ITCH Manual of Operations

Table of Contents

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

CHAPTER 2. STUDY ADMINISTRATION

2.1 Study Personnel

2.2 Pre-Study Documentation Required

2.3 Study Start-Up Process

2.4 Study Documentation and Storage

2.5 Chapter References

2.5.1 LUM001-301 ITCH Pre- Study Questionnaires
2.5.2 Site Contact and Shipment Information Form
2.5.3 Lumena Regulatory Documents Guidelines (USA)
2.5.4 Statement of Investigator (1572 Form)
2.5.5 Certification/Disclosure Form (Financial Disclosure by Clinical Investigator
2.5.6 Investigator Site File Index
2.5.7 Protocol Signature Page
2.5.8 Investigator Brochure Signature Page
2.5.9 LUM001-301 ITCH Site Readiness Guide (also known as Eight Steps for Obtaining the "Green Light"

CHAPTER 3. STUDY ROSTER

3.1 Description

3.2 Chapter References

3.2.1 Study Directory
3.2.2 DSMB Roster (found in the DSMB report)

CHAPTER 4. STUDY OVERVIEW

4.1 Background and Rationale

4.2 Objectives

4.3 Investigational Plan

4.4 Efficacy Evaluations

4.5 Chapter References

4.5.1 ITCH Study Protocol Number LUM001-301
Protocol Amendment 3: February 11, 2015

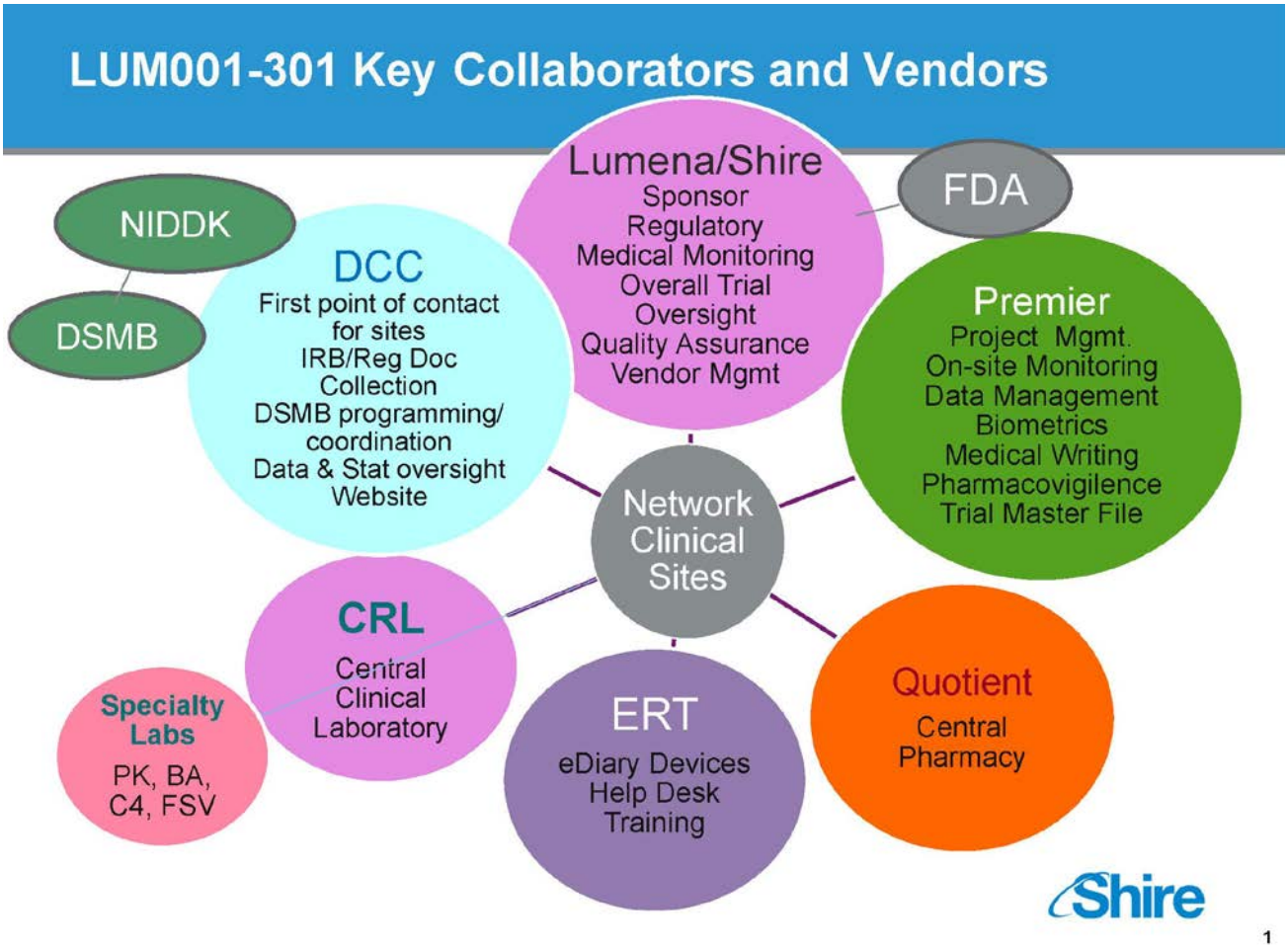
CHAPTER 1. STUDY ORGANIZATION AND RESPONSIBILITIES

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

ChiLDReN
Childhood Liver Disease Research Network



1.1 Background

Shire is developing LUM001 (also referred to as SHP625) to address the progressive liver damage and the debilitating symptoms associated with a number of rare diseases that cause impaired bile flow and retention of bile in the liver and the body. Note: Lumena Pharmaceuticals, the original Sponsor of the ITCH study, was acquired by Shire in June 2014. LUM001 works by preventing recycling of bile acids back to the liver, thereby reducing bile acid accumulation, improving liver function and potentially relieving the extreme itching associated with the disease.

The **Chi**ldhood **L**iver **D**isease **R**esearch **N**etwork (ChiLDReN) is a collaborative team of doctors, nurses, research coordinators, medical facilities and patient support organizations. The ChiLDReN Network was developed to support the discovery of new diagnostics, etiologic, and treatment options for children with liver disease, and those who undergo liver transplantation. The ChiLDReN Network is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a division of the National Institutes of Health.

The ITCH study was developed through a collaborative effort between Lumena Pharmaceuticals and the ChiLDReN Network protocol operations committee. The primary objective of the study is to evaluate the safety and tolerability of LUM001 in pediatric subjects with ALGS and to evaluate the effect of LUM001 versus placebo on pruritus, serum bile acids associated with ALGS, and other biochemical markers of cholestasis and liver disease.

1.2 Study Roles and Responsibilities

Shire is the Sponsor of the ITCH study and will be working with several key collaborators in the conduct of the study. Their specific roles and responsibilities in the conduct of the ITCH study are listed below.

1.2.1 Shire

- Study sponsor and responsible for the overall study conduct and execution in accordance with
  - Good Clinical Practice (GCP)
  - All applicable regulatory requirements
  - Project Timelines
  - LUM001 Development Plan
- Medical Monitoring
- Primary contact with FDA, Health Canada, and all other applicable regulatory agencies
- Manage CRO, vendors, and consultant collaborations
- Review Trial Master File (TMF) – including site level regulatory documents
- Co-Monitor alongside Premier's CRA's
- Provides study drug to central pharmacy

1.2.2 Premier Research

Premier Research is a contract research organization (CRO) and provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

- Project Management
  - Manage study timelines and deliverables
  - Co-develop study tools (manual of operations, communication plan, monitoring plan, etc.) with the DCC and Shire
  - Review site level regulatory documentation
- Maintain Trial Master File (TMF)
- Perform routine on site monitoring to ensure compliance with Good Clinical Practice (GCP)
- Provide routine screening and enrollment reports
- Develop and maintain database
- Design EDC system, provide system support and training
- Generate data queries
- Biometrics
- Medical Writing

1.2.3 ERT

ERT is a global company specializing in clinical services and customizable medical devices to biopharmaceutical and healthcare organizations

- Develop and provide ITCH-RO eDiary devices
- Provide training and help desk support
- Managed by Shire

1.2.4 CRL

Clinical Reference Laboratory is a privately held clinical testing laboratory offering leading edge services in the areas of Global Clinical Trials, Wellness, Molecular Diagnostics, Insurance Risk Assessment, and Drugs of Abuse Testing.

- Central laboratory services
- Provide protocol-specific lab kits and shipping materials
- Analyze and report routine clinical laboratory test results
- Coordinate distribution of samples to specialty labs (PK, BA, C4, and FSV)
- Managed by Shire

1.2.5 Specialty Laboratories

- Huntingdon Life Sciences

- LUM001 – PK
- Cincinnati Children's Hospital Medical Center Mass Spectrometry Lab
  - Serum Bile Acids 7 C4
- Children's Hospital Colorado CTRC Core Lab
  - Fat Soluble Vitamins
- Baylor College of Medicine Medical Genetics Laboratory
  - JAGGED1

1.2.6 Quotient Clinical (Quotient)

The Central Pharmacy for the ITCH study.

- Prepare and provide randomized, double-blind study drug for each enrolled subject
- Randomize subjects according to study code
- Maintain study blind
- Managed by Shire

1.2.7 The ChiLDReN Data Coordinating Center

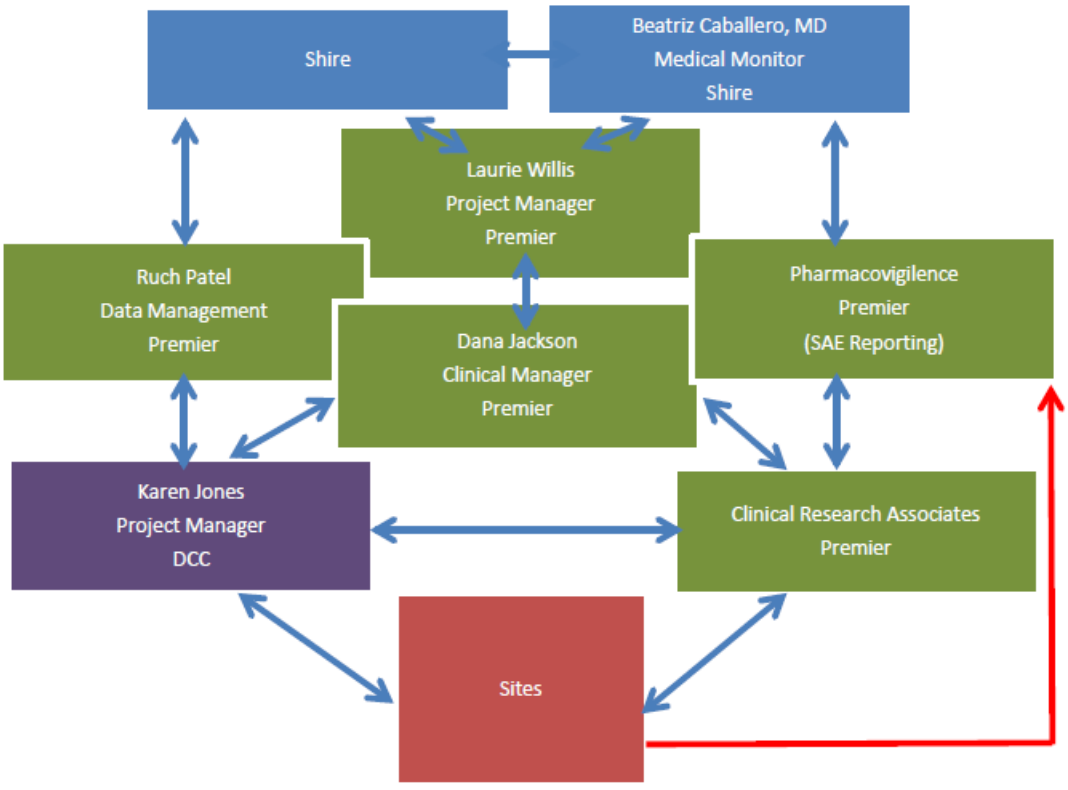
The ChiLDReN Data Coordinating Center (DCC) is located at the University of Michigan in Ann Arbor and operates under the direction of Principal Investigator John C. Magee, M.D. The DCC provides support for the network of clinical sites studying biliary atresia, cholestatic liver disease and liver disease in cystic fibrosis in infants and children. The DCC collaborates with clinical investigators on study design and analysis, and provides leadership in the operational aspects of studies, including database development, data entry and management, data collection forms and processes, manuals of operations, and adherence with regulatory and protocol requirements.

- First point of contact along with Premier CRA's
- Co-develop study tools (manual of operations, communication plan, monitoring plan, etc.) along with Premier and Shire
- Manage regulatory document and IRB submission process
- Review the Trial Master File (TMF)
- Co-Monitor along with Premier CRA's
- Grant Administration
- Maintain study website
- Participate in eCRF user acceptance testing (UAT)
- Provide EDC system support
- Review data queries
- Prepare briefing materials and coordinate DSMB A meetings

1.2.8 The ChiLDReN Clinical Sites

One of the primary goals of the Network is to provide a way for patients to join with doctors and researchers by participating in research studies. Thirteen ChiLDReN clinical network sites will be participating in the ITCH study. Study sites, under the direction of the Principal Investigator (PI), will conduct the study in accordance with the Code of Federal Regulation (CRF) Title 21 and by the standards of Good Clinical Practice/International Conference on Harmonization (GCP/ICH)

- Coordinate, develop, submit, and obtain Institutional Review Board (IRB) approval for the protocol, as well as, its subsequent amendments. In addition, approval of the informed consent/assent documents
- Maintain the study binders and other study related documents. Use the correct version of the protocol.
- Assure that the study is conducted according to the protocol
- Identify, recruit, screen, and enroll subjects
- Protect subject's rights
- Obtain informed consent/assent from each subject and/or their legally acceptable representative(s)
- Collect study data and follow subject through study completion
- Collect specimens per protocol and follow appropriate procedures for collections
- Prepare and send required reports to the Data Coordinating Center (DCC) and the Sponsor.
- Communicate questions, concerns, and/or observations through the appropriate channels



1.2.9 Data Safety and Monitoring Board (ChiLDReN DSMB)

The Data and Safety Monitoring Board (ChiLDReN 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.

1.3 Chapter References

Related references are located on the ChiLDReN Network website:
Log into https://childrennetwork.org/ is required.

1.3.1 Sponsor, Collaborator, and Vendor Address Information

1.3.2 ChiLDReN Network Directory by Site

1.3.3 LUM001-301 ITCH Site Numbering Convention

1.3.4 Investigational New Drug (IND) Memo

1.3.5 Health Canada Approval Letter

1.3.6 ITCH May Proceed Letter

1.3.7 ITCH Sponsorship Letter

CHAPTER 2. STUDY ADMINISTRATION

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2.1 Study Personnel

Prior to the start of this study, the Investigator must supply the Sponsor and the ChiLDReN Network Data Coordinating Center (DCC) with a list of the name(s) 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 study duties are recorded on a Sponsor approved Delegation of Site Responsibilities Form.

Pre-Study information provided to the Sponsor and the DCC will be captured on the LUM001-301 ITCH Pre-Study Questionnaire and the Site Contact and Shipment Information Form, both referenced at the end of this document.

2.2 Pre-study Documentation Required

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

1. Completed and signed Statement of Investigator (Form FDA 1572)
2. Principal Investigator and Sub-Investigator required documents
   - Medical License consistent with Section 1 of 1572 and CV
   - Financial Disclosure
   - Curriculum Vitae (signed and dated within 2 years of signature date on 1572)
   - ICG GCP Training certificate (current within last 2 years or in past 5 years with refresher course in last 2 years

3. Signed and dated Protocol Signature Page
4. Signed and dated Investigator Brochure Signature Page
5. Letter of approval from the IEC/IRB for both protocol and consent/assent forms
6. Copy of the IEC/IRB-approved written informed consent/assent forms, and any other written information and/or advertisement to be used
7. IEC/IRB membership list or compliance certification letter
8. Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, including a copy of the CLIA laboratory certificate or waiver and a copy of IATA certification for individuals that will ship study samples.
   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
9. List of normal laboratory values (where applicable)

In addition each site must have an approved contract and budget

2.3 Study Start-Up Process

The documents, registrations, and training that are required prior to the Site Initiation Visit and that are required for a center to be approved for a "Green Light"

- Registration with the Central Laboratory is complete and access to the lab's website has been issued
- All required Regulatory and Essential Documents have been accurately completed and submitted to the DCC
- Individuals listed on the 1572 and the lead Study Coordinator have evidence of having completed GCP training (within the last 2 years)
- The local pharmacy has been notified about the study and confirmed that they are ready to receive study drug
- Individuals who will use the DataLabs EDC system to enter, review, or approve data have completed DataLabs training
- DataLab accounts have been registered and activated
- The lead study coordinator has registered for an EPX account and completed ERT (ediary) training
- The lead study coordinator has confirmed receipt of study supplies needed to enroll the first subject

A site initiation visit will be scheduled when the eight steps for obtaining the "Green Light" have been completed. Final confirmation from the DCC, Lumena, and Premier that all requirements have been met, will result in a "Green Light" letter that is sent to the site indicating that approval has been granted to begin consenting and screening subjects.

2.4 Study Documentation and Storage

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 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 DCC.
- 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 DCC 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 DCC.

2.5 Chapter References

Related references are located on the ChiLDReN Network website.
Log into https://childrennetwork.org/ is required.

2.5.1 LUM001-301 ITCH Pre-Study Questionnaire

2.5.2 Site Contact and Shipment Information Form

2.5.3 Lumena Regulatory Document Guidelines (USA)

2.5.4 Statement of Investigator (1572 form)

2.5.5 Certification/Disclosure Form (Financial Disclosure by Clinical Investigator)

2.5.6 Investigator Site File Index

2.5.7 Protocol Signature Page

2.5.8 Investigator Brochure Signature Page

2.5.9 LUM001-301 ITCH Site Readiness Guide (also known as Eight Steps for Obtaining the "Green Light")

CHAPTER 4. STUDY OVERVIEW

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

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4.1 Background and Rationale

Alagille syndrome (ALGS) is a 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.

In patients with ALGS, impairment of the egress of bile acids from the liver leads to cholestasis, hepatocellular injury and damage, and progressive liver disease that may ultimately lead to the need for liver transplantation. Patients with ALGS and cholestatic liver disease frequently present with pruritus. 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.

LUM001 is an inhibitor of ASBT/IBAT (apical sodium-dependent bile acid transporter; ileal bile acid transporter) preventing recycling of bile acids. Bile acids are excreted in feces instead of being returned to the liver. Reducing the reuptake of bile acids by inhibition of the main bile acid transporter (ASBT) in the gut has the potential to improve liver function, slow disease progression, reduce itching, and improve the quality of life.

The ITCH (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) study is proposed to evaluate LUM001 for the indication of reduction in pruritus in patients with Alagille syndrome.

4.2 Objectives

The objectives of the ITCH 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.

4.3 Investigational Plan

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:

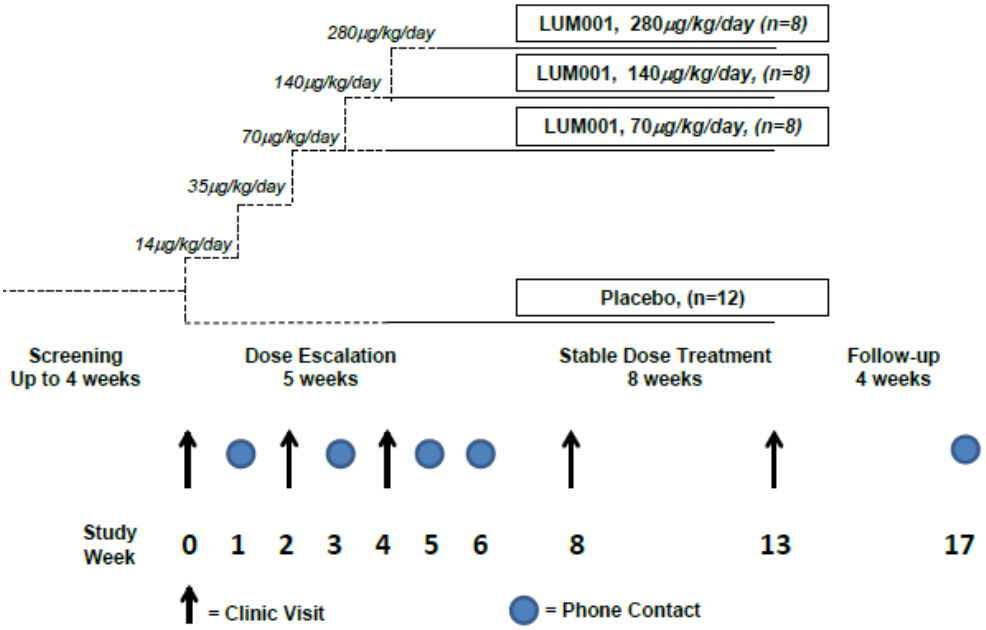
- LUM001 low dose: 70 µg/kg/day (maximum daily dose of 5 mg/day)
- LUM001 mid dose: 140 µg/kg/day (maximum daily dose of 10 mg/day)
- LUM001 high dose: 280 µg/kg/day (maximum daily dose of 20 mg/day)
- Placebo

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.

This is a multi-center study to be conducted in approximately 14 clinical sites which are part of The Childhood Liver Disease Research Network. Approximately 36 ALGS subjects are planned to be enrolled.

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.

Study Design for LUM001-301



Each subject who provides informed consent/assent will complete all screening activities in ≤ 4 weeks. Eligible subjects will be randomized during the screening period, approximately 7 days prior to Study Day 0 (baseline visit). Dosing will occur over a 13 week 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 1: Dose Escalation Regimens**

Dose Escalation Period	Dose Level	Assigned Treatment Group (µg/kg/day)				Dosing Duration
		Placebo	Low Dose LUM001 70 µg/kg/day	Mid Dose LUM001 140 µg/kg/day	High Dose 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.

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.

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

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 study 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.

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.

4.4 Efficacy Evaluations

- Primary Efficacy Evaluation
  - Comparison to placebo of mean changes from baseline to Week 13 in pruritus as measured by the average daily score for the ItchRO(Obs)
    - A daily score is the highest score between the morning and evening reports

        - The average daily score is the sum of all daily scores divided by the number of days the ItchRO was completed
        - 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 Evaluation
    - Comparison to placebo of mean changes from baseline to Week 13 in
        - Fasting serum bile acid level
        - ALT, ALP, GGT, and bilirubin (total and direct)
        - 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

4.5 Chapter References

A Reference Protocol is located on the ChiLDReN Network website:
Log into https://childrennetwork.org/ is required.

4.5.1 ITCH Study Clinical Protocol Number LUM001-301 Protocol Amendment 3: February 11, 2015

4.5.2 Protocol Notes to File

CHAPTER 5. SCREENING AND RECRUITMENT

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5.1 Population

The study population will consist of male and female subjects between the ages 12 months through 18 years of age, inclusive. All racial and ethnic groups will be included.

5.2 Screening and Recruitment Plan

Subjects will be recruited from patients evaluated at, referred to, and followed at the Childhood Liver Disease Research Network (ChiLDReN) study sites. In addition, IRB approved recruitment materials can be used to make people who are interested in these disorders aware of this study. Recruitment materials for the ITCH study will be developed and provided by the Sponsor. Copies can be found on the ChiLDReN website.

Recruitment is competitive and each clinical site is expected to enroll 2 -3 subjects.

The Principal Investigator (PI) or Clinical Research Coordinator (CRC) will recruit the subject and/or their legally acceptable representative(s) during clinic visits. They will discuss the study design, benefits and possible risks with the family. Printed information about the study and the informed consent form will be given to the family and questions about the study will be answered.

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 forms (ICF), and all other applicable subject information and/or recruitment materials.

The Institutional Review Board IEC approved consent forms will include:

- Purpose of the trial.
- Research procedures used in the trial.
- Responsible parties and investigators.
- Potential benefits.
- Risks of participation.
- Right to refuse to be in the study.
- Right to withdraw from the study under no penalty.
- Contact numbers and information about the responsibility for injury and payment for medical care.

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. The ID number will be a 6 digit, unique number comprised of the 3 digit center ID and a 3 digit sequential number. 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.

5.3 Eligibility

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

5.3.1 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 of the protocol.
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 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.

5.3.2 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

Note: 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 rescreen at a later date. Screening procedures should be repeated at that time.

5.4 Exception to the Eligibility Criteria

Whenever the answer to an inclusion criterion is no or to an exclusion criterion is yes (even if the condition for the exclusion is fulfilled), an exception will be required.

To be eligible to participate in the study, candidates must meet the protocol's inclusion and exclusion criteria. Any exception to these criteria must be reviewed and approved in writing by the Sponsor prior to a candidate's participation in the study.

To discuss an exception to the study's eligibility criteria, contact your CRA or the Sponsor Medical Monitor directly. The Sponsor Medical Monitor and ChiLDReN's Protocol Chair will review each exception on a case-by-case basis. Exceptions will be agreed upon by the Medical Monitor and the Protocol Chair prior to issuing a decision on a candidate's eligibility.

5.5 Details about Certain Eligibility Criteria

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	3 or more

		identified[c]	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

5.6 Subject Screening/Enrollment Log

The Subject Screening/Enrollment Log is an essential document that records all subjects who have been consented, screened and/or enrolled into the study. If a subject is not enrolled in the study then the reason for exclusion will be captured. The screening log demonstrates the lack of bias in the selection of subjects and the investigator's attempt to enroll a representative sample of subjects.

The following information will be recorded on the Subject Screening/Enrollment Log:

- Subject Number/Initials
- Screening Date
- Informed Consent/Assent Obtained
- Enroll Date
- Complete/Terminate Early
- Completion/Termination Date
- Reason for Early Termination

The Subject Screening/Enrollment Log should be kept up to date throughout the study and be kept in a secured location with procedures in place regarding who has access to remove and under what conditions.

5.7 Chapter References

Related references are located on the ChiLDReN Network website:
Log into https://childrennetwork.org/ is required.

5.7.1 Subject Screening/Enrollment Log

5.7.2 Confidential Subject Identification List

5.7.3 ITCH Social Media (Possible ITCH Trial Facebook Post)

5.7.4 ITCH Study Newsletter Article

5.7.5 ITCH Banner – Horizontal

5.7.6 ITCH Banner – Vertical

CHAPTER 6. INFORMED CONSENT

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

6.1 Informed Consent Document

Lumena and the Childhood Liver Disease Research Network (ChiLDReN) have developed informed consent and assent templates.

The Data Coordinating Center (DCC) will provide protocol-specific informed consent and assent templates for all ChiLDReN study sites. Each site will customize the templates and receive approval from their study site's human subject protection committee. IRB/IEC approved versions of the informed consent documents should be sent to the DCC (children-essentialdocs@umich.edu) and the Sponsor.

The written informed consent should be brief and written in plain language so that a subject who has not graduated from high school can understand the contents

6.2 Obtaining Informed Consent

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 their legally acceptable representative(s). 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, if applicable, based on age and local IRB requirements. The person who conducted the informed consent discussion (not necessarily an Investigator) should also sign and date the ICF/IAF. The original signed ICF/IAF should be retained in accordance with institutional policy. Subjects and/or their legally acceptable representative(s) will be given a copy of their ICF, and IAF.

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

6.3 Re-Consent

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.

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.

6.4 Clinical Trial Liability Insurance

As the regulatory agent (IND holder), Lumena Pharmaceuticals maintains human clinical trial liability insurance coverage for all clinical protocols conducted by the company. Certificates evidencing such insurance will be made available for examination upon request. Any claims made on this insurance will be directed to the Insurer(s) and will be managed by the Insurer(s) thereafter per standard clinical trial insurance protocols.

6.5 Health Insurance Portability and Accountability Act (HIPPA) Compliance

At most study sites, a HIPAA form is presented to a potential subject for signature, in addition to the informed consent form, unless the necessary assurances are incorporated into the informed consent form. The HIPAA form describes subject and data confidentiality associated with the study.

6.6 Chapter References

Related references are located on the ChiLDREN website:
Log into https://childrennetwork.org/ is required.

6.6.1 Informed Consent Assent Log
6.6.2 ITCH Study Clinical Protocol Number LUM001-301, Protocol Amendment 3: February 11, 2015, Section 7.1.7
6.6.3 Lumena Memo Re: Clinical Trial Liability Insurance
6.6.4 Consent to Take Part in a Research Study (Parental)
6.6.5 Consent to Take Part in a Research Study (Subject Age 18)
6.6.6 Documentation of Assent from Pediatric Subjects (Recommended for Ages 7-11)
6.6.7 Documentation of Assent from Pediatric Subject (Recommended for Ages 12-17)

CHAPTER 7. STUDY DRUG

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

7.1 Preparation and Dispensing

The dose of study drug (LUM001 or placebo) will be prepared for each subject by a central pharmacy based on the subject's weight at screening. 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.

LUM001 is a powder that is dissolved with an appropriate diluent in order to administer the study drug as an oral solution. The matching placebo contains the diluent with no active ingredient. Diluent will be added by the central pharmacy pharmacist prior to shipping study drug vials to the site. Once study drug has been added to the diluent the resulting solution is stable at temperatures ranging from 2-8^{o}C. Subjects/caregivers will be instructed to store study drug vials in a provided vial container holder in the refrigerator for security and safety of the drug.

At each clinic visit, study drug will be dispensed to subjects/caregivers along with a dosing pack which will contain a supply of syringes. Subjects/caregiver's will be instructed to use a new syringe each day, for each dose. 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. Study drug should be administered approximately at the same time every day.

Study staff will need to document the receipt, dispensing and return/destruction of study drug supplies provided by the Sponsor on the appropriate forms.

7.2 Dose Escalation

Eligible subjects will be randomized to one of the 4 treatment groups. There is a 2:1 randomization ratio between LUM001 and placebo.

- LUM001 low Dose, 70 µg/kg/day (up to a maximum daily dose of 5 mg/day)
- LUM001 mild Dose, 140 µg/kg/day (up to a maximum daily dose of 10 mg/day)
- LUM001 high Dose, 280 µg/kg/day (up to a maximum daily dose of 20 mg/day)
- Placebo

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

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). 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 mild 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 4.

Table 1: Dose Escalation Regimens

Dose Escalation Period	Dose Level	Assigned Treatment Group (µg/kg/day)				Dosing Duration
		Placebo	Low Dose LUM001 70 µg/kg/day	Mid Dose LUM001 140 µg/kg/day	High Dose 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.

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.

7.3 Stable Dosing Period

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

7.4 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 study 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.

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 each day indicating the date

and time they took their study medication, the time they ate breakfast and the dose and batch number of study medication.

7.5 Concomitant Medications

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. 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. No new medications used to treat pruritus may be added during the course of the study.

7.6 Chapter References

Related references are located on the ChiLDREN website:
Log into https://childrennetwork.org/ is required.

7.6.1 Master Study Drug Accountability Log

7.6.2 Individual Subject Study Drug Accountability Log

7.6.3 Subject Diary Booklet for Study Drug

7.6.3.1 LUM001-301 Week 1
7.6.3.2 LUM001-301 Week 2
7.6.3.3 LUM001-301 Week 3
7.6.3.4 LUM001-301 Week 4
7.6.3.5 LUM001-301 Week 5-12

7.6.4 Investigator's Brochure

CHAPTER 8. STUDY PROCEDURES

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

8.1 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	
Randomization[7]	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)
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

8.2 Study Visits

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 3-4 week dose escalation period followed by an up to 9-10 week period at a stable dose), and a follow-up period of up to 4 weeks. Study visits will include both clinics visits and telephone contact visits.

8.2.1 Screening Period (Day -28 to Day -1)

Screening evaluations will be performed from Day -28 to Day -1.

Subjects and caregivers will be required to read, sign, and date an IEC/IRB approved consent/assent form before any screening tests or assessments are performed.

During the consenting process, sexually active female subjects of childbearing potential must be made aware that they will be required 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.

After obtaining informed consent (and assent when appropriate), subjects and/or caregivers will:

- Provide demographic data (gender, age, and race)
- Provide a medical history (including current medical problems and symptoms)
- Provide a list of current concomitant medications

Subjects will:

- Undergo a physical examination including body weight, height, and vital signs
- Have a 12-lead electrocardiogram (ECG)
- Have blood and urine samples taken for clinical laboratory testing
  - CBC with Differential
  - Coagulation
  - Chemistry Panel
  - Lipid Panel*
  - Cholestasis Biomarkers*
  - Fat Soluble Vitamins*^
  - Urinalysis

Note: Please refer to Lab Manual for specific order of collection and reference documents "Lab Sample Priority" and "Min/Max Samples"
Subjects are required to fast at least 4 hours (only water) permitted prior to collection

^Blood samples must be drawn before administration of vitamin supplementation

- Females who are of childbearing potential (defined as onset of menses) will have a serum pregnancy test
- In the absence of documented JAGGED1 or NOTCH2 mutation prior to screening, genetic testing will be performed for JAGGED1. Results of genetic screen will not impact continued participation in the study. However, if a subject/caregiver does not wish to have the genetic testing, they are no longer eligible for the study.

In addition:

- 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 scores
- The physician will provide an assessment of itch severity using the clinician administered clinician scratch scale during screening.

Upon completion of the screening visit, (Form A) "Notification and Screening" must be completed and emailed to the Central Pharmacy along with the estimated date of 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 under a new screening identification number.

8.2.2 Pre-Randomization

Once eligibility has been confirmed, and a Baseline Visit (Day 0) has been scheduled, (Form B) "Instruction to Randomize and Prepare Dose" must be completed and emailed to the Central Pharmacy. Form B should be sent 4-7 days prior to the Baseline visit. Study drug will be sent to the site within 2-4 days. Subjects will be randomized approximately 7 days prior to the Baseline/Day 0 Visit.

8.2.3 Treatment Period

8.2.3.1 Baseline Clinic Visit (Day 0)

Subjects will be assessed to confirm study eligibility and:

- Undergo a physical examination including body weight, height, and vital signs
- Have blood and urine samples taken for clinical laboratory testing
  - CBC with Differential
  - Coagulation
  - Chemistry Panel
  - Lipid Panel*
  - Cholestasis Biomarkers*
  - Fat Soluble Vitamins*^
  - Plasma Sample for LUM001
  - Urinalysis

Note: Please refer to Lab Manual for specific order of collection and reference documents "Lab Sample Priority" and "Min/Max Samples"
****Subjects are required to fast at least 4 hours (only water) permitted prior to collection***
^Blood samples must be drawn before administration of vitamin supplementation

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- The clinician scratch scale will be administered
- The degree and severity of xanthomatosis will be evaluated
- The PedsQL questionnaire will be administered
- Concomitant medications will be review and updated

Adverse/Serious Adverse Events will be recorded

Female subjects who are of childbearing potential (defined as onset of menses) will have a urine pregnancy test at all clinic visits prior to dispensing study drug.

Study drug, dosing instructions, and diaries for Weeks 1 and 2 will be supplied at the baseline visit (Day 0) to eligible subjects. Dosing will begin on Study Day 1 and will continue at the initial dose for at least 7 days. The dose will escalate to Dose Level 2 on Study day 8, if there are no tolerability issues. If there is any dose intolerance, phone contact must be made prior to changing dose level.

Schedule a date for a Week 1 phone call to assess tolerability in accordance with the protocol.

8.2.3.2 Week 1 Phone Contact (Day 7 ±2)

Reference: Optional language template for telephone contact visits

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- Concomitant medications will be review and updated
- Adverse/Serious Adverse Events will be recorded

Review dosing instructions and confirm dose escalation to Dose Level 2 on Study day 8 if there are no tolerability issues.

Schedule a date and time for the next clinic visit based on the protocol specific window for each visit and specific blood sample collection requirements.

8.2.3.3 Week 2 Clinic Visit (Day 14 ±2)

- Undergo a physical examination including body weight, height, and vital signs
- Have blood and urine samples taken for clinical laboratory testing
  - CBC with Differential
  - Coagulation
  - Chemistry Panel
  - Lipid Panel*
  - Cholestasis Biomarkers*
  - Plasma Sample for LUM001°
  - Urinalysis

Note: Please refer to Lab Manual for specific order of collection and reference documents "Lab Sample Priority" and "Min/Max Samples"
****Subjects are required to fast at least 4 hours (only water) permitted prior to collection***
°Blood sample will be drawn approximately 4 hours post dosing for drug level analysis

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- The clinician scratch scale will be administered
- Concomitant medications will be review and updated
- Adverse/Serious Adverse Events will be recorded
- Collect all returned study drug vials, perform accountability and compare amount of drug return against study drug diary

Female subjects who are of childbearing potential (defined as onset of menses) will have a urine pregnancy test at all clinic visits prior to dispensing study drug.

Study drug, dosing instructions, and diaries for Weeks 3 and 4 will be supplied at the Week 2 Clinic Visit (Day 14 ±2). Dosing will continue at the Week 3 dose for at least 7 days if tolerated. Dose will escalate to Dose Level 4 on Study day 22, if there are no tolerability issues. If there is any dose intolerance, phone contact must be made prior to changing dose level.

Schedule a date for a Week 3 phone call to assess tolerability in accordance with the protocol.

8.2.3.4 Week 3 Phone Contact (Day 21 ±2)

Reference: Optional language template for telephone contact visits

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- Concomitant medications will be review and updated
- Any adverse/Serious Adverse Events will be recorded

Review dosing instructions and confirm dose escalation to Dose Level 4 on Study day 22 if there are no tolerability issues.

Schedule a date and time for the next clinic visit based on the protocol specific window for each visit and specific blood sample collection requirements.

8.2.3.5 Week 4 Clinic Visit (Day 28 ±2)

- Undergo a physical examination including body weight, height, and vital signs
- Have blood and urine samples taken for clinical laboratory testing
  - CBC with Differential
  - Coagulation
  - Chemistry Panel
  - Lipid Panel*
  - Cholestasis Biomarkers*
  - Plasma Sample for LUM001°
  - Urinalysis

Note: Please refer to Lab Manual for specific order of collection and reference documents "Lab Sample Priority" and "Min/Max Samples"

****Subjects are required to fast at least 2 hours (only water) permitted prior to collection***

°Blood sample will be drawn approximately 2 hours post dosing for drug level analysis

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- The clinician scratch scale will be administered
- Concomitant medications will be review and updated
- Any adverse/Serious Adverse Events will be recorded
- Collect all returned study drug vials, perform accountability and compare amount of drug return against study drug diary

Female subjects who are of childbearing potential (defined as onset of menses) will have a urine pregnancy test at all clinic visits prior to dispensing study drug.

Study drug, dosing instructions, and diaries for Weeks 5 and 6 and Weeks 7 and 8 will be supplied at the Week 4 Clinic Visit (Day 28 ±2). Dosing will continue at the Week Dose Level 4 for this period or the highest tolerated dose below Dose Level 4.

Schedule a date for a Week 5 phone call to assess tolerability in accordance with the protocol.

8.2.3.6 Week 5 Phone Contact (Day 35 ±2)

Reference: Optional language template for telephone contact visits

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- Concomitant medications will be review and updated
- Any adverse/Serious Adverse Events will be recorded

Schedule a date for a Week 6 phone call to assess tolerability in accordance with the protocol.

8.2.3.7 Week 6 Phone Contact (Day 42 ±5)

Reference: Optional language template for telephone contact visits

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- Concomitant medications will be review and updated
- Any adverse/Serious Adverse Events will be recorded

Schedule a date and time for the next clinic visit based on the protocol specific window for each visit and specific blood sample collection requirements.

8.2.3.8 Week 8 Clinic Visit (Day 56 ±5)

- Undergo a physical examination including body weight, height, and vital signs
- Have blood and urine samples taken for clinical laboratory testing
  - CBC with Differential
  - Coagulation
  - Chemistry Panel
  - Lipid Panel*
  - Cholestasis Biomarkers*
  - Fat Soluble Vitamins*^
  - Plasma Sample for LUM001°
  - Urinalysis

Note: Please refer to Lab Manual for specific order of collection and reference documents "Lab Sample Priority" and "Min/Max Samples"

Subjects are required to fast at least 4 hours (only water) permitted prior to collection
°Blood sample will be drawn approximately 4 hours post dosing for drug level analysis
^Blood samples must be drawn before administration of vitamin supplementation

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed
- The clinician scratch scale will be administered
- Concomitant medications will be review and updated
- Any adverse/Serious Adverse Events will be recorded
- Collect all returned study drug vials, perform accountability and compare amount of drug return against study drug diary

Female subjects who are of childbearing potential (defined as onset of menses) will have a urine pregnancy test at all clinic visits prior to dispensing study drug.

Study drug, dosing instructions, and diaries for Weeks 9 and 10 and Weeks 11 and 12 will be supplied at the Week 8 Clinic Visit.

Schedule a date and time for the next clinic visit based on the protocol specific window for each visit and specific blood sample collection requirements.

8.2.3.9 Week 13 (or Early Termination) Clinic Visit (Day 91 ±5)

- Undergo a physical examination including body weight, height, and vital signs
- Have a 12-lead electrocardiogram (ECG)
- Have blood and urine samples taken for clinical laboratory testing
  - CBC with Differential
  - Coagulation
  - Chemistry Panel
  - Lipid Panel*
  - Cholestasis Biomarkers*
  - Fat Soluble Vitamins*^
  - Plasma Sample for LUM001°
  - Urinalysis

Note: Please refer to Lab Manual for specific order of collection and reference documents "Lab Sample Priority" and "Min/Max Samples"
Subjects are required to fast at least 4 hours (only water) permitted prior to collection
^Blood samples must be drawn before administration of vitamin supplementation
°Blood sample will be drawn approximately 4 hours post dosing for drug level analysis

- Caregiver ItchRO/ Patient ItchRO compliance will be assessed and the eDiary will be returned/collected at this visit
- The clinician scratch scale will be administered
- The degree and severity of xanthomatosis will be evaluated
- The PedsQL questionnaire will be administered
- Patient Impression of Change (PIC) assessment will be completed if subject was 9 years of age or older at the screening visit
- Caregiver Impression of Change (CIC) assessment will be completed
- Caregiver Global Therapeutic Benefit (CGTB) questionnaire will be completed
- Concomitant medications will be review and updated
- Adverse/Serious Adverse Events will be recorded
- Collect all returned study drug vials, perform accountability and compare amount of drug return against study drug diary. All study drugs (active and placebo) will be discontinued at Week 13. Complete Form D (Subject Completion or Withdrawal) and send to the IDS Central Pharmacy.

Female subjects who are of childbearing potential (defined as onset of menses) will have a urine pregnancy test.

Schedule a date for a Week 17 Follow-up phone call.

8.2.3.10 Follow-up Phone Contact (Day 119)

Reference: Optional language template for telephone contact visits

- Concomitant medications will be review and updated
- Any adverse/Serious Adverse Events will be recorded

Subjects who complete the study may be eligible for participation in an extension study of LUM001. Subjects who enroll in an extension study will be followed at Week 17 under the extension study's protocol.

8.3 Optional Visits

8.3.1 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, bile acids, other cholestasis biochemical markers, fat soluble vitamins, and drug level. In addition the following assessments should be completed:

- Caregiver ItchRO/ Patient ItchRO
- The clinician scratch scale
- The clinician xanthoma scale

- Patient Impression of Change (PIC) assessment if subject was 9 years of age or older at the screening visit
- Caregiver Impression of Change (CIC) assessment
- Caregiver Global Therapeutic Benefit (CGTB) questionnaire

Collect all returned study drug vials, perform accountability and compare amount of drug return against study drug diary. Complete Form D (Subject Completion or Withdrawal) and send to the IDS Central Pharmacy.

For safety reason, efforts must be made to follow subjects for at least 30 days following their last dose of study drug.

If a pregnancy is confirmed during the study, the subject will be immediately withdrawn from treatment with study drug and will be encouraged to complete the Early Termination procedures to the extent that study procedures do not interfere with the pregnancy. The progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion).

Initial notification about the pregnancy and follow-up information about the pregnancy outcome, including delivery or termination, will be reported on the:

- LUM001-301 Pregnancy Data Collection Form

Pregnancy reporting requirements are found in the

- Manual of Operations:

Chapter 9 Adverse Event (AE) and Serious Adverse Event (SAE) Regulatory Reporting

- Section 9.2.2 Pregnancy Reporting

8.3.2 Unscheduled Visits

If at any time during the study, the subject experiences intolerance due to the study drug, the Investigator in consultation with the Medical Monitor may choose to lower the dose of study drug down to the previously tolerated dose for the remainder of the trial. Once it is decided that the subject needs to be down titrated to the previously tolerated dose, they cannot decide to go back up to another dose. They must remain on this dose throughout the duration of the trial, or discontinue if no longer tolerated.

If at any time during the subject's participation in the study, it is determined that the subject cannot tolerate their current study drug dose, an unscheduled visit must be scheduled and communications documented between subject and Investigator with the Medical Monitor.

- Complete **FORM C** *"Dose Down Titration"*

- Send FORM C to Quotient immediately once it is known that a dose down titration will take place. This allows time for Quotient to prepare and ship the correct new lower dose.
- At the unscheduled visit, collect all returned study drug vials, perform accountability and compare drug return against study drug diary.
- A new Dosing Pack, diaries and syringes will be dispensed at this visit.

8.4 Study Instruments

Itch Reported Outcome (ItchRO™)

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

To be eligible for randomization, caregivers 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.

Clinician Scratch Scale

A clinician's assessment of pruritus will be made by the principal investigator or sub-investigator using the clinician scratch scale. This assessment will be completed 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.

Clinical Xanthoma Scale

A clinician's assessment of xanthomatosis will be made by the principle investigator or sub-investigator using the clinician xanthoma Scale. This assessment will be completed at Baseline (Day 0) and at Weeks 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 5 represents xanthomas that interfere with function (such as hand use or ability to walk) because of excess size or number (Emerick & Whitington, 2002).

Pediatric Quality of Life Inventory (PedsQL)

The PedsQL™ is a one-page questionnaire that will be administered to subjects and or caregivers at the Week 0 (baseline) and Week 13 visits using the age-appropriate PedsQL module. NOTE: The age of the subject 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. 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.

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 at the Week 13 visit by subjects who were 9 years of age or older at the screening visit.

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.

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.

8.5 Data Entry and Source Documentation

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 into the electronic case report form must be maintained and be readily available for review.

A set of worksheets has been compiled for the ITCH visits. They are intended to serve as a guide to collect the data that's pertinent to the study and to facilitate data entry into Datalabs eCRF's. Visit checklists are also incorporated into the worksheets so that sites can have comprehensive operational guidance readily available in a visit specific format. The worksheets and checklists are not meant to replace normal documentation or established procedures already in place at sites. However, they can be used as source documents or to supplement other forms customarily used at individual sites.

Data entry will be captured electronically using DataLabs eCRF. Comprehensive eCRF guidelines can be accessed through the ChiLDReN website.

8.6 Chapter References

Related references are located on the ChiLDReN Network website.
Log into https://childrennetwork.org/ is required.

8.6.1 Study Visit Worksheets

8.6.2 Subject Status Flow and Form Submission Guide

8.6.3 Optional language template for telephone contact visits

8.6.4 LUM001-301/ITCH Study: Estimated Minimum/Maximum blood/urine volumes by visit

8.6.5 LUM001-301 Laboratory testing Limited Sample Volume (Lab Sample Priority)

8.6.6 Caregiver ItchRO/Patient ItchRO

8.6.5.1 eDiary PT Training Guide

8.6.5.2 Quick Start Training Guide

8.6.5.3 Help Desk Sticker

8.6.7 Clinician Scratch Score

8.6.8 Clinician Xanthoma Assessement

8.6.9 Peds QL

8.6.10 Patient Impression of Change

8.6.11 Caregiver Impression of Change

8.6.12 Caregiver Global Therapeutic Benefit (CGTB)

8.6.13 301 Questionnaire Tool with Schedule

8.6.14 DataLabs eCRF guidelines

8.6.15 Data pro training manual

8.6.16 Form A – Notification and Screening

8.6.17 Form B – Instruction to Randomize and Prepare Dose

8.6.18 Form C – Dose Down Titration

8.6.19 Form D – Withdrawal Notification

8.6.20 LUM001-301 Pregnancy Data Collection Form

8.6.21 Central Pharmacy FAQ

8.6.22 eDiary FAQ

CHAPTER 9. ADVERSE EVENT (AE) / SERIOUS ADVERSE EVENT (SAE) / REGULATORY REPORTING

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

9.1 Definitions

9.1.1 Adverse Event

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

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

9.1.2 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.

9.1.3 Serious Adverse Event (SAE)

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 30 days after the last dose of study drug for those subjects that terminate the prior to the Week 13 visit.

Serious Adverse Event (SAE): Reporting

The investigative site is required to report any serious adverse event (SAE) within 24 hours of becoming aware of the event, directly to Premier's Global Pharmacovigilance (PV) using the following contact information as outlined on the SAE form.

Serious Adverse Events (SAEs) must be reported immediately to Premier Research via the following SAE fax line or email:

US/Canada Cases: fax 215-972-8765 or e-mail **mmands@premier-research.com**

Given that patient safety is paramount to all of our processes, a critical link in the SAE Reporting process is the confirmation of a fax transmittal of SAE forms. **This confirmation should be obtained via your receipt of a "successful fax" confirmation page from your fax machine, and this confirmation page should be filed in your study binder with the SAE form.** If the fax was not successfully transmitted, please retry. If you are still unsuccessful, call the SAE Hotline +1 215-282-5434. Please leave your name, telephone number, Sponsor, Study drug, Protocol number, Site number, Subject number and initials and the SAE event. Please state that you were unable to successfully transmit to the SAE fax number. The message will provide you with an alternative number to fax your SAE form. Please fax it to this alternative number. For Medical Monitor contact info, please refer to your study materials.

Serious Adverse Events (SAE): Updates

If there are any changes or updates for an SAE, the changes should be made on the SAE form and reported via the same process that the original SAE report was reported.

If additional information is required to process the SAE, then the site will be contacted by the Premier PV representative directly. Communication will be via telephone, fax or e-mail.

Serious Adverse Events (SAE): Narrative

Premier will write a narrative report describing the SAE. This narrative will be included as part of the information collected on the SAE form. Once a final SAE form has been generated by Premier, the Investigator will be required to sign-off on the report. A copy of the signed, final SAE form should be submitted to Premier via the same process that the original SAE report was reported.

Serious Adverse Event (SAE): Criteria

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 <u>not</u> considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is <u>not</u> considered an AE.
  Complications that occur during hospitalization <u>are</u> 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)
- <u>Important medical events</u> 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.

Serious Adverse Event (SAE): Expedited Reporting

Reporting to Regulatory Authority(ies): If an adverse event report meets the following three criteria, then the event is reportable in an expedited manner to the appropriate Regulatory Authority(ies) and to the appropriate Ethic Committee(s)/IRB(s):

- Serious
- Unexpected
- Associated with the use of the study drug

All relevant information about suspected serious unexpected adverse reactions (SUSAR) that are fatal or life-threatening is reported as soon as possible and in any case no later than seven (7) days after knowledge by Shire of such case. Relevant follow-up information is subsequently communicated within an additional eight (8) days. It is the responsibility of Shire to submit SUSAR reports to the appropriate regulatory authorities accordingly.

Reporting to the Local Institutional Review Board (IRB): All SUSAR reports will be submitted to all IRBs. For SAEs that are **not** categorized as SUSAR, the study site at which the SAE occurred is responsible for reporting of the event to their respective IRB according to their institution's guidelines. In consultation with the ChiLDReN's LUM001-301 Protocol Chair, Shire will decide if notification of an individual non-SUSAR SAE should be made to the IRBs of all participating ChiLDReN study sites.

9.1.4 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.

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

Information about adverse events (serious and non-serious) will be collected and documented on the Adverse Event Case Report Form.

Adverse Events: Severity

The Common Terminology Criteria for Adverse Events (CTCAE) grade of the event should be reported according to CTCAE Version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). 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

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)
  Note: A non-serious AE marked as "related to study drug" will NOT automatically trigger the Medical Monitor to call or email the Investigator.
- 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

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

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).

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 an 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).

9.2 Procedures for Handling Special Situations

9.2.1 Intolerance to Study Drug

Intolerance reported at any time during the study should be discussed with the Shire Medical Monitor. The Investigator should contact the Medical Monitor directly.

If a subject experiences intolerance due to gastrointestinal symptoms, the Investigator in consultation with the Shire 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. In the interim, the Investigator and Medical Monitor will decide on the best approach for continued dosing so there is not a complete interruption in study drug administration. Such determinations will be made on a case-by-case basis.

9.2.2 Pregnancy Reporting

If a subject becomes pregnant or a pregnancy is suspected during the study, the study center staff must be informed as soon as the subject or caregiver is aware of the event. In turn, the Premier PV should be notified by the site 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.

9.2.3 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.

9.2.4 Medical Monitoring & Pharmacovigilance Contact Information

[1]**Shire Medical Monitoring Contact:**	**Premier Pharmacovigilance Contact:**	**ChiLDReN Contact:**
Beatriz Caballero MD, PhD Global Development Team Lead Shire Zahlerweg 10 6300 Zug-Switzerland Office: + 41 (0)22 419 42 30 Cell: +41 (0)79711 28 15 Email: bcaballero@shire.com	Fax: 215-972-8765 e-mail: mmands@premier-research.com	Benjamin Shneider MD Protocol Chairman Texas Children's Hospital Houston, TX Phone: 832 822 3608 Benjamin.Shneider@bcm.edu

9.3 Chapter References

Related references are located on the ChiLDReN website:
Log into https://childrennetwork.org/ is required.

9.3.1 SAE Reporting and Flow

CHAPTER 11. STUDY MANAGEMENT AND MONITORING

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

11.1 Study Monitoring – On Site 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 (a Premier CRA) 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 CRA will need access to subject medical records and other study-related records needed to verify the entries on the case report forms. The CRA 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 CRA 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 CRA 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.

11.2 Site Initiation Visit

Premier Research will conduct a site SIV at all participating sites; the duration of each SIV is expected to be approximately 6 hours. A Confirmation Letter will be sent to the site prior to the scheduled visit, which will outline the date of the visit, the approximate duration of the visit, the roles/names requiring attendance (sub-investigator, study coordinator, pharmacy, and lab) confirmed and topics to be covered, with an agenda for the visit contained within the body of the letter.
The responsibilities of the CRA during the SIV include, but are not limited to:

11.2.1 Meeting with Principal Investigator (PI), Sub-Investigators *(Sub-I)*, Study Coordinators *(SC)*, Pharmacy Staff *(Pharm.)*, and Laboratory Staff *(Lab)*:

1) Detailed review of the Protocol, including:
    a. Study Drug Overview *(PI, Sub-I, SCs, Pharm.)*
    b. Inclusion/Exclusion Criteria *(PI, Sub-I, SC)*
    c. Prohibited and Concomitant Meds *(PI, Sub-I, SC)*
    d. Procedures/Assessments *(PI, Sub-I, SC, Lab)*
    e. Study Drug Administration, Dose Escalation and Stable Dosing processes, Distribution of color-coded weekly Drug Administration Diaries, vials and vial holder to subjects/caregivers. Follow up phone calls to caregiver to discuss tolerability. Notification to central pharmacy of screens, subjects planned to dose, subject status and timeframes for submitting the forms to the pharmacy *(PI, Sub-I, SC, Pharm.)*
    f. Tolerability and Stopping Rules *(PI, Sub-I, SC, Pharm.)*
2) Discuss Medical Monitoring, monitoring of liver chemistry and stopping rules ALT changes compared to baseline, Bilirubin changes, triglyceride levels, Fat soluble vitamin monitoring, stopping rules for coagulation panel, AEs/SAEs and Pregnancy Reporting *(PI, Sub-I, SC)*
3) Discuss Principal Investigator Responsibilities *(PI, Sub-I, SC)*
4) Discuss Site process/SOP for Informed Consent with particular attention paid to age-specific assents based on local, state and country laws *(PI, Sub-I, SC)*
5) Discuss Study Timelines *(PI, Sub-I, SC, Pharm., Lab)*
6) Complete Monitor Visit Log and discuss frequency, duration, attendees, expectations and activities for Routine Monitoring Visits *(PI, Sub-I, SC, Pharm., Lab)*
7) Discuss and begin/complete the Delegation of Authority (DOA) *(PI, Sub-I, SC, Pharm., Lab)*
8) Discuss eCRF, eCRF Completion Guidelines and Confirm DataLabs eCRF training/access for entry/review/approval of eCRF data *(PI, Sub-I, SC)*
9) Confirm eDiary staff training, completed qualification exam, and active EPX account (portal registration with token) (*Sub-I, SC)*
10) Discuss CRL Laboratory Manual, OASIS Access for review of online lab results and sample collection/processing/storage and shipping *(PI, Sub-I, SC, Lab)*
11) Confirm current GCP Training for all Site Staff listed on the Delegation of Authority (DOA) Log, Discuss 100% Source Document Verification and direct access to original source documentation *(PI, Sub-I, SC, Pharm., Lab)*

11.2.2 Conduct Facility Tour

1) Laboratory
    a. Confirm availability and temperature logs/monitoring for: -20°C, -70°C freezers and 2-8°C, refrigerator, confirm presence and calibration records for ambient and 2-8°C centrifuges. Confirm centrifuge capabilities are adequate for use according to the laboratory manual specifications.
    b. Confirm person who will be processing and shipping lab specimens has IATA (or equivalent certification). Confirm presence of current CLIA Waiver or CLIA Certificate for the location where Point-of Care lab tests (e.g.- Urine Pregnancy Tests) will be processed
    c. Completion of Individual Study Drug Accountability Log
    d. Confirm the site has adequate storage for used and unused Study Drug
    e. Confirm daily temperature logs/monitoring system, secured and limited study drug access, etc.
2) ECG Machine
    a. Confirm availability, current calibration records and ability to print source document reports for medical charts
3) Non-Clinical Study Supplies
    a. Inventory and confirm appropriate storage of CRL Lab Supplies, visit-specific paper diaries, eDiaries, operations manuals, etc.
4) Study Document Storage
    a. Inventory and confirm appropriate storage plan for ISF Binder, Subject/Subject Charts, Lab Reports, ICFs, etc.
5) Detailed review and reconciliation of the Investigator Site File, including but not limited to:
    a. Review IRB Approval Documentation
    b. Review and reconciliation of Essential Documents (including reconciliation 1572s, FDFs, IB Receipt Acknowledgement and Protocol Signature Pages against the eTMF) Collect a copy of any document not present in the eTMF at the time of the visit.

11.3 Interim Monitoring Frequency

The Premier CRA will generally conduct the first Routine Monitoring Visit (RMV) within ten (10) to fifteen (15) working days after the first subject is enrolled. Subsequent visits for these sites will occur approximately every 8-12 weeks depending on site enrollment. The duration of each RMV is expected to be 8-16 hours (1-2 days) onsite again depending on enrollment. Additional visits may be performed for high enrolling or struggling sites, or where there are issues of concern noted, as agreed to by Lumena. CRAs will review the amount of data in the eCRF and plan RMVs accordingly. In order to assess the need for a visit approximately 50-60 pages of data should be entered to trigger a monitoring visit. Sites are expected to complete eCRFs within 48-72 hours after the visit.

11.4 Routine Monitoring Visits

A signed RMV (Routine Monitoring Visit) Confirmation Letter will be sent to the site via email prior to the scheduled visit, which will outline the date of the visit, the approximate duration of the visit, the expected attendees and a summary of required activities for the visit.

The responsibilities of the CRA during the RMV include, but are not limited to:

- Sign the Monitor Visit Log
- Verify Enrollment Log, Informed Consent Log, Master Study Drug Accountability Log, Individual Subject Study Drug Accountability Log, DOA Log, and Confidential Subject List is current and complete. Identify the number of subjects entered, completed, withdrawn (including reason of withdrawal) and currently active. Confirm investigator involvement and determine continued acceptability of study staff and facilities
- Verify GCP Guidelines are being followed
- Verify protocol consent process is in compliance and is properly documented
- Review the ISF (Investigator Site File), including but not limited to Essential Documents and significant correspondence to ensure it is complete, current and collect copies of any updated documents
- Review Source Documents, eCRFs, ICFs, and other related source documentation for compliance with protocol and regulatory requirements.
- Assess adequacy and availability of source documentation
- Assess accurate and complete reporting of Adverse Events.
- Confirm accurate, complete, and timely reporting of all serious adverse events (SAEs) and pregnancies per Safety Management Plan
- Assist site with resolving outstanding data queries
- Review proper eDiary management, subject compliance and device supply needs.
- Review proper lab specimen collection, processing, shipment and presence of adequate lab supplies.
- Conduct relevant Study Drug management activities e.g., to verify ongoing suitability of storage facilities, assess Study Drug supply needs, perform Study Drug accountability, ensure proper completion of Master Study Drug Accountability Logs and Individual Subject Study Drug Accountability Logs, etc. Identify dosing errors, if applicable.
- Meet with Principal Investigator and/or Sub-Investigators to review any issues found in the above. A set pre-arranged appointment should be made with the PI and/or Sub-I when possible).

11.5 Site Close-Out Visit

An on-site Close-out Visit (COV) will be conducted at each site after the database has been locked; however, early closure of investigative sites may be conducted if warranted and will be decided on a case-by case basis following discussion with Lumena. A signed Confirmation Letter will be sent to the site via email prior to the scheduled visit, which will outline the date of the visit, the approximate duration of the visit, the attendees, and a summary of required activities for the visit.

The responsibilities of the CRA during the COV include, but are not limited to:

- Sign the Monitor Visit Log and verify signatures for all previous monitoring visits
- Verify Enrollment Log, Informed Consent Log, Master Study Drug Accountability Log, Individual Subject Study Drug Accountability Log, DOA Log, and Confidential Subject List are current and complete. Copies of all logs except the Confidential Subject List will be collected during this visit and originals will remain at the site in the ISF
- Reconcile the ISF with the Premier eTMF (Electronic Trial Master File)
- Retrieve a copy of the IRB/IEC site closure report
- Ensure return of all eDiaries and supplies, as applicable
- Perform 100% accountability of all Study Drug and return or destruction as appropriate
- Determine if site will return or destroy unused laboratory supplies and collect corresponding documentation
- Confirm accurate, complete, and timely reporting of all SAEs and pregnancies
- Meet with Principal Investigator and/or Sub-Investigators to review any issues found in the above (set pre-arranged appointment when possible).

11.6 Communication

The DCC for US/Canada sites will be the primary contacts for the investigative sites. Premier Research CRAs will communicate with the US and Canadian site(s) to schedule and to follow up on action items from their monitoring visits.

The DCC will maintain bi-weekly routine communication with the sites and will document communications in a Communication Spreadsheet. This communication spreadsheet will include questions to the sites regarding subjects planned to screen, enrollment, confirmed entry of all AEs and study drug compliance, and resolution of queries.

Following all site visits (SIV, RMV, and COV) the Premier CRA will send a signed PDF of the Follow-up Letter to the site via email. The Follow-up Letter will outline the date of the visit, the attendees, a brief description of what was accomplished and any significant issues.

11.7 Chapter References

Related references are located on the ChiLDREN Network website.
Log into https://childrennetwork.org/ is required.

11.7.1 Site Personnel Training Log

11.7.2 Delegation of Authority Log

11.7.3 Monitor Visit Log

11.7.4 Site Initiation Visit Confirmation Letter

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Contact Information

- Premier Research Data Management

Ruchi Patel – LUM001-301 / ITCH Lead DM

215-282-5457

ruchi.patel@premier-research.com

Jennifer Glonke – LUM001 Program Data Manager (DM)

630-821-6213

jennifer.glonke@premier-research.com

Contact Information

- Perceptive Informatics (DataLabs) Help Desk

  Study Reference Number: LUM001-301 / ITCH / PRG116

  Phone Numbers: http://www.clinphone.com/support/phones/

  Email: customercare@perceptive.com

Websites of Interest

- Self Administration Tool (SAT)

  https://edcsat.perceptive.com/satpxl2/

  Study Code: 67555

- DataLabs EDC for LUM001-301

  https://PRG116.edc.perceptive.com

- eLearning Registration

  https://elearning.datalabs.com/f30328346/

  EDC login will be provided via email when training is complete

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Requirements

- Operating System:
  - Windows XP
  - Windows Vista
  - Windows Server 2003
- Browser:
  - Microsoft Internet Explorer 8 and 9
  - Apple Safari 5
  - Mozilla Firefox 3.6 and 10
- Processor: 2 GHz or faster
- RAM: 2 GB or greater
- *Turn off pop up blocker*