the duration of the study regardless of a subsequent birthday during the study.

8.5.5 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 screening visit, at the Week 13 visit, see Section 16.8.

8.5.6 Caregiver Impression of Change

The Caregiver Impression of Change (CIC) is designed to assess the caregiver's perception of the subject's itch related symptoms and xanthoma severity at the end of study drug treatment compared to his/her itch related symptoms and xanthoma severity prior to the start of treatment with study drug. The CIC will be completed by all caregivers at the Week 13 visit, see Section 16.9.

8.5.7 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 visit, see Section 16.10.

8.6 Restriction on the Lifestyle of Subjects

8.6.1 Contraception Requirements

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

8.6.2 Fasting Requirements

On study days in which blood samples are collected for the lipid panel and/or cholestasis biomarkers, all subjects will be required to fast for at least 2 hours (Week 4 only) or 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

LUM001 is a powder that is to be dissolved with an appropriate diluent in order to administer the study drug as an oral solution. The composition of LUM001 study drug 1.0 mL oral solution is described in Table 5. The composition of LUM001 study drug 0.5 mL oral solution is described in Table 6.

Table 5: Composition of LUM001 1.0 mL Oral Solution

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

Table 6: Composition of LUM001 0.5 mL Oral Solution

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

9.1.2 Placebo

The matching placebo contains the diluent with no active ingredient. The composition of placebo 1.0 mL study drug oral solution is described in Table 7**.** The composition of placebo 0.5 mL oral solution is described in Table 8.

Table 7: Composition of Placebo 1.0 mL Oral Solution

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

Table 8: Composition of Placebo 0.5 mL Oral Solution

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

9.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged study drug labeled in accordance with specific country regulatory requirements. Standard syringes will be provided for 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 drugs (including placebo), 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 or placebo) in this study is based on weight. Given the relatively short duration of the study, the subject's weight determined at the screening visit will be used to calculate the administered dose of study drug for the duration of the study.

Study drug will be prepared for each subject 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. Study drug will be dispensed to subjects/caregivers at the study site. Grape flavored diluent will be added by the pharmacist prior to dispensing a pre-mixed solution to subjects. Once study drug has been added to the diluent the resulting solution is stable at temperatures ranging from 4-8^{o}C to room temperature for at least 8 weeks.

Each subject dose for subjects who weigh 10 kg or more will be administered orally as a 1.0 mL solution containing study drug (LUM001 or placebo) using the syringe provided. Each subject dose for subjects who weigh less than 10 kg will be administered orally as a 0.5 mL solution containing study drug (LUM001 or placebo) using the syringe provided. Study drug should be taken at least 30 minutes prior to the first meal of the day (qAM, ac) and should be administered approximately at the same time each day for the duration of the treatment period. See Sections 5.5.2, 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.

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 at Week 17).

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 course of the study. 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. Patients are expected to maintain a stable dose and administration schedule for all permitted concomitant medications throughout the course of the study.

10.5 Safety Monitoring Rules

10.5.1 General Monitoring Rules

In the evaluation of adverse events and the potential relationship to study drug it is important to note that due to their liver disease many patients with Alagille syndrome have abnormal liver enzyme levels (e.g. ALT, ALP) and total bilirubin at baseline. If an individual subject exhibits a CTCAE Grade 3 treatment emergent toxicity, with the exception of the specific rules outlined below (Sections 10.5) dosing will be suspended. Continued dosing with study drug (LUM001 or placebo) may be considered following discussion with the Sponsor Medical Monitor. The Investigator and Sponsor Medical Monitor will evaluate the subject's safety data and make a decision to either restart dosing at the same level, restart dosing at a lower dose level, or discontinue dosing.

To ensure subject safety, 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), with the exception of the specific rules outlined below, 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 randomized 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.

10.5.2 Safety Monitoring Rules

The following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study, the initial clinical laboratory results exceeding the safety monitoring criteria presented below **must be confirmed** by performing measurements (in the central laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place within 48 to 72 hours of the initial report. The results from the retest **must be available** prior to the next scheduled clinic visit or phone follow-up.

Stopping Rule Guidance: Subject dosing must be suspended until the retest results are available. If any of the stopping criteria described below (refer to Section 10.5.1) are confirmed, the physician investigator (PI) in consultation with the Sponsor Medical Monitor or appropriately qualified designee, will permanently discontinue the subject from further treatment with study drug (LUM001 or placebo). The subject will be evaluated as outlined below and will be encouraged to complete the early termination study procedures (Week 13 visit). Subjects who do not meet the stopping rules based on retest may continue dosing and the Investigator and the Sponsor 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 initial report.

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

Baseline Total Bilirubin	Total Bilirubin
Total Bilirubin 1-10 mg/dL	3 mg increase
Total Bilirubin >10 mg/dL	5 mg 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 if pediatric hepatic diseases. For subjects with a confirmed elevation in ALT or total bilirubin level, as described above, the following evaluations should be performed as clinically indicated:

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

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 Sponsor Medical Monitor,** discontinuation of dosing of a subject with study drug (LUM001 or placebo) will be considered if:

Baseline Tests	Change Observed
ALT (any level)	ALT ≥ 20 x ULN
Total Bilirubin 1-10 mg/dL	5 mg increased **and** a 2 x increase over baseline level
Total Bilirubin >10 mg/dL	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, the Investigator and the Sponsor Medical Monitor may consider a temporary

interruption of study drug (LUM001 or placebo). Dosing may resume when the triglyceride level returns to <300 mg/dL 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 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 Sponsor 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 that is unresponsive to vitamin K therapy, the Investigator and the Sponsor Medical Monitor may consider a temporary interruption of study drug (LUM001 or placebo). Dosing may resume when the INR falls below 1.5 or returns to the subject's baseline level.

10.6 Adjustment of Dose

Gastrointestinal intolerance, as evidenced by diarrhea/loose stools, abdominal pain/cramping and nausea, is expected to be the most frequent manifestation of a lack of tolerability to study drug. If an individual subject exhibits a treatment emergent CTCAE Grade 2 or greater drug-related GI toxicity, study drug dose may be lowered to a previously well tolerated dose. This decision should be made in consultation with the Sponsor Medical Monitor. A requirement for intravenous fluids as treatment for diarrhea will lead to discontinuation of study drug.

10.7 Withdrawal of Subjects from the Study

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

Any investigator decision to withdraw a subject from the study must first be discussed with the sponsor 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 or placebo), 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 must also be retrieved.

For safety reasons, efforts must be made to follow subjects for at least 28 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 serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonisation (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

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

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

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

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

11.2 Definitions

11.2.1 Adverse Event

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

An adverse event <u>does not</u> include the following:

- Continuous persistent disease/symptom present before the start of study drug, which does not unexpectedly progress, or change in severity following drug administration.
- Disease being studied and/or signs and symptoms associated with the disease, such as jaundice or itching, or abnormalities in liver enzymes already present 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 adverse event caused by the study drug.

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

11.2.3 Serious Adverse Event (SAE)

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

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

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

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

  Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization. Admission to the hospital is the criterion that defines "serious", not the duration of hospital stay.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female)

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

11.3 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. 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 at the end of the subject's follow-up period which is defined as Week 17, or 28 days after the last dose of study drug for those subjects that terminate the prior to the Week 13 visit.

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 at the end of the subject's follow-up period, which is defined as Week 17. 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 16.11). If the CTCAE does not have a grading for a particular adverse event, the severity of the event should be reported based on the following:

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

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

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
- Treatment unblinding for any reason (see Section 6.4)

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 Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

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

12 STATISTICAL CONSIDERATIONS

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

Continuous variables will be summarized using descriptive statistics including n, mean, median, standard deviation, range (e.g., minimum and maximum). Qualitative variables will be summarized using counts and percentages. Summaries will be provided by treatment group and overall. Unless otherwise specified, statistical analyses will be performed using SAS Version 9 or higher. Where appropriate, statistical tests will be conducted at the 0.05 significance level using two-tailed tests and p-values will be reported. Given the rare nature of Alagille syndrome, the statistical power of any comparisons is limited. As such the analysis will be largely descriptive in nature.

12.1 Sample Size Considerations

Alagille syndrome is a rare disease. The planned sample size of 36 evaluable Alagille subjects is based on practical considerations, rather than a desired power for a pre-specified difference. With the proposed sample of 28 subjects for the primary efficacy analyses (16 LUM001, from the two highest tolerated dose arms, and 12 placebo), there would be 80% power to detect an effect size of 1.12, or greater.

12.2 Populations

12.2.1 Safety Population

The Safety Population is defined as all subjects who were randomized and received at least one dose of the study drug. The Safety Population will be used for all safety analyses. Subjects will be analyzed by treatment received. If subjects inadvertently receive both active drug and placebo, they will be included in the LUM001 group.

12.2.2 Efficacy Populations

The intention-to-treat (ITT) Population includes all subjects who were randomized and dosed. Subjects will be analyzed by assigned treatment.

The main population for efficacy will be the modified intention-to-treat population (MITT), defined as all subjects randomized, 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.

Membership in the analysis populations will be determined before study unblinding.

12.2.3 Siblings

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

12.2.4 Demographic and Baseline Characteristics

12.2.4.1 Subject Disposition

Subject disposition will be summarized descriptively. The number and percentage of subjects randomized, completed, and withdrawing, along with reasons for withdrawal, will be tabulated overall, and by treatment group. The number of subjects in each analysis population will be reported.

The number and percentage of subjects receiving study drug following the protocol specified dose escalation procedure and stable dosing regimen will be tabulated by treatment group. Line listings will be prepared for all subjects not following the planned dosing schedule, showing all doses and dose changes occurring.

Other disposition and study conduct information, including major protocol violations will be listed. Duration of the follow-up period will be tabulated.

12.2.4.2 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

Demographic and baseline characteristics will be summarized descriptively for each treatment group and overall.

Treatment group comparisons will be made using analysis of variance for continuous measures and the chi-square test for categorical measures. These analyses will be conducted on the Safety Population.

Medical history information will be presented in listings.

12.2.5 Efficacy Analyses

The primary analysis population for the efficacy analysis will be the MITT population defined in Section 12.2.2. Analyses for the primary and secondary efficacy outcome variables will also be done on the ITT population. No adjustment for multiplicity will be made. All data will be included in data listings.

For efficacy analyses the first statistical test performed for each primary and secondary outcome measure will be the comparison between the active and placebo groups, that is, the two highest tolerated active dose groups will be combined. In addition, all active doses combined as well as each individual dose will be compared to placebo.

A dose will be considered "not-tolerated" if more than 50% of subjects in that dose cohort do not tolerate the treatment. A lack of tolerability on a subject level is defined as a subject who lowers, suspends, or stops dosing due to gastrointestinal tolerability related to LUM001.

12.2.5.1 Efficacy Variables

The primary efficacy endpoint is the mean change from baseline to Week 13 in pruritus as measured by ItchRO observer (ItchRO(Obs)). The average daily score will be calculated using the 7 days pre-treatment for baseline, and the last 7 days of treatment for Week 13. Secondary efficacy endpoints include mean change from baseline to Week 13 in fasting serum bile acid level and liver enzymes (ALP, ALT, GGT and bilirubin (total and direct)).

The primary assessment of pruritus in this study will be 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 study period for 13 weeks. 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. A daily score

is the higher of the scores from the morning and evening ItchRO, 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 Week 13 average daily ItchRO score is defined as the average daily ItchRO score in the week consisting of the 7 days immediately prior to the Week 13 visit.

The additional questions included in the ItchRO that are not scored, will be tabulated overall and by treatment group.

Exploratory efficacy endpoints include:

- Mean change from baseline in fasting serum bile acid level at Weeks 4 and 8
- Mean change from baseline for liver enzymes (ALT, ALP, GGT) at Weeks 4 and 8
- Mean change from baseline in pruritus as measured by the average daily ItchRO(Obs) at Weeks 5, and 8. The average daily score will be calculated using the 7 days prior to each visit.
- Mean change from baseline in pruritus as measured by the average daily ItchRO(Pt) at Weeks 5, 8, and 13. The average daily score will be calculated using the 7 days prior to each visit.
- Mean change from baseline for other biochemical markers of cholestasis [total and direct bilirubin, total cholesterol, low-density lipoprotein cholesterol (LDL-C)] at Weeks 4, 8 and 13
- Responder analysis: pruritus response rates as measured by ItchRO (Observer ItchRO and patient ItchRO) at Weeks 5, 8 and 13.
- Mean change from baseline in the clinician administered pruritus scale, at Weeks 2, 4, 8 and 13
- Mean change from baseline in bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)] at Weeks 4, 8 and 13

Change from baseline to Week 13 in:

- PedsQL [PedsQL core module, PedsQL multidimensional fatigue module, and PedsQL family impact module]
- Patient Impression of Change (PIC)
- Caregiver Impression of Change (CIC)
- Caregiver Global Therapeutic Benefit (CGTB) assessment
- Xanthoma severity as measured by clinician xanthoma scale

If a caregiver is not compliant with the ItchRO(Obs) at Week 13, 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.

12.2.5.2 Primary efficacy analysis

The change from baseline in pruritus as measure by the ItchRO(Obs) will be displayed for each treatment group by study visit, using summary statistics including the number of observations, the mean, median, standard deviation, minimum and maximum. Differences from baseline will be calculated and summarized as above, with a 95% confidence interval for the mean.

The difference between treatment groups in change from baseline to Week 13 in the average daily ItchRO(Obs) scores will be evaluated using an ANCOVA model with treatment and baseline average daily ItchRO(Obs) score as a covariate. For efficacy analyses, the first statistical test performed for each primary and secondary outcome measure will be the comparison between the two highest tolerated active dose groups combined and placebo, where the definition of what is a tolerated dose is given earlier. In addition, all active doses combined as well as each individual dose will be compared to placebo.

Where sample size allows, treatment effects over time will be examined using methods appropriate for repeated observations.

12.2.5.3 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 analyzed using the chi-square test. They will be summarized by frequencies and percents, overall, and by treatment group. P-values from the secondary and exploratory efficacy analyses will be interpreted as hypothesis generating and not definitive.

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.

12.2.6 Safety Analyses

Safety analyses will be performed on the Safety Population.

12.2.6.1 Safety Assessments

The following assessments will be used to monitor safety:

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

12.2.7 Planned Method of Analysis

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

12.2.8 Safety Analysis

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

12.2.8.1 Adverse Events

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

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

12.2.8.2 Laboratory Tests

Clinical laboratory (chemistry panel, complete blood count (CBC) with differential, coagulation, lipid panel, cholestasis biomarkers, fat soluble vitamins, and urinalysis parameters) test parameters will be listed for individual subjects and summarized using descriptive statistics by study visit and treatment group. Change 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, where normal ranges for this population are outlined in the SAP. Changes within a treatment group for selected safety measures will be assessed at Weeks 2, 4, 8, 13 and final study evaluation visit using methods to be specified in the SAP prior to unblinding the data.

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

12.2.8.3 Physical Exams, Vital Signs and Weight/Height Measurements

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

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

12.2.8.4 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.

12.2.8.5 Study Drug Exposure

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

12.2.9 Additional Analyses

Additional analyses may be performed to explore both safety and efficacy measures collected in this study. The precise methods and analyses will be determined after the database is locked and the blind is broken. Thus all such analyses will be interpreted cautiously and not used for formal inference, although inferential statistics may be used as part of the data summary.

13 INVESTIGATOR'S REGULATORY OBLIGATIONS

13.1 Informed Consent

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

The Investigator is responsible for obtaining written informed consent/assent from the subject and/or their legally acceptable representative(s). Before any 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 already 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 serious adverse events occurring at the study center and other adverse event reports received from the Sponsor or designee, in accordance with local procedures.

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

13.4 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 Lumena Pharmaceuticals LLC; it shall not be disclosed to others without written consent of Lumena Pharmaceuticals LLC; 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 Lumena Pharmaceuticals LLC, 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 Lumena Pharmaceuticals LLC, 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 at 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.

15 REFERENCES

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16 APPENDICES

16.1 Schedule of Procedures

Study Period	Screening	Treatment Period									Follow Up
		Dose Escalation[1]						Stable Dosing			
Study Week	≤ -4	0	1	2	3	4	5	6	8	13 (or Early Term[10])	17 [11]
Study Day	-28 to -1	0	7	14	21	28	35	42	56	91	119
Window (in days)[1]		0	(±2)	(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)
Informed Consent	X										
Eligibility Assessment (Inclusion/Exclusion)	X										
Demographics	X										
Medical History	X										
Physical Exam	X	X		X		X			X	X	
Body Weight & Height	X	X		X		X			X	X	
Vital Signs[2]	X	X		X		X			X	X	
ECG	X									X	
Serum Pregnancy Test (if indicated)[3]	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	
JAGGED1 Genotyping (if needed)	X										
Plasma Sample for LUM001		X[a]		X[a]		X[a]			X[a]	X[a]	
Urinalysis[4]	X	X[b]		X		X			X	X[b]	
Urine Pregnancy Test (if indicated)[3]		X		X		X			X	X	
Caregiver ItchRO/Patient ItchRO	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d, e]	
Clinician Scratch Score	X	X		X		X			X	X	
Clinician Xanthoma Assessment		X								X	
PedsQL		X								X	

Study Period	Screening	Treatment Period									Follow Up
		Dose Escalation[1]						Stable Dosing			
Study Week	≤ -4	0	1	2	3	4	5	6	8	13 (or Early Term[10])	17 [11]
Study Day	-28 to -1	0	7	14	21	28	35	42	56	91	119
Window (in days)[1]		0	(±2)	(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)
Randomization[7]	X										
Patient[8]/Caregiver Impression of Change										X	
Caregiver Global Therapeutic Benefit										X	
Study Drug Supplied		X		X		X			X		
Study Drug Adherence Assessment				X		X			X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[9]			X		X		X	X			X

1. Dosing begins on Study Day 1 (Week 0); subjects should be dosed for at least 7 days at each assigned dose level, if tolerated. In the event that a clinic visit or phone contact does not occur according to the Schedule of Procedures Study Day, the Dose Escalation schedule should be as follows:
   - Week 1 (Phone Contact): Dose-escalate to Dose Level 2 at Study Day 8 if no tolerability issues; if any dose intolerance, phone contact must be made prior to changing dose level
   - Week 2 (Clinic Visit): Must return to clinic by Study Day 16 (within 2 days of scheduled visit) to receive additional study drug supplies
   - Week 3 (Phone Contact): Dose-escalate to Dose Level 4 at Study Day 22 if no tolerability issues; if any dose intolerance, phone contact must be made prior to changing dose level
   - Week 4 (Clinic Visit): Must return to clinic at Study Day 30 (within 2 days of scheduled visit) to receive additional study drug supplies
   - Week 5 (Phone Contact): Dose-escalate to Dose Level 5 at Study Day 36 if no tolerability issues; if any dose intolerance, phone contact must be made prior to changing dose level; subject should remain at Dose Level 5 for this period, or the highest tolerated dose below Dose Level 5
2. BP, HR, temperature, respiration rate
3. Females of childbearing potential, defined as onset of menses
4. See Table 1 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. Randomization will occur during the Screening Period, after eligibility criteria have been met, ~7 days prior to Baseline Visit
8. Applies only to subjects 9 yrs of age or older
9. Subjects must be available to receive a phone call from study staff
10. Subjects who withdraw early should be encouraged to complete all evaluations at this visit
11. Subjects who enroll in an extension study will be followed at Week 17 under the extension study's protocol.

a. At Weeks 2, 8 and 13 blood will be drawn approximately 4 hours post dosing for drug level analysis. At Week 4, blood will be drawn approximately 2 hours post-dosing for drug level analysis.
b. At the indicated visits during the Treatment Period, oxylate will be part of the urinalysis
c. ItchRO training and dispensing of the diary (eDiary/paper) will occur at the Screening visit
d. ItchRO compliance will be assessed at each visit/phone contact after the ItchRO has been dispensed
e. ItchRO will be collected at Week 13 or final Study Visit (if Early Term)

☐ Clinic Visit
☐ Phone Contact

16.2 List of Laboratory Analytes

Screening Tests

JAGGED1 Genotyping (if indicated)

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

Coagulation

aPTT (sec)

PT (sec)

INR

Clinical Chemistry

Sodium

Potassium

Chloride

Bicarbonate

Total protein

Albumin

Calcium

Phosphorus

Glucose

BUN

Creatinine

Uric Acid

Total bilirubin

Direct bilirubin

Alkaline phosphatase

AST (SGOT)

ALT (SGPT)

GGT

Lipid Panel[1]

Total cholesterol

LDL-C (direct)

HDL-C

Triglycerides (TG)

Cholestasis Biomarkers[1]

Serum bile acids

7α hydroxy-4-colesten-3-one (C4)

Fat Soluble Vitamins[1]

25-hydroxy vitamin D

Retinol

Retinol binding protein

Tocopherol (α)

Total lipids

Urinalysis

pH

Specific gravity

Protein

Glucose

Ketones

Bilirubin

Occult blood and cells

Nitrite

Urobilinogen

Leukocyte esterase

Microscopic examination[2]

Oxylate[3]

LUM001 Drug Levels

LUM001 in plasma

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

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 Alagille Syndrome Diagnostic Criteria

Major clinical criteria/features for Alagille syndrome include: cholestasis, consistent cardiac, renal, vascular, ocular, skeletal involvement, or characteristic "Alagille" facies.

ALGS Family History[a]	Paucity	JAGGED1 or NOTCH2 mutation	# Major Clinical Criteria needed for Diagnosis
Present or Absent	Present	Identified[b]	Any or no features
None (proband)	Absent or unknown	Identified	1 or more features
None (proband)	Present	Not identified[c]	3 or more features
None (proband)	Absent or unknown	Not identified	4 or more features
Present	Absent or unknown	Identified	Any or no features
Present	Present	Not identified	1 or more features
Present	Absent or unknown	Not identified	2 or more features

[a]Family history = ALGS present in a first degree relative

[b]Identified = JAGGED1 or NOTCH2 mutation identified in clinical laboratory

[c]Not identified = Not identified on screening, or not screened for

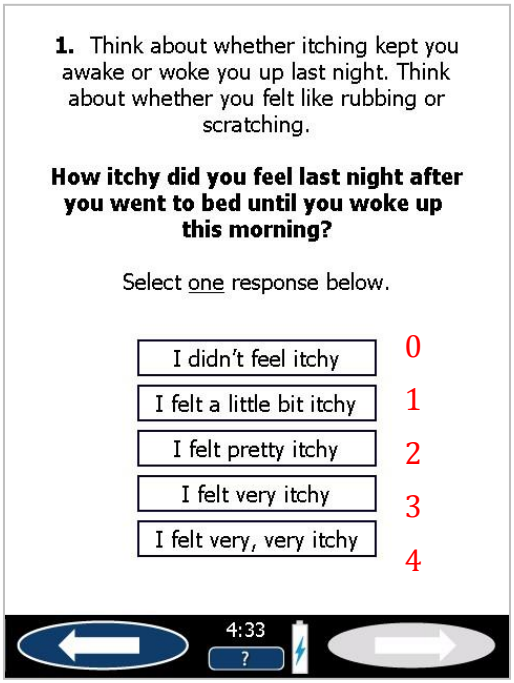
16.4 Itch Reported Outcome Instrument (ItchRO™)

Many of the ALGS subjects in this study are expected to be between the ages of 12 months and 10 years 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 (PRO) instrument 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.

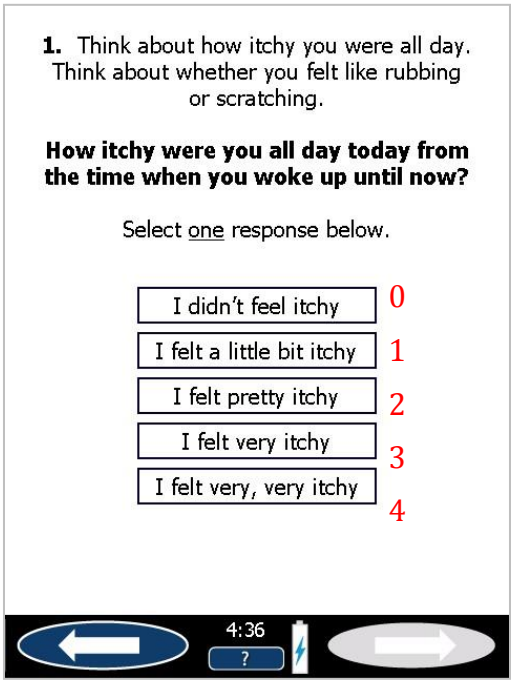
16.4.1 Patient Itch Reported Outcome Instrument, ItchRO(Pt)™

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.

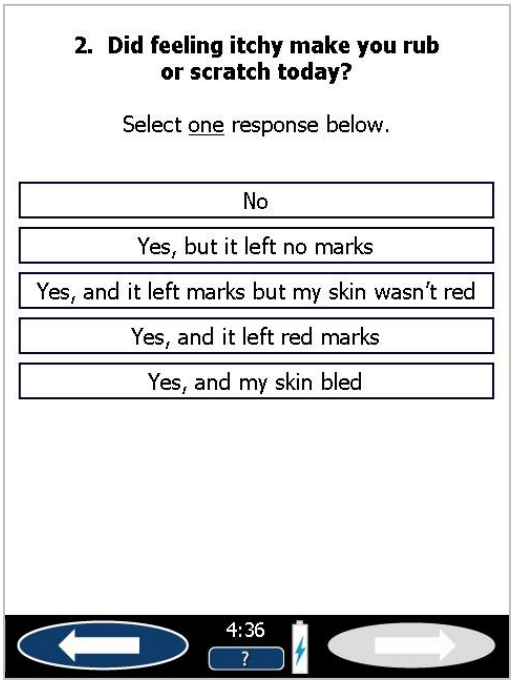


If the patient selects "I didn't feel itchy at all" the diary is complete, if not the following screens will be shown on the eDiary:

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.

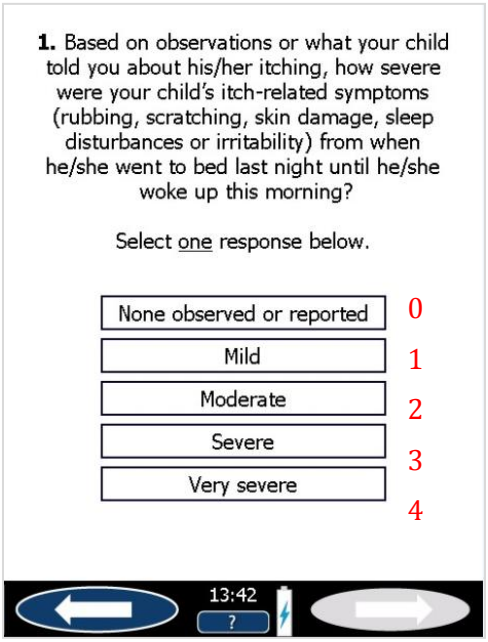


If the patient selects "I didn't feel itchy" the diary is complete, if not the following screen will be shown on the eDiary:

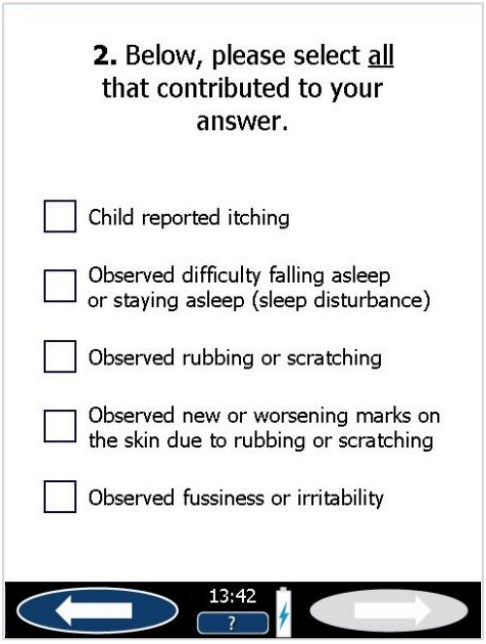


16.4.2 Observer Itch Reported Outcome Instrument, ItchRO(Obs)™

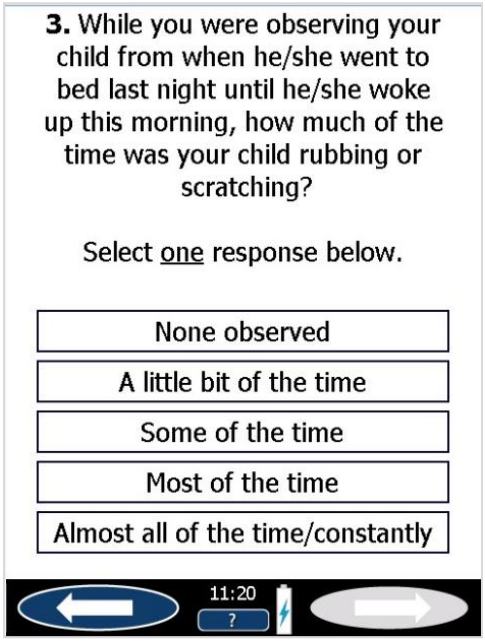
A screen shot from the ItchRO(Obs) **morning report** is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) morning report score is 0 and the maximum score is 4.



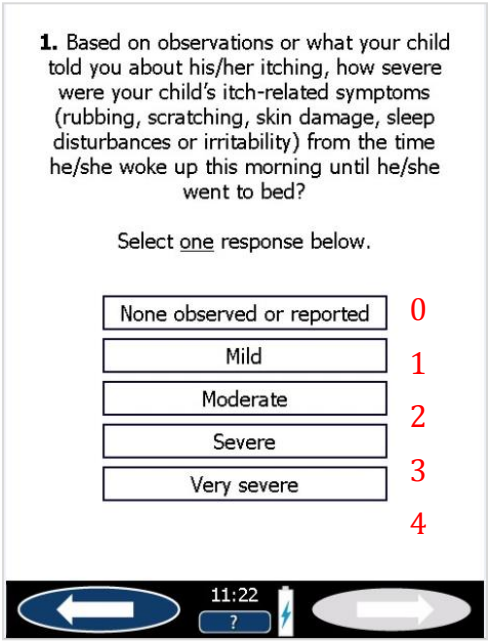
If the caregiver selects "None observed or reported" the diary is complete, if not the following screen will be shown on the eDiary:



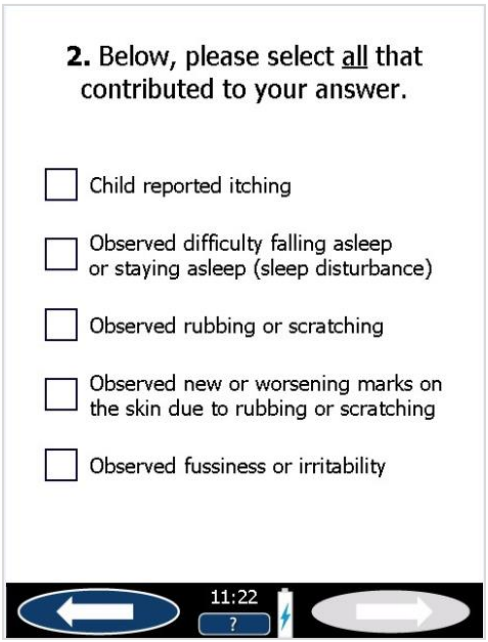
All caregivers will also be required to answer the following question on the ItchRO(Obs) **morning report**:



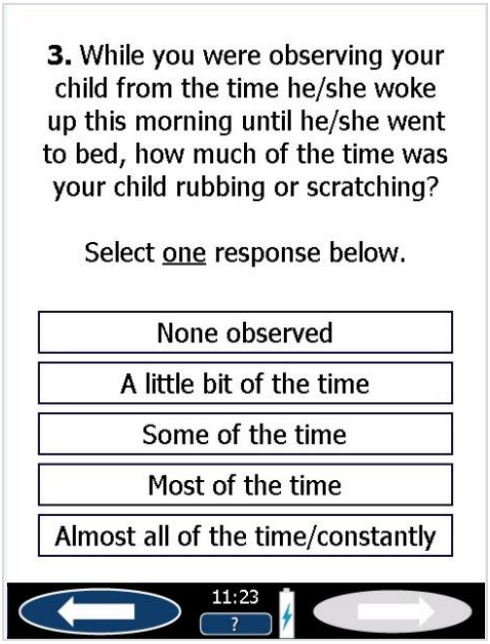
A screen shot from the ItchRO(Obs) **evening report** is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) evening report score is 0 and the maximum score is 4.



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



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



16.5 Clinician Scratch Scale

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

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

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

16.6 Clinician Xanthoma Scale

This scoring scale was originally developed to assess xanthomas before and after surgical intervention in children with ALGS (Emerick & Whitington, 2002).

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

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

In the study in which this scale was used to assess xanthomas before and after surgical intervention in children with ALGS (Emerick & Whitington, 2002), "minimal" xanthomas represented fewer than 20 scattered individual lesions, "moderate" represented more than 20 lesions that did not interfere with or limit activities, "disfiguring" represented large numbers of lesions that by their large numbers or size caused distortion of the face or extremities, and "disabling" represented xanthomas that interfered with function (such as hand use or ability to walk) because of excess size or number.

16.7 Pediatric Quality of Life Inventory (PedsQL™)

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

Pediatric HRQoL measurement instruments must be sensitive to cognitive development and must include both child self-report and parent proxy-report. Accordingly, the PedsQL consists of developmentally appropriate forms for children ages 1-12 months, 13- 24 months, 2-4, 5-7, 8-12, and 13-18 years. Pediatric self-report is measured in children and adolescents ages 5-18 years, and parent proxy-report of child HRQOL is measured for children and adolescents ages 12 months to 18 years.

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

16.7.1 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-Infant-(1-12Months) - United States/English - Mapi.
PedsQL-Infant-(1-12Months)_AU1.0_eng-USori.doc

PedsQL 3

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 13-24 months)

DIRECTIONS

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

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

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

PedsQL-Infant(13-24Months) - United States/English - Mapi.
PedsQL-Infant(13-24Months)_AU1.0_eng-USori.doc

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-Infant(13-24Months) - United States/English - Mapi.
PedsQL-Infant(13-24Months)_AU1.0_eng-USori.doc

PedsQL 3

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

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

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

PedsQL-Infant(13-24Months) - United States/English - Mapi.
PedsQL-Infant(13-24Months)_AU1.0_eng-USori.doc

16.7.3 Parent Report for Toddlers (ages 2-4)

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

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

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

PedsQL 2

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

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

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

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

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

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

16.7.5 Parent Report for Children (ages 8-12)

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

PedsQL 4.0 - Parent (8-12) Not to be reproduced without permission 01/00

PedsQL-4.0-Core PC - United States/English
PedsQL-4.0-Core-PC_AU4.0_eng-USori.doc

16.7.6 Parent Report for Teenagers (ages 13-18)

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

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

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-4.0-Core - United States/English - Mapi.
PedsQL-4.0-Core-YC_AU4.0_eng-USori.doc

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-4.0-Core - United States/English - Mapi.
PedsQL-4.0-Core-YC_eng-USorl.doc

PedsQL 3

How much of a problem is this for you?

Not at all

Sometimes

A lot

PedsQL 4.0 - (5-7)

PedsQL-4.0-Core - United States/English - Mapi.
PedsQL-4.0-Core-YC_eng-USorl.doc

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

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

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

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

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

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

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

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

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

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

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

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

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

ID# _____

Date: _____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

Instructions for interviewer:

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

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

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

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

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

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

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

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

PedsQL 2

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

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

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

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

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

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

PedsQL 3

How much of a problem is this for you?

Not at all

Sometimes

A lot

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

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

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

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

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

16.7.17 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

16.8 Patient Impression of Change (PIC)

The Patient Impression of Change (PIC) is designed to assess the subject's perception of his/her itching and his/her xanthomas at the end of study drug treatment compared to his/her itching and his/her xanthomas 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 screening visit, at the Week 13 visit.

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)

16.9 Caregiver Impression of Change (CIC)

The Caregiver Impression of Change (PIC) is designed to assess the caregiver's perception of the subject's itch related symptoms and xanthoma severity at the end of study drug treatment compared to his/her itch related symptoms and xanthoma severity prior to the start of treatment with study drug. The CIC will be completed by all caregivers at the Week 13 visit.

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 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)

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

☐ Much better (1)

☐ Better (2)

☐ A little better (3)

☐ No change (4)

☐ A little worse (5)

☐ Worse (6)

☐ Much worse (7)

16.10 Caregiver Global Therapeutic Benefit (CGTB)

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

The questions are designed for self-administration. Question 1 uses a 5-point scale in which 1 designates the best outcome and 5 designates the worst outcome. Question 2 is based on the opinion of the caregiver.

CGTB

1. 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)

2. What treatment do you think your child received in this study?

☐ Placebo drug
☐ Active drug (LUM001)

16.11 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)].