CLINICAL PROTOCOL

PROTOCOL NUMBER: LUM001-304

ICONIC STUDY

LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Protocol Amendment 5.1: 08 February 2019

Protocol History

Protocol Amendment 5:	06 Nov 2017
Protocol Amendment 4:	28 Mar 2017
Protocol Amendment 3:	13 Nov 2015
Protocol Amendment 2:	08 May 2015
Protocol Amendment 1:	06 Mar 2015
Original Protocol:	20 Mar 2014

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

SPONSOR SIGNATURE PAGE

LUM001-304

ICONIC STUDY

LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BL**I**ND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN API**C**AL S**O**DIUM-DEPE**N**DENT B**I**LE A**C**ID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Protocol Amendment 5.1:	**08 February 2019**
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Sponsor:
Mirum Pharmaceuticals, Inc.
70 Willow Road, Suite 200
Menlo Park, California 94025
USA

TITLE PAGE

Study Drug:	LUM001
Protocol Number:	LUM001-304
Protocol Amendment:	5.1
Date:	08 February 2019
EudraCT No:	2013-005373-43
Study Phase:	2
Protocol Title:	Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome
Sponsor:	Mirum Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, California 94025 USA
Medical Monitor:	Cagil Ozen, MD Premier Research Office: +1 215 282 5406 Cell: +1 267 838 2380 Email: medmonitorLUM304@premier-research.com
Medical Lead:	Thomas Jaecklin, MD Mirum Pharmaceuticals AG Innere Margarethenstrasse 5 4051 Basel Switzerland Phone: +41(0) 79 850 77 18 Email: tjaecklin@mirumpharma.com
Compliance Statement:	This study will be conducted in accordance with all applicable clinical research guidelines including the International Conference on Harmonization (ICH) Guidelines for current Good Clinical Practice (GCP). Study documents will be maintained in accordance with applicable regulations.

PROTOCOL SIGNATURE PAGE

Sponsor's (Mirum) Approval

Signature:	**Date:** 10.2.2019
Thomas Jaecklin, MD SVP Clinical Development	

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

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

Clinical Study Title:

LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Protocol Number:	LUM001-304
Protocol:	Amendment 5.1
Date:	08 February 2019
EudraCT No:	2013-005373-43
Sponsor:	Mirum Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, California 94025 USA

As Agreed:

_____

Investigator's Signature **Date**

_____

Investigator's Name (Please print)

EMERGENCY CONTACT INFORMATION

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

Premier Research SAE Reporting:

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

EU/ROW sites: fax +421 2 6820 3713 or e-mail PVDS-ROW@premier-research.com

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

Cagil Ozen, MD, Medical Director

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

European and ROW sites:
Central phone number: +44 118 936 4096 (United Kingdom)

For non-emergencies, the Premier Research Medical Monitor may be contacted by e-mail: medmonitorLUM304@premier-research.com

PRODUCT QUALITY COMPLAINTS

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

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

Origin of Product Quality Complaint	E-mail Address
North and South America	medinfo@mirumpharma.com
European Union and Rest of World	medinfo@mirumpharma.com

Telephone numbers (provided for reference if needed):

Mirum, Menlo Park, CA (USA)

1-650-667-4085

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PROTOCOL AMENDMENT 5.1 SUMMARY OF CHANGES

Protocol Number: LUM001-304

Protocol Title: LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BL**I**ND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN API**C**AL S**O**DIUM-DEPE**N**DENT B**I**LE A**C**ID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Amendment: **5.1**

Date: **08 February 2019**

The LUM001-304 protocol is being amended to reflect the change of sponsorship from Lumena Pharmaceuticals LLC (Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc) to Mirum Pharmaceuticals, Inc.

The following changes have been made to the Protocol Amendment 5 (06 Nov 2017). Note that correction of typographical and grammatical errors are not captured in the below table.

Section	Description of Change
Cover page, Sponsor; Title Page, Sponsor; Sponsor Signature Page, Sponsor; Protocol Signature page, Sponsor	**Changed from:** Lumena Pharmaceuticals LLC* 300 Shire Way Lexington, MA 02421 USA *Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc **To:** **Mirum Pharmaceuticals, Inc.** **70 Willow Road, Suite 200** **Menlo Park, California 94025** **USA**
Title Page, Medical Lead; Protocol Signature page, Sponsor (Mirum) Approval	**Changed from:** **Medical Lead:** Thomas Jaecklin, MD, MSc Shire Zahlerweg 10 6300 Zug Switzerland Phone: +41(0) 79 850 77 18 Email: thomas.jaecklin@shire.com **To:** **Medical Lead:** **Thomas Jaecklin, MD, MSc** **Mirum Pharmaceuticals AG** **Innere Margarethenstrasse 5** **4051 Basel** **Switzerland** **Phone: +41(0) 79 850 77 18** **Email**: tjaecklin@mirumpharma.com **Changed from:** **Sponsor Medical Monitor:** Susanne Schmidt, MD **To:** **Medical Monitor:** **Cagil Ozen, MD**
Emergency Contact Information	Changed the Premier Medical Monitor from Susanne Schmidt to Cagil Ozen.

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

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1-800-828-2088

To:

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

Mirum, Menlo Park, CA (USA)
1-650-667-4085</td></tr>
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1 SYNOPSIS

Sponsor	Mirum Pharmaceuticals, Inc.
Protocol Number	LUM001-304
Protocol Title	Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome
Study Phase	2
Indication	Treatment of Patients with Alagille Syndrome (ALGS)
Objectives	• To evaluate the long-term safety and tolerability of LUM001 in children with ALGS. • To evaluate the effect of LUM001 on serum bile acid levels in children with ALGS. • To evaluate the effect of LUM001 on biochemical markers of cholestasis and liver disease in children with ALGS. • To evaluate the effect of LUM001 on pruritus in children with ALGS. • To evaluate the long-term effect of LUM001 in children with ALGS 48 weeks of treatment. <u>Objectives of Long-term Optional Follow-up Treatment Period (After Week 48):</u> • To offer eligible subjects treated in the LUM001-304 study continued study treatment after Week 48 until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication. • To explore twice a day (BID) dosing regimen and higher daily dosing of LUM001. • To obtain safety and efficacy data in subjects treated long term on LUM001 including genotyping characteristics. • To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma. • To assess palatability of the LUM001 formulation.
Study Design	This is a long-term, open-label study with a double-blind, placebo-controlled, randomized drug withdrawal period in children with ALGS designed to evaluate the safety and efficacy of LUM001. The study is divided into 6 parts: a 6-week open-label dose escalation period at doses up to 400 µg/kg/day, a 12-week open-label stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, a 26-week long-term stable dosing period at doses up to 400 µg/kg/day, a 52-week optional follow-up treatment period, and a long-term optional follow-up treatment period for eligible subjects who choose to stay on treatment with LUM001. During this long-term optional follow-up period, subjects may have their dose of LUM001 increased to a maximum of 800 µg/kg/day (400 µg/kg BID), based on efficacy (sBA level and ItchRO Observer [Obs] score) and safety assessment. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication. Subjects who do not consent to Protocol Amendment 4 will continue their treatment as outlined in Protocol Amendment 3.
Number of Subjects	Approximately 30 subjects will be enrolled in this study.
Study Population	<u>Inclusion Criteria</u> To participate in this study, subjects must meet all of the following criteria:

	1. Male or female between the ages of 12 months and 18 years inclusive. 2. Diagnosis of ALGS based on the diagnostic criteria. 3. Evidence of cholestasis (one or more of the following): a. Total serum bile acid >3x ULN for age. b. Conjugated 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. Females of childbearing potential must have a negative serum pregnancy test during Screening. 5. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and for 30 days following the last dose of study drug, must agree to use acceptable contraception during the trial. 6. Subject is expected to have a consistent caregiver(s) for the duration of the study. 7. Informed consent and assent (per IRB/IEC) as appropriate. 8. Access to phone for scheduled calls from study site. 9. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study. 10. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the eDiary software. 11. 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 (maximum possible reports = 14 per week). 12. Average daily score >2 on the Itch Reported Outcome (ItchRO™) questionnaire (maximum possible daily score of 4) for two consecutive weeks in the screening period, prior to dosing. A daily score is the higher of the scores for the morning and evening ItchRO. The average daily score is the sum of all daily scores divided by the number of days the ItchRO was completed. <u>Exclusion Criteria</u> Subjects will be excluded from the study if they meet any of the following criteria: 1. Chronic diarrhea requiring ongoing intravenous fluid or nutritional intervention. 2. Surgical interruption of the enterohepatic circulation. 3. Previous liver transplant. 4. Decompensated cirrhosis (ALT >15 x ULN, INR >1.5 [unresponsive to vitamin K therapy], albumin <3.0 g/dL, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy). 5. History or presence of other concomitant liver disease. 6. 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 (eg, inflammatory bowel disease). 7. History or presence of gallstones or kidney stones. 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. Recent medical history or current status that suggests that the subject may be unable to

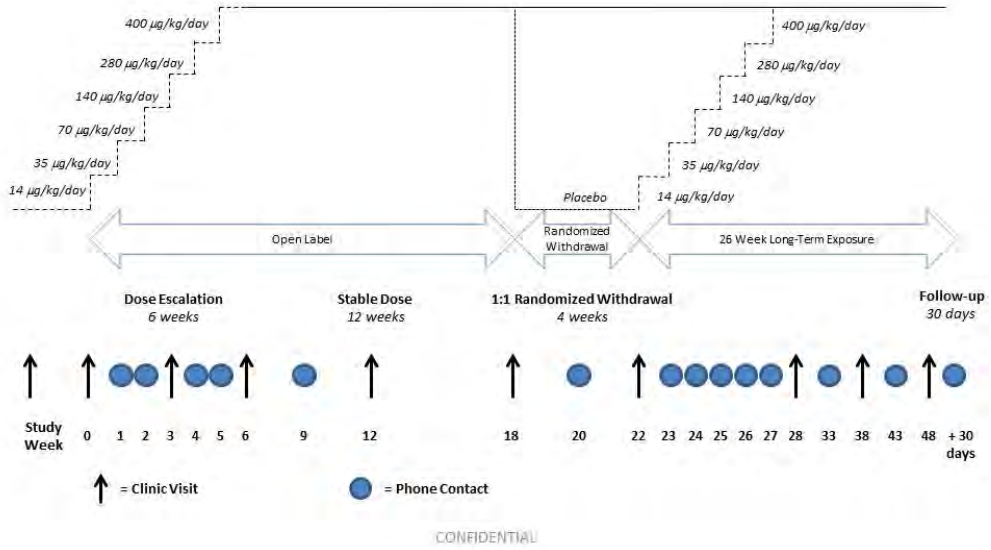
	complete the study. 11. Any female who is pregnant or lactating or who is planning to become pregnant during the study period. 12. Known history of alcohol or substance abuse. 13. Administration of bile acid or lipid binding resins within 28 days prior to screening and throughout the trial. 14. Known hypersensitivity to LUM001or any of its components. 15. Receipt of investigational drug, biologic, or medical device within 28 days prior to Screening, or 5 half-lives of the study agent, whichever is longer. 16. History of non-adherence to medical regimens, unreliability, mental instability or incompetence that could compromise the validity of informed consent or lead to non-adherence with the study protocol based upon investigator judgment. 17. Any other conditions or abnormalities which, in the opinion of the investigator or medical monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study. 18. Subjects weighing over 50 kg at screening. <u>Protocol Amendment #3: Eligible subjects for the 52-week optional follow-up period:</u> Subjects will be considered eligible for the 52-week optional follow-up treatment period if they have: • Completed the protocol through the Week 48 visit with no safety concerns. Subjects who were discontinued due to safety reasons can be rechallenged if blood tests are back to relatively normal values for this patient population and subject does not meet any of the protocol's stopping rules. The decision will be made by the investigator in consultation with the medical monitor. • Subjects who have undergone a surgical disruption of the enterohepatic circulation will not be eligible to enter into the follow up treatment period. • Subjects who were discontinued for other reasons will be considered for the 52-week optional follow-up treatment period on an individual basis. The decision will be made by the investigator in consultation with the medical monitor. <u>Protocol Amendment 4: Eligible subjects for the long-term optional follow-up period</u>: <u>Inclusion Criteria for subjects with LUM001 dosing interruption <7 days, or ≥7 days:</u> Subjects will be considered eligible for the long-term optional follow-up treatment period if they meet the following criteria: 1. The subject has either: o Completed the protocol through the Week 48 visit with no major safety concerns OR o Discontinued due to safety reasons judged unrelated to the study drug, and laboratory results have returned to levels acceptable for this patient population or individual and subject does not meet any of the protocol's stopping rules at the time of entry into the follow-up period. The decision will be made by the investigator in consultation with the medical monitor. [Subjects who were discontinued for other reasons will be considered on an individual basis.] 2. Females of childbearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at the time of entry into the long-term optional follow-up treatment period. 3. Males and females of child-bearing potential who are sexually active, or are not

	currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug, must agree and use acceptable contraception during the trial. 4. Informed consent and assent (per IRB/EC) as appropriate. 5. Access to phone for scheduled calls from study site. 6. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study. <u>Exclusion Criteria for Subjects with LUM001 dosing interruption ≥7 days :</u> All exclusion criteria mentioned for the core study apply upon entry into the long-term optional follow-up period, with the exception of exclusion criterion #18.
Treatment Groups	All subjects will receive LUM001 up to 400 µg/kg/day or a maximum daily dose of 20 mg/day. After completion of the 12-week stable dosing period, subjects will be randomized 1:1 to either a 4-week double-blind study drug withdrawal period during the study or will remain on study drug. Subjects will then enter a 26-week long-term stable dosing period and all subjects will receive LUM001 up to 400 µg/kg/day or a maximum daily dose of 20 mg/day. Subjects will be considered for a 52-week optional treatment period, if eligible, receiving up to 400 µg/kg/day, or the highest tolerated dose below the 400 µg/kg/day dose. Subjects will then be considered for the long-term optional follow-up treatment, if eligible, receiving up to 800 µg/kg/day (given as twice daily doses of 400 µg/kg), or to a maximum possible daily dose of 50 mg/day.
Study Drug Dosage and Administration	**Study Drug Administration** Subjects will receive a grape-flavored solution containing LUM001, administered orally once a day (QD) or twice a day (BID) using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the dose should be taken approximately at the same time each day for the duration of the treatment period. **QD Dosing Regimen** For QD dosing, the required dose will be delivered in 0.5 mL volume for subjects who weigh less than 10 kg and in 1.0 mL for subjects who weigh 10 kg or more. **BID Dosing Regimen** For BID dosing, the required dose is delivered in half the dosing volume: 0.25 mL BID for subjects who weigh less than 10 kg and 0.50 mL BID for subjects who weigh 10 kg or more. For subjects weighing less than 10 kg at study entry, once a weight of 10 kg is reached while in the study, the subject will be moved from 0.5 mL maximum daily dosing volume (0.25 mL BID) to 1.0 mL maximum daily dosing volume (0.50 mL BID). **Study Drug Dosage** Initially, the LUM001 dose will be administered as a daily morning dose in either a 1.0 mL or 0.5 mL solution. The dose will be increased weekly over a 6-week period <u>up to</u> 400 µg/kg/day QD or a maximum daily dose of 20 mg/day QD as follows: Week 1 Dose: 14 µg/kg/day QD Week 2 Dose: 35 µg/kg/day QD Week 3 Dose: 70 µg/kg/day QD Week 4 Dose: 140 µg/kg/day QD Week 5 Dose: 280 µg/kg/day QD

	Week 6 Dose: 400 µg/kg/day QD (maximum daily dose of 20 mg QD) Subjects will continue dosing for another 12 weeks during the stable dosing period (to Week 18) using the dose administered at Week 6, which may be 400 µg/kg/day or the highest tolerated dose below 400 µg/kg/day. At the Week 18 visit, subjects will be randomized 1:1 to continue to receive study drug or a corresponding placebo for 4 weeks (1:1 randomized double-blind withdrawal period). Following the 4-week study drug randomized withdrawal period, subjects who received placebo will receive LUM001 dosed according to a dose escalation schedule that mirrors the initial escalation (ie, the LUM001 dose will be increased weekly over a 6-week period to the maximum tolerated dose up to 400 µg/kg/day or 20 mg/day or the highest tolerated dose below the 400 µg/kg/day dose). Subjects who were randomized to receive LUM001 will undergo a simulated dose escalation to maintain the blind in the randomized withdrawal period and will continue to receive LUM001 during the long-term exposure period, at the same dose administered at Week 22. Dosing with LUM001 will continue in a 26-week long-term exposure period to complete 48 weeks of study. **Optional Follow-up Treatment Period** At Week 48, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the 52-week optional follow-up treatment period. The 3 following possible scenarios may occur: • Subjects who are eligible to roll over into the optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level. • Subjects who are eligible to roll over into the optional follow-up treatment period with a LUM001 dosing interruption of ≥7 days will be dose escalated beginning at 35 µg/kg/day and up to a maximum of 400 µg/kg/day or highest tolerated dose. • Subjects who do not wish to enter the follow-up treatment period will be contacted via telephone by the study site approximately 30 days after the last dose of study drug. **Long-term Optional Follow-up Treatment Period** Upon completion of the 52-week follow-up treatment period and/or implementation of this amendment, whichever occurs first, subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over (or enter) into the long-term optional, follow-up treatment period. The 3 following possible scenarios may occur: **Scenario 1: Subjects eligible to roll over into the long-term optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days:** • Subjects with normal sBA level AND ItchRO(Obs) score <1.5 will be maintained at the same dose level and will continue morning dosing only. • Subjects with sBA level above normal AND/OR ItchRO(Obs) score ≥1.5 will start BID dosing (afternoon dose escalation; ADE) as follows: o The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated. o The afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg.

	Scenario 2: Subjects eligible to roll over into the long-term optional follow-up treatment period with a LUM001 interruption of ≥7 days: • First, the morning dose is escalated up to 400 µg/kg/day or highest tolerated dose following a 5-week dose escalation beginning at 35 µg/kg/day. • Once the morning dose of 400 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO(Obs) score will be evaluated. o Subjects with normal sBA AND ItchRO(Obs) score <1.5 after morning dose escalation will be maintained at the same dose level and will continue morning dosing only. o Subjects with sBA above normal AND/OR ItchRO(Obs) score ≥1.5 will begin BID dosing (afternoon dose escalation) as follows: ▪ The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated. ▪ The afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg. The following parameters apply to both dosing scenarios outlined above: • The afternoon dose will only be initiated once the subject has been treated on stable morning doses for at least 4 weeks. • The sBA value used for determination of ADE eligibility will be the most recent available value collected within the prior 16 weeks. The ItchRO(Obs) score used for ADE eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 16 weeks. • The maximum daily dose will be 400 µg/kg BID, ie, 800 µg/kg/day (up to a maximum possible daily dose of 50 mg/day). **Scenario 3: Subjects who do not consent to Protocol Amendment 4 will continue their treatment as outlined in Protocol Amendment 3**.
Rationale for Dose and Schedule Selection	During the study, the study drug may be adjusted if there is a change of ≥10% in body weight since the screening visit or if there is a change of ≥10% in weight since the last weight based medication adjustment to maintain the target dose. If a subject experiences intolerance due to gastrointestinal symptoms (eg, diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator in consultation with the medical monitor may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose. The dosage of LUM001 is based upon prior experience with this investigational product in healthy volunteers and adult and pediatric subjects with hypercholesterolemia. In these subjects, with normal bile flow and without liver disease, an increase in gastrointestinal (GI) adverse events (AEs) was observed in those receiving doses above 10 mg per day. These signs and symptoms were believed to be caused by increases in the concentration of free bile acids in the lower colon. Subjects with cholestatic liver disease have reduced bile flow compared to healthy volunteers and LUM001 is likely to produce a correspondingly smaller increase in free bile acids in the lower colon. There is evidence in subjects with cholestasis to suggest that ASBT expression may be upregulated and higher ASBTi concentrations may be

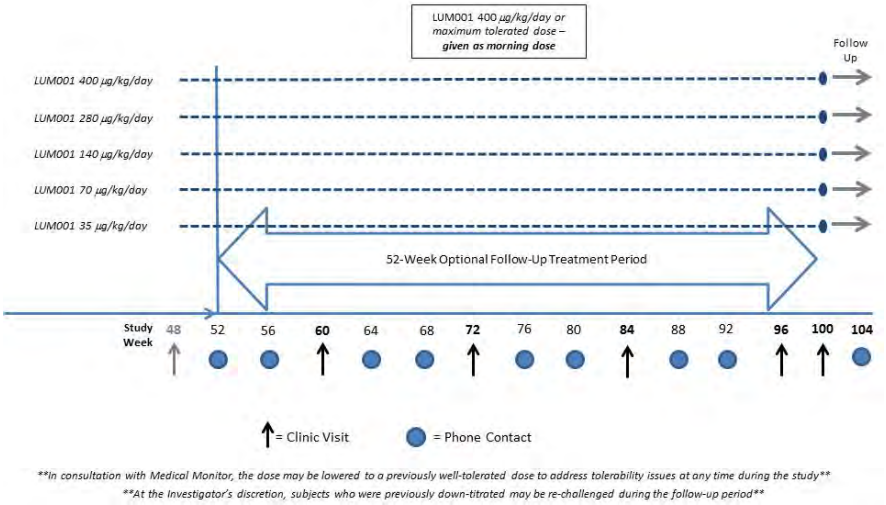
	required to achieve the desired target inhibition. Dosing in pediatric subjects will be based on the subject's weight. The appropriate dose of LUM001 for the lowering of bile acid concentrations and the reduction of pruritus in cholestatic populations is not known. Earlier studies in healthy volunteers and hypercholesterolemic subjects demonstrated that doses of 10 mg to 30 mg daily (equivalent to 140 µg/kg/day to 400 µg/kg/day for a 70 kg subject) led to a decrease in serum bile acids by >50% following 2 weeks of treatment. In previous studies with LUM001, GI-associated AEs were generally recorded in the first weeks of LUM001 dosing and then at levels similar to those in the placebo group. In a 4-week dose finding study in healthy volunteers, a dose escalation regimen was evaluated to mitigate the risk of loose stools, diarrhea and abdominal pain or cramps. When the LUM001 dose was increased after each 7-day dosing period, to a maximum of 5 mg daily, the incidence of GI-associated AEs in the LUM001 treatment arm was comparable to the reported incidence in the placebo group. To reduce the risk of loose stools, diarrhea and abdominal pain or cramps in this study, the LUM001 dose will be escalated over the first 6 weeks. Dosing will start at 14 µg/kg/day, and will then be increased at 7 day intervals to a maximum dose of 400 µg/kg/day (equivalent to approximately 20 mg daily dose in a 50 kg subject). For subjects in the long-term optional follow-up treatment period with ≥7 days since the last dose of LUM001, dosing will start at 35 µg/kg/day, and will then be increased over the first 5 weeks up to 400 µg/kg/day or to the maximum tolerated dose. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001 and allows for subjects to reach 400 µg/kg/day or a maximum tolerated dose within a 5-week period. Under Protocol Amendment 4, an afternoon dose is introduced for eligible subjects in the long-term optional follow up treatment period. LUM001 doses will be escalated over a period of 4-8 weeks up to a maximum dose of 400 µg/kg BID (or maximum tolerated dose). The afternoon dose is only initiated and escalated in subjects with elevated sBA and/or ItchRO(Obs) ≥1.5 on the maximum (or maximum tolerated) morning dose. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001. Twice daily dosing is used in this study based on the findings of a healthy volunteers study in adult males (Study SHP625-101), which demonstrated that bile acid levels in feces increase with escalating doses and twice-daily regimen of LUM001 (up to 100 mg QD and 50 mg BID). In this study, subjects who were randomized to LUM001 treatment, received 1 of 4 doses of LUM001 (10, 20, 50, 100 mg) during 7 days. No titration was used in this study. There was a dose-dependent increase in total fecal BA excretion. In addition, BID dosing (ie, 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (ie, 100 mg QD). It is therefore hypothesized that twice-daily dosing has the potential to allow for more complete target engagement throughout the day at the level of the distal ileum. The higher dosing level is also supported by favorable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (PND21 through PND63). As expected for a drug intentionally designed to be minimally absorbed, systemic LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies in adult rats. No adverse effects were observed on postnatal growth and development of offspring at the highest doses tested (200 mg/kg/day in males, 1000 mg/kg/day in females). This study was initiated in juvenile animals at PND21, which from a whole animal development perspective, is typically representative of a 2-year old child. However, given the fact that LUM001 is a minimally absorbed drug, of particular importance is the age at which the GI tract is considered functionally mature. In humans this is considered to have occurred by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs

	during the first 3 weeks of life. Therefore, results from this study can be used to support the dosing levels proposed here for children 12 months of age and older.
Study Visit Schedule and Procedures	Study activities will be conducted as described in the Schedule of Procedures. The dosage and dosing regimen of concomitant drug therapy other than that specified by the protocol should not change during the first 22 weeks of the study, with the exception of weight-based study drug adjustments and vitamin supplementation. No new medications used to treat pruritus may be added during the first 22 weeks of the study. **Synopsis Figure 1: Study Design for LUM001-304 (Up to and including Week 48)**  <u>Screening Period (Day -28 to Day -1)</u>: After obtaining informed consent (and/or assent when appropriate), demographic data (gender, age, and race) will be collected and subjects will undergo a medical history and physical examination including body weight, height, and vital signs, compilation of concomitant medications, and have blood and urine samples taken for clinical laboratory testing. For subjects who do not have documentation of a JAGGED-1 or NOTCH2 mutation, a blood sample may be obtained for genotyping. The physician will provide an assessment of itch severity using the clinician scratch score during Screening. The eDiary for assessing pruritus with the Itch Reported Outcome (ItchRO) instrument will be dispensed and subjects and caregivers will undergo training during the Screening visit. The patient/caregiver ItchROs will be completed twice daily during the Screening period to establish eligibility and a baseline score. Subjects 9 years of age and older will continue independent twice daily completion of their ItchRO. Subjects 5-8 years of age will continue twice daily completion of their ItchRO with the assistance of their caregivers, if needed. Caregivers will continue twice daily completion of their ItchRO. 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, (maximum possible reports = 14 per week). Subjects are required to discontinue bile acid resins for at least 28 days prior to screening and throughout the study. Females who are of childbearing potential will have a serum pregnancy test. Eligibility criteria will be reviewed to confirm a subject's eligibility 4-7 days prior to the Baseline Visit. <u>Dose Escalation Treatment Period (Day 0 to Week 6)</u>: At the Baseline Visit (Day 0), subjects will be assessed to confirm continued study eligibility and undergo a physical examination including body weight, height, and vital signs, and have urine and blood samples taken for hematology, chemistry, fasting lipid panel, baseline levels of bile acids and other cholestasis biochemical markers. Blood will also be collected for determination of

	baseline fat-soluble vitamins and a plasma LUM001 drug level. Compliance with ItchRO will be assessed. The clinician scratch scale, xanthoma scale, and PedsQL questionnaires will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study medication for Weeks 1, 2, and 3 will be supplied at the Baseline Visit to eligible subjects. Subjects and caregivers will continue twice daily completion of their ItchRO throughout the Dose-Escalation Treatment Period. Subjects will return to the clinic at Weeks 3 and 6 and follow-up phone calls will be made at Weeks 1, 2, 4, and 5. On clinic visit days, safety and clinical laboratory evaluations will be performed, and a physical exam will be performed (including collection of vital signs, height and weight measurements). Clinician scratch scale, adherence to study medication, and ItchRO compliance will be assessed. Concomitant medications and any adverse events will be recorded. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study drug will be supplied at Weeks 3 and 6. Stable Dosing Treatment Period (Week 7 to Week 18): Each subject will continue dosing with study drug during a 12-week Stable Dosing Treatment Period using the dose administered at Week 6, which may be 400 µg/kg/day or the highest tolerated dose below 400 µg/kg/day. Subjects 9 years of age and older will continue independent twice daily completion of their ItchRO. Subjects 5-8 years of age will continue twice daily completion of their ItchRO with the assistance of their caregivers, if needed. Caregivers will continue twice daily completion of their ItchRO. Subjects will receive a follow-up phone call at Week 9 and return to the clinic at Weeks 12 and 18. At the Week 12 and 18 visits, safety and clinical laboratory evaluations will be performed, and a physical exam will be performed (including collection of vital signs, height and weight measurements). Blood samples will be taken for fasting lipid panel, serum bile acids, fat soluble vitamins, and other cholestasis biochemical markers. Blood sampling for study drug determination may also be performed. After the baseline pharmacokinetic analysis, blood sampling for an additional pharmacokinetic analysis will be done at one additional time point at Week 12, 18, 38, or 48 – to be selected by the site/investigator (sample to be taken approximately 4 hours post-dosing). Clinician scratch scale, adherence to study medication, ItchRO compliance, and the PedsQL questionnaire will be assessed and concomitant medications and any adverse events will be recorded. In addition, at the Week 18 visit the Clinician Xanthoma Scale, Patient Impression of Change (PIC), Caregiver Impression of Change (CIC), and Caregiver Global Therapeutic Benefit (CGTB) assessments will be completed. At the Week 18 visit, subjects will also be randomized 1:1 to either continue to receive study drug or a corresponding placebo between Week 19 and Week 22. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study drug will be supplied at Week 12 and study drug (or placebo) supplied at Week 18. Double-Blind, Placebo-Controlled Study Drug Withdrawal Period (Week 19 to Week 22): Age appropriate subjects and caregivers will continue twice daily completion of their ItchRO. Subjects will receive a follow-up phone call at Week 20 and return to the clinic at Week 22. At the Week 22 visit, safety and clinical laboratory evaluations will be performed, and a physical exam will be performed (including collection of vital signs, height and weight measurements). Blood samples will be taken for fasting lipid panel, serum bile acids, fat soluble vitamins, and other cholestasis biochemical markers. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study drug will be supplied at Week 22. Clinician scratch scale, adherence to study medication, ItchRO compliance, PIC, CIC, CGTB, and the PedsQL questionnaires will be assessed and concomitant medications and any adverse events will be recorded. Long-Term Exposure Period (Week 23 to Week 48): Following the 4-week double-blind study drug withdrawal period, subjects who received placebo will once again receive LUM001 according to the schedule where the dose is increased weekly over a 6-week period up to 400 µg/kg/day or a maximum daily dose of 20 mg/day. Subjects who were randomized to receive LUM001 will undergo a simulated dose escalation to maintain the blind in the

	randomized withdrawal period and will continue to receive LUM001 during the long-term exposure period, at the same dose administered at Week 22. Subjects and caregivers will continue twice daily completion of their ItchRO throughout the long-term exposure period to the Week 48 clinic visit. Subjects will return to the clinic at Weeks 28, 38, and 48. At these visits, safety and clinical laboratory evaluations will be performed, and a physical exam will be performed (including collection of vital signs, height and weight measurements). Blood samples will be taken for fat soluble vitamins, as well as possible pharmacokinetic blood sampling for study drug determination (if not done previously at Week 12 or 18). Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Clinician scratch scale, adherence to study medication, and ItchRO compliance will be assessed. Subjects/caregivers will receive follow-up phone calls at the end of Weeks 23-27, 33, and 43. Concomitant medications and adverse events will be recorded at all clinic visits and at scheduled telephone contacts. At the investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the long-term exposure period. Additional study drug will be supplied at each clinic visit during the long-term exposure period. Week 48: Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the optional follow-up treatment period. Eligible subjects must have documented consents in order to continue in the optional follow-up treatment period. A physical exam (including collection of vital signs, height and weight measurements) will be performed. Blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids, other cholestasis biochemical markers, and possibly LUM001 drug level analysis. Female subjects who are of childbearing potential will have a urine pregnancy test. The Clinician Scratch Scale, Clinician Xanthoma Scale, and PedsQL questionnaires will be completed. The PIC, the CIC, and the CGTB assessments will be completed. Concomitant medications and adverse events will be recorded. ItchRO and study drug compliance will be assessed and all remaining study drug and study supplies will be collected. eDiaries will be returned to the site and Study drug will be discontinued at this visit if the subject chooses not to participate in the optional follow-up treatment period. Subjects who withdraw from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week 48/Study Termination visit. Follow-up Phone Call: For subjects who do not roll over into the optional follow-up treatment period, a safety follow-up phone call will be made 30 days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded. Follow-up Treatment Period (post-Week 48): **Subjects who are eligible to roll over into the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days** will be maintained at the same dose level within the 52-week Optional Follow-Up Treatment period. During this period, subjects will return to the clinic at Weeks 60, 72, 84, 96, and 100; telephone contacts will occur at Weeks 64, 68, 76, 80, 88, and 92.

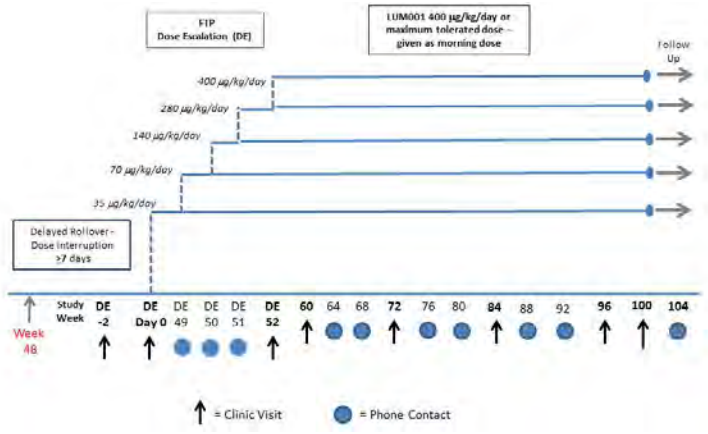
Synopsis Figure 2: 52-week Optional Follow-up Treatment (<7 days from last LUM001 dose)



Subjects with ≥7 days since last dose of LUM001 will be dose escalated up to 400 µg/kg/day or to the highest tolerated dose. The dose escalation (DE) period will proceed as follows:

- Week DE-2 Clinic Visit: obtain consent, weight, and draw blood for laboratory analyses
- Week DE 0 Clinic Visit: investigator evaluates laboratory results, study drug is dispensed, and subject begins at 35 µg/kg/day dose level (if no safety concerns)
- Week DE 49 Telephone Contact: subject escalates to 70 µg/kg/day dose level if prior dose level was tolerated
- Week DE 50 Telephone Contact: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated
- Week DE 51 Telephone Contact: subject escalates to 280 µg/kg/day dose level if prior dose level was tolerated
- Week DE 52 Clinic Visit: laboratory tests and dose escalates to 400 µg/kg/day dose (maximum daily dose of 20 mg), if prior dose level was tolerated

Synopsis Figure 3: 52-week Optional Follow-up Treatment (≥7 days from last LUM001 dose)



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

Long-term Optional Follow-up Treatment Period

Upon completion of the additional 52-week follow up treatment period and/or implementation of this amendment, whichever occurs first, subjects who are eligible to roll over onto the long-term optional follow-up treatment period will continue to receive study drug until the first of the following occurs:

i. The subjects are eligible to enter another LUM001 study,

ii. LUM001 is commercially available, or

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

Once Protocol Amendment 4 is implemented at the site, a determination about ADE will be made.

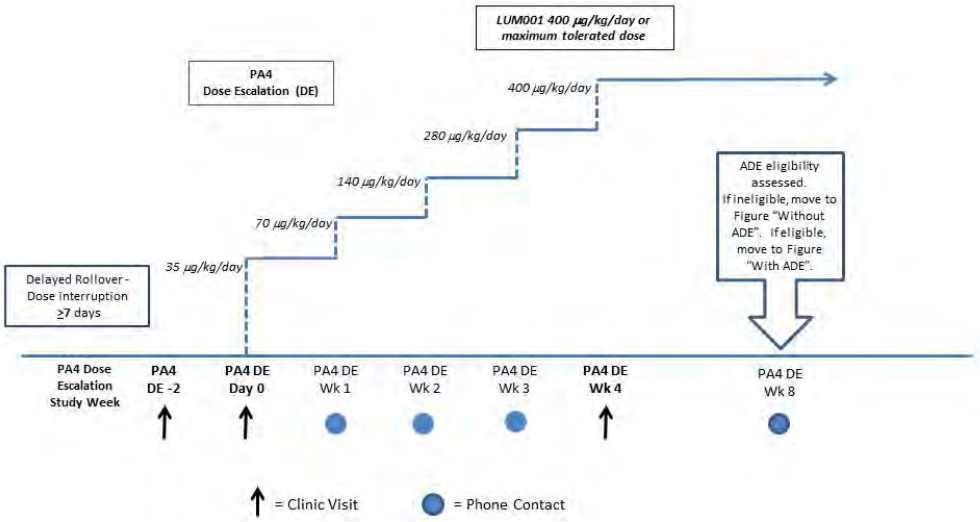
Subjects who are eligible to roll over from the 52-week follow up treatment period into the long-term optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days prior to implementation of Protocol Amendment 4 will be consented and evaluated for eligibility for ADE. Once a determination about ADE has been made, the subject will then either initiate the ADE (Synopsis Figure 6) or continue receiving the same dose of LUM001 once a day (Synopsis Figure 5), depending on whether they meet criteria for initiating ADE.

Subjects with ≥7 days since last dose of LUM001 prior to implementation of Protocol Amendment 4 who are eligible to enter the long-term optional follow-up treatment period will be dose escalated up to 400 µg/kg/day or to the highest tolerated dose beginning with 35 µg/kg/day, as outlined in Synopsis Figure 4.

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

- Protocol Amendment 4 DE-2 Clinic Visit: obtain consent, weight, and draw blood for laboratory analyses
- Protocol Amendment 4 DE Day 0 Clinic Visit: PI evaluates laboratory results, study drug is dispensed, and subject begins at 35 µg/kg/day dose level (if no safety concerns)
- Protocol Amendment 4 DE Week 1 Telephone Contact: subject escalates to 70 µg/kg/day dose level
- Protocol Amendment 4 DE Week 2 Telephone Contact: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated
- Protocol Amendment 4 DE Week 3 Telephone Contact: subject escalates to 280 µg/kg/day dose level if prior dose level was tolerated
- Protocol Amendment 4 DE Week 4 Clinic Visit: laboratory tests and dose escalates to 400 µg/kg/day dose (maximum daily dose of 20 mg), if prior dose level was tolerated
- Protocol Amendment 4 DE Week 8 Telephone Contact: eligibility for ADE will be determined.

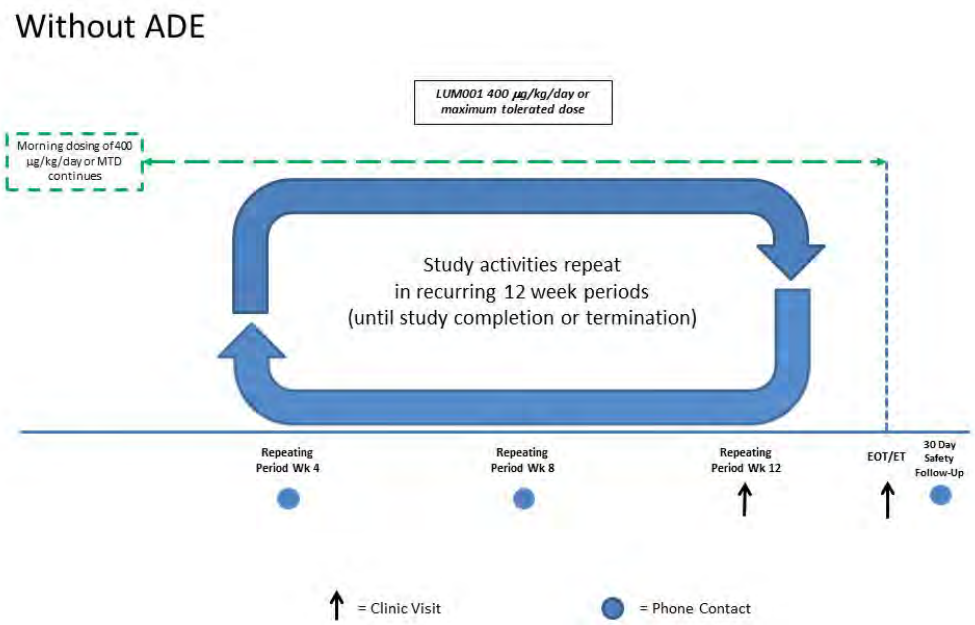
Synopsis Figure 4: Long-term Optional Follow-up Treatment (≥7 Days from last LUM001 dose between Protocol Amendment 3 and Protocol Amendment 4)



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

- Repeating Period Week 4 (ie, beginning 4 weeks after consent to Protocol Amendment 4) Telephone Contact: Collection of concomitant medications and any adverse events.
- Repeating Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.
- Repeating Period Week 12 Clinic Visit: Physical exam, body weight and height, vital signs, and blood samples for clinical laboratory testing including fasting lipid panel. Blood will also be collected for determination of baseline fat-soluble vitamins. Urine samples for clinical laboratory testing will be collected at every other visit. ItchRO compliance will be assessed, the electronic diary will be issued, the Clinician Scratch Scale and Clinician Xanthoma Scale will be administered, and the PedsQL questionnaire will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected.
- Subjects who do not qualify for ADE may be assessed at a later time point on a case by case basis following discussions between the investigator and medical monitor. Such re-evaluations may only occur at the Week 12 visit of any Repeating Period beginning with RP2. If in the course of the ADE re-evaluation, a subject is found to qualify for ADE, then the subject will move into Schedule F or G, as outlined in Section 16.1. During the follow-up treatment period, subjects will return to the clinic every 3 months.

Synopsis Figure 5: Long-term Optional Follow-up Treatment without Afternoon Dose Escalation (ADE)



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

- On ADE Day 0, morning dosing will continue at 400 µg/kg or the maximum tolerated dose. However, the volume of the morning dose will be reduced by half. Of note: Morning dosing must have been stable for ≥4 weeks prior to initiation of ADE.
- On ADE Day 0, the afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg.

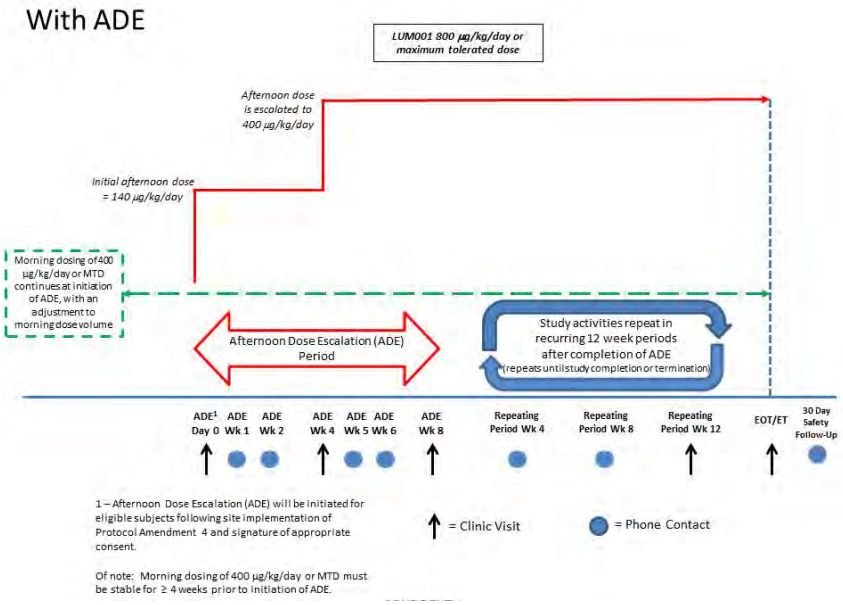
The following procedures will occur during the ADE period:

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

administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and any adverse events will be collected.

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

Synopsis Figure 6: Long-term Optional Follow-up Treatment, with Afternoon Dose Escalation (ADE)



If any subject experiences intolerance, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period; later attempts to escalate the dose are permitted. At the investigator's discretion, and in consultation with the medical monitor subjects who were previously down titrated may be rechallenged during the follow-up treatment period. If the subject is on a twice daily dosing regimen, dose lowering should be first attempted with the afternoon dose.

Safety and clinical laboratory evaluations and a physical exam (including collection of vital signs, height and weight measurements) will be completed at each clinic visit. In addition, the Clinician Scratch Scale, Clinician Xanthoma Scale, and PedsQL will be administered and study drug compliance will be assessed (PedsQL will not be performed at certain clinic visits – please refer to schedule of procedures). The PIC and CIC and the CGTB assessments will be completed at Weeks 84, 96, 100, and the End of Treatment (EOT)/Early Termination (ET)

	visit. Palatability data will be collected at each clinic visit during the long-term optional follow up treatment period (including the EOT/ET visit), with the exception of the PA4 DE, and ADE visits. Plasma samples will be obtained for LUM001 pharmacokinetics at the ADE Day 0, ADE Week 4, and ADE Week 8 visits, and at the 3 scheduled clinic visits following completion of the ADE period. Subjects/caregivers will receive follow-up phone calls at Weeks 64, 68, 76, 80, 88, 92, as well as those outlined within the PA4 DE, ADE, and repeating 12-week periods. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts. Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, 84, 96 clinic visits, at PA4 DE Week 4, and every clinic visit within the repeating 12-week periods. Electronic diaries will be provided to subjects and caregivers at these visits and re-training on the use of the diary will occur, as appropriate. At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the long-term exposure period. With the exception of the EOT/ET visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every visit. Subjects will be encouraged to complete all study activities and visits. Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo safety and clinical laboratory evaluations, including pharmacokinetic sampling of LUM001, determination of serum bile acids, other cholestasis biochemical markers, fat soluble vitamins, and AFP. In addition the following assessments should be completed: the Clinician Scratch Scale, the Clinician Xanthoma Scale, the PedsQL, the PIC, the CIC, the CGTB, and the palatability questionnaire, as defined for ET. For subjects who complete the study, an EOT visit will be completed; the assessments performed at this visit will be identical to the assessments performed at the ET visit. <u>Following completion of the Follow-up Treatment Period or early discontinuation:</u> a safety follow-up phone call will be made 30 days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded.
Safety and Tolerability Evaluations	The safety and tolerability of LUM001 will be assessed by determining the incidence, relationship to study drug, and severity of treatment-emergent AEs, withdrawals due to AEs, and changes in vital signs, laboratory and other safety parameters. Alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma, will be measured every 6 months throughout the long-term optional extension period. A Data Monitoring Committee (DMC) will review serious adverse event data, and other key subject safety and study data at specified intervals for the duration of the study.
Safety Evaluations	The following assessments will be used to evaluate safety: • Adverse events (AEs) and serious adverse events (SAEs). • Clinical laboratory results, including alpha-fetoprotein (AFP) as a screening for hepatocellular carcinoma. • Vital signs. • Physical exam findings, including body weight and height. • Concomitant medication usage.

Efficacy Evaluations	The primary efficacy endpoints will be the mean change from Week 18 to 22 of fasting serum bile acid levels in subjects who previously responded to LUM001 treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18. A sensitivity analysis will also be conducted using subjects who experienced a reduction from baseline in serum bile acids of ≥50% at the Week 48 measurement. The secondary efficacy evaluations will include: • Change from Week 18 to Week 22 in: o Liver enzymes [alanine aminotransferase (ALT), alkaline phosphatase (ALP)] and bilirubin (total and direct). o Pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO) in subjects who previously responded to LUM001 treatment, as defined by a reduction in ItchRO scale >1 point from baseline to Week 12 or Week 18. • Change from baseline to Week 18 in: o Fasting serum bile acid levels. o Liver enzymes (ALT, ALP) and bilirubin (total and direct). o Pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO). The following additional efficacy evaluations will be assessed: • Change from baseline to Weeks 18, 22 48, and then every 12 weeks in: o Fasting serum bile acid levels. o Liver enzymes (ALT, ALP) and bilirubin (total and direct). Pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO). o Other biochemical markers of cholestasis [total cholesterol, low-density lipoprotein cholesterol (LDL-C)]. o Bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)]. • Responder analysis at Weeks 18 and 48 in: o Pruritus response rates as measured by ItchRO (Observer ItchRO/patient ItchRO). o Clinician scratch score. • Change from baseline for PedsQL at Week 18 and Week 48 and change from Week 18 to Week 22. • PIC at Week 18 and 48 and change from Week 18 to Week 22. • CIC at Week 18 and 48 and change from Week 18 to Week 22. • CGTB assessment at Weeks 18 and 48 and change from Week 18 to Week 22. • Change from Baseline (Day 0) to Week 48 in xanthomas, as measured by Clinician Xanthoma Scale. Additional assessments of efficacy variables will occur during the 52-week and long-term optional treatment periods in 12 weekly intervals. Any of the above evaluations may also occur at clinic visits during the DE, PA4 DE, and ADE periods. Additional exploration of evaluations of safety will be specified in the statistical analysis plan.
Palatability Data	Palatability data will be collected at each clinic visit in the follow up treatment period, with the exception of the PA4 DE, and ADE visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age). Assessment of change over time will be evaluated.

Statistical Considerations	Sample Size The planned sample size of 30 evaluable subjects was based on practical considerations, rather than on statistical considerations and desired power for a pre-specified difference. Safety All safety analyses will be performed on the Safety Population, defined as all subjects who were assigned and received at least one dose of the study drug. Safety measures including AEs, clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively by study period and over the entire study duration (Weeks 0-EOT Visit). For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation and range will be given for the values themselves as well as for change from baseline at each study visit. Qualitative variables will be summarized using counts and percentages at each study visit. Drug Level Analysis Plasma concentrations of LUM001 will be examined descriptively by visit. Efficacy The main population for efficacy will be the modified intention-to-treat population (MITT), defined as all subjects who were enrolled, received study medication through Week 18, and had a reduction from baseline in serum bile acids of ≥50% at the Week 12 or Week 18 measurement. Subjects will be analyzed by assigned treatment. Efficacy endpoints will be displayed by study visit, using summary statistics including the number of observations, the mean, median, standard deviation, and range for continuous measures and counts and percentages for categorical measures. Actual values as well as change from baseline will be presented. The change from baseline will be tested using the paired t-test, or comparable nonparametric measures if appropriate. Examination of potential treatment effects by dose will be done if the sample sizes in the dose groups during the stable dosing phase of the study permit. In addition to absolute change from baseline, a responder analysis will also be considered. The response definition and its appropriate analysis methodology will be outlined in the Statistical Analysis Plan (SAP) for the study. Supportive and exploratory efficacy measures will be analyzed similarly as above. Details of the analysis methods will be outlined in the SAP. Interim Analysis There will be an interim analysis (IA) conducted after all subjects complete or discontinue the study after Week 48 to guide the future of the program. At the IA the study will be unblinded. Siblings The enrollment of siblings is allowed. During the double-blind, placebo-controlled, randomized drug withdrawal period, siblings will be assigned in a blinded manner to the same treatment arm. The data from all enrolled participants (including siblings) will be used for the safety analysis. For the efficacy analysis, data from only one of the siblings will be used. The choice of which subject's data to use in the efficacy analysis will be done in a random fashion before the LUM001-304 study is unblinded. Details of the analysis methods will be outlined in the SAP. All data will be included in data listings.

2 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
β-hCG	beta-sub-unit of human chorionic gonadotropin; pregnancy test
µg	microgram
µM	micromolar
7αC4, C4	7α-hydroxy-4-cholesten-3-one; an indirect method of bile acid synthesis
ac	before meals
ADE	afternoon dose escalation
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AFP	alpha-feto protein
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibody
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ASBT	apical sodium-dependent bile acid transporter
ASBTi	apical sodium-dependent bile acid transporter inhibitor
AST	aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical; classification for drugs
ATX	autotaxin
BA	bile acid
BID	twice a day
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CGTB	Caregiver Global Therapeutic Benefit questionnaire
cholesterol 7α-hydroxylase	rate-limiting enzyme in the synthesis of bile acid from cholesterol
CIC	Caregiver Impression of Change questionnaire
CRF	case report form

Abbreviation	Definition
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
DE	dose escalation
dL	deciliter
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic case report form
EOT	End of Treatment
ET	Early Termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor 19; regulates carbohydrate, lipid and bile acid metabolism
FGF-21	fibroblast growth factor 21; modulates hepatic metabolism
g	gram
GCP	good clinical practices
GGT	gamma-glutamyltransferase
GGTP (γGTP)	gamma-glutamyl transpeptidase
GI	gastrointestinal
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl-CoA reductase; rate-controlling enzyme of the pathway that produces cholesterol
HR	heart rate
HRQoL	health related quality of life
IAF	informed assent form
IB	investigator's brochure
IBAT	ileal bile acid transporter

Abbreviation	Definition
IBATi	ileal bile acid transporter inhibitor
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ItchRO™	Itch Reported Outcome
ItchRO(Obs)™	Itch Reported Outcome observer instrument
ItchRO(Pt)™	Itch Reported Outcome patient instrument
ITT	intention-to-treat
IU	international unit(s)
IUD	intrauterine device
kg	kilogram
L	liter
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LPA	lysophosphatidic acid
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MITT	modified intention-to-treat
mL	milliliter
mmol	millimole
NBD	nasal biliary drainage
NCS	not clinically significant
ng	nanogram
ObsRO	observer reported outcome
PBC	primary biliary cirrhosis
PEBD	partial external biliary diversion

Abbreviation	Definition
PedsQL	Pediatric Quality of Life Inventory
PFIC	progressive familial intrahepatic cholestasis
PI	principal investigator
PIC	Patient Impression of Change questionnaire
PK	pharmacokinetic
PSC	primary sclerosing cholangitis
PND	post-natal day
Pt	patient
PT	prothrombin time
qAM	every morning
QD	once daily
q.s.	quantity sufficient
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD-5613	original designation for LUM001
sec	second
SLC10A2	solute carrier family 10 member 2; gene that encodes IBAT protein
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TG	triglycerides
TGR5	a G protein-coupled receptor for bile acids
UDCA	ursodeoxycholic acid, ursodiol
ULN	upper limit of normal
US, USA	United States of America
WBC	white blood cell
WHO	World Health Organization
WMA	World Medical Association
yr(s)	year(s)

3 STUDY OBJECTIVES

The objectives of this study (up to and including Week 48) are:

- To evaluate the long-term safety and tolerability of LUM001 in children with ALGS.
- To evaluate the effect of LUM001 on serum bile acid levels in children with ALGS.
- To evaluate the effect of LUM001 on biochemical markers of cholestasis and liver disease in children with ALGS.
- To evaluate the effect of LUM001 on pruritus in children with ALGS.
- To evaluate the long-term effect of LUM001 in children with ALGS during 48 weeks of treatment.

Objectives of Long-term Optional Follow-up Treatment Period (after Week 48):

- To offer eligible subjects treated in the LUM001-304 study continued study treatment at Week 48 until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
- To explore twice a day (BID) dosing regimen and higher daily dosing of LUM001.
- To obtain safety and efficacy data in subjects treated long term on LUM001 including genotyping characteristics.
- To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma.
- To assess palatability of the LUM001 formulation.

4 BACKGROUND AND RATIONALE

LUM001 is an inhibitor of the ileal bile acid transporter/apical sodium-dependent bile acid transporter/soluble carrier family 10 member 2 (IBAT/ASBT/SLC10A2), initially developed as a lipid lowering agent (SD-5613). By virtue of its ability to inhibit bile acid absorption, LUM001 is being developed as a therapeutic agent for signs and symptoms of cholestatic liver disease.

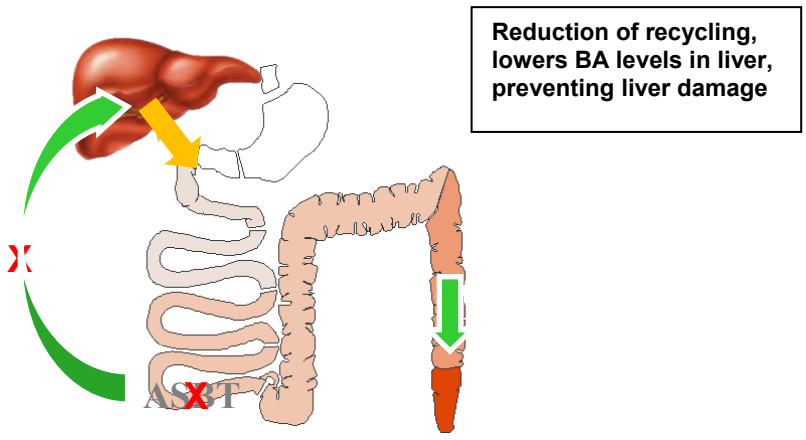
4.1 Therapeutic Rationale

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

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

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

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



ASBT=apical sodium-dependent bile acid transporter.

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

4.2 Alagille Syndrome

Alagille syndrome (ALGS) is an autosomal dominant with variable penetration genetic multisystem disorder. The clinical diagnosis is based on the presence of intrahepatic bile duct paucity on liver biopsy in association with at least three of the major clinical features: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities and characteristic facial features. Fewer than 200 patients with ALGS are born each year in the United States. The estimated prevalence in the United States is 3 per 100,000. Elevations of serum bilirubin up to 30 times normal and serum bile salts up to 100 times normal are common. Levels of markers of bile duct damage, including gamma-glutamyltransferase (GGTP or GGT) and alkaline phosphatase (ALP), usually are significantly elevated. Cholesterol levels may also be elevated. Multiple xanthomas are common sequelae of severe cholestasis. The pruritus seen in patients with this condition is among the most severe of any chronic liver disease and it is present in most children by the third year of life. Although surgical interruption of the enterohepatic circulation has been successfully employed in the treatment of cholestasis and hypercholesterolemia in ALGS (Emerick and Whitington, 2002; Modi et al., 2007), the management of cholestasis in ALGS remains largely supportive at this time. As cholestasis tends to improve over the first 5 to 10 years, therapies that ameliorate the complications of cholestasis, without a commitment to liver transplantation, are highly desirable (Emerick et al., 1999).

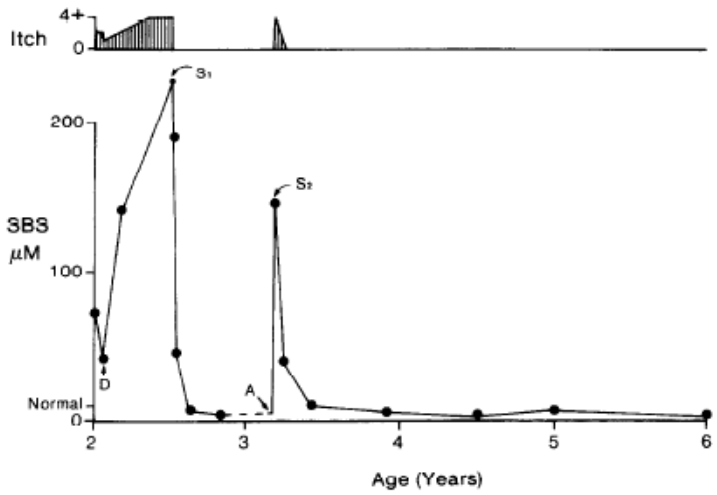
4.3 Pruritus

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

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

from the original description of this procedure by (Whitington and Whitington, 1988). Rapid lowering of bile acids, bilirubin, and ALT has also been observed (Table 1).

Figure 2: Serum Bile Salt Concentration and Degree of Itch



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

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

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

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

4.4 LUM001

4.4.1 Nonclinical Studies

4.4.1.1 Pharmacology

LUM001 is a minimally-absorbed, potent selective inhibitor of the ileal apical sodium-dependent bile transporter, a transmembrane protein localized on the luminal surface of ileal enterocytes, commonly referred to as ASBT/IBAT. The drug is a competitive inhibitor for bile acid substrate

with a high affinity for the transporter. Nonclinical studies indicate that selective inhibition of ASBT by LUM001 results in increased fecal bile acid excretion, inhibition of the postprandial rise in serum bile acids, and decrease in serum total cholesterol. It also increases the activity of hepatic cholesterol 7α-hydroxylase and 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, consistent with inhibition of bile acid reabsorption as the mechanism of action.

4.4.1.2 Pharmacokinetics

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

4.4.1.3 Toxicology

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

To support the use of LUM001 in young children, a toxicity study in juvenile animals was completed. As expected for a drug intentionally designed to be minimally absorbed, LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies with adult rats. No adverse effects were observed on postnatal growth and development of offspring at a dose of 200 mg/kg/day in males and 1000 mg/kg/day in females, the highest doses tested. This study was initiated in juvenile animals at PND21, which from a whole animal development perspective is typically representative of a 2 year old child. However given the fact that LUM001 is a minimally absorbed drug, as evidenced by this and multiple other studies, of particular importance is the age at which the GI tract is considered functionally mature. In humans this occurs by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs during the first three weeks of birth. Therefore this study presented evidence to support the safety of LUM001 in future clinical trials in children 12 months of age and older. These trials have the promise to address a life-threatening clinical need in this patient population.

Additional toxicology information can be found in the investigator's brochure.

4.4.2 Previous Clinical Experience

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

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

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

Administration of LUM001 at doses up to 100 mg once daily over a four-week period was generally safe in healthy volunteers and at doses up to 40 mg once daily for up to 10 weeks in subjects with hypercholesterolemia. The most commonly reported adverse drug reactions in LUM001-treated subjects were abdominal cramping (pain) and diarrhea and loose stools. These GI AEs are also observed in patients who undergo biliary diversion, are believed to be mechanism-based, due to elevated bile acid concentrations in the colon. With the exception of a single serious adverse event of cholecystitis no other SAEs possibly related or related to LUM001 have been reported in the 12 studies conducted to date (over 1,400 subjects exposed).

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

No clinically significant laboratory abnormalities were documented in LUM001-treated subjects. LUM001 was associated with mild, often transient elevations of serum ALT in a small percentage of subjects. Clinically significant reductions of serum fat-soluble vitamin levels were not observed with LUM001 treatment in humans; however, levels of the carotenoid β-carotene were mildly reduced. No alterations in coagulation parameters were observed, indicating no

functional changes in vitamin K status. Fecal fat excretion was not increased compared to placebo after four weeks of LUM001 treatment at doses up to 100 mg.

4.5 Rationale for Dose and Schedule of Administration

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

Ideally, dosing in pediatric subjects should be scaled from that in adults based on intestinal length, ie, mg of drug per cm of intestine. Differing relationships between intestinal mucosal surface area, age, and body weight have been reported in the literature (Weaver et al., 1991) provided data indicating that the average length of the small intestine increases with age from birth through 20 years; this relationship followed a curve that is similar to the height and weight growth curves (Weaver et al., 1991). However, a plateau had not been reached at the maximum age examined (20 years), precluding predictions of intestinal length for older adults and thus scaling to infants and children based on estimated intestinal length. An analysis of intestinal length as a function of age, weight, and height in adult cadavers was conducted by Hounnou et al (2002). Their analysis demonstrated that age had a negative correlation and body weight a positive correlation with intestinal length. Taken as a whole, the existing analyses are inconclusive with respect to the dependent variables that predict intestinal length. Consequently, the most reasonable approach is to calculate doses in a pediatric subject from those in adults based on using a direct mg/kg scaling. For reference in an average adult subject, weighing 70 kg, a 10 mg daily dose is equivalent to 140 µg/kg/day.

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

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

Weight (kg)	LUM001					
	Dose Level 1 (14 µg/kg/day)	Dose Level 2 (35 µg/kg/day)	Dose Level 3 (70 µg/kg/day)	Dose Level 4 (140 µg/kg/day)	Dose Level 5 (280 µg/kg/day)	Dose Level 6 (560 µg/kg/day)
10	0.14	0.35	0.70	1.40	2.80	5.60
15	0.21	0.53	1.05	2.10	4.20	8.40
20	0.28	0.70	1.40	2.80	5.60	11.20
25	0.35	0.88	1.75	3.50	7.00	14.00
30	0.42	1.05	2.10	4.20	8.40	16.80

In a previous study (Study 014), LUM001 was administered to 40 hyperlipidemic pediatric subjects (n=5, children ages 10-11; n=35 adolescents ages 12-17), up to a maximum tested dose of 5 mg/day for 14 days. The average subject weight in Study 014 was 60 kg and a 5 mg/day

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

In Study 014 no drug related serious AEs were observed. The most frequently reported AEs in all treatment groups (LUM001 and placebo) were diarrhea, abdominal pain, loose stools, and nausea. A total of 49 of 50 subjects completed 14 days of treatment. Most AEs were assessed with a probable or uncertain relationship to study medication and were generally characterized as mild or moderate in severity, except for those in six subjects who experienced severe nausea, diarrhea, or abdominal pain. These GI events usually resolved during continued treatment. It is noteworthy that the AEs were generally recorded in the first seven days of LUM001 dosing, and observed at a four-fold lower frequency from Day 8 to 14. This is consistent with the extensive adult dosing experience, where GI events were observed at levels similar to those in the placebo group after two weeks of continuous dosing.

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

Table 3: GI-associated Adverse Events in Study 003

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

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

The appropriate efficacious dose of LUM001 for the lowering of bile acid concentrations and the reduction of pruritus in cholestatic populations is not known. However, earlier studies demonstrated that doses of 10 mg daily (equivalent to 140 µg/kg/day for a 70 kg subject) led to a decrease in serum bile acids in healthy volunteers by >50% following 2 weeks of treatment. In

the PFIC population, there is some evidence that ASBT is upregulated, suggesting that higher doses may be required to saturate transporters and reach the desired effect in PFIC disease.

The doses explored in the current study (up to 400 µg/kg/day BID) in subjects with ALGS are supported by the safety profile observed in completed and ongoing clinical studies of LUM001. Twice daily dosing is used in this study based on the findings of a healthy volunteers study in adult males (Study SHP625-101), which demonstrated that bile acid levels in feces increase with escalating doses and twice-daily regimen of LUM001 (up to 100 mg QD and 50 mg BID, respectively). In this study, subjects who were randomized to LUM001 treatment, received 1 of 4 doses of LUM001 (10, 20, 50, 100 mg) during 7 days. No titration was used in this study. There was a dose-dependent increase in total fecal BA excretion. In addition, BID dosing (ie, 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (ie, 100 mg QD). It is therefore hypothesized that higher doses and twice-daily dosing both have the potential to allow for more complete target engagement throughout the day at the level of the distal ileum.

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

5 INVESTIGATIONAL PLAN

5.1 Study Design

This is a long-term open-label study with a double-blind, placebo-controlled, randomized drug withdrawal period in children with ALGS designed to evaluate the safety and efficacy of LUM001. The study is divided into 6 parts: a 6-week open-label, dose escalation period at doses up to 400 μg/kg/day, a 12-week open-label stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, a 26-week long-term stable dosing period at doses up to 400 μg/kg/day, a 52-week optional follow-up treatment period, and a long-term optional follow-up treatment period for eligible subjects who choose to stay on treatment with LUM001. During this long-term optional follow-up period, subjects may have their dose of LUM001 increased to a maximum of 800 μg/kg/day (400 μg/kg BID), based on efficacy (sBA level and ItchRO[Obs] score) and safety assessment. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occurs: i) the subjects are eligible to enter another LUM001 study, ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.

Subjects who do not consent to Protocol Amendment 4 will continue their treatment as outlined in Protocol Amendment 3.

5.2 Data Monitoring Committee

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

5.3 Number of Study Centers

This will be a multi-center study in approximately 9 clinical sites.

5.4 Number of Subjects

Approximately 30 subjects will be enrolled in this study.

5.5 Overall Study Duration and Follow-up

For an individual subject, the study participation period will consist of a screening period of up to 4 weeks, a 48-week treatment period (including a 6-week, open-label dose escalation period, a 12-week open-label stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, a 26-week long-term stable dosing period) as well as a 52-week optional follow-up treatment period, and a long-term optional follow-up treatment period. A safety follow-up phone call will be made by the study site 30 days after the last dose of study drug.

Following screening, during the 48-week treatment period, subjects who meet all eligibility criteria will return to the clinic for 9 visits and will receive 14 telephone contacts from the study staff (see Figure 3). Subjects who complete 48 weeks of treatment may be eligible to receive further treatment during the 52-week optional follow-up treatment period and the long-term optional follow-up treatment period. Subjects' participation in the long-term optional follow-up treatment period will continue until the first of the following occurs: (i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.

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

Figure 3: Study Design for LUM001-304 (Day 0 – Week 48)

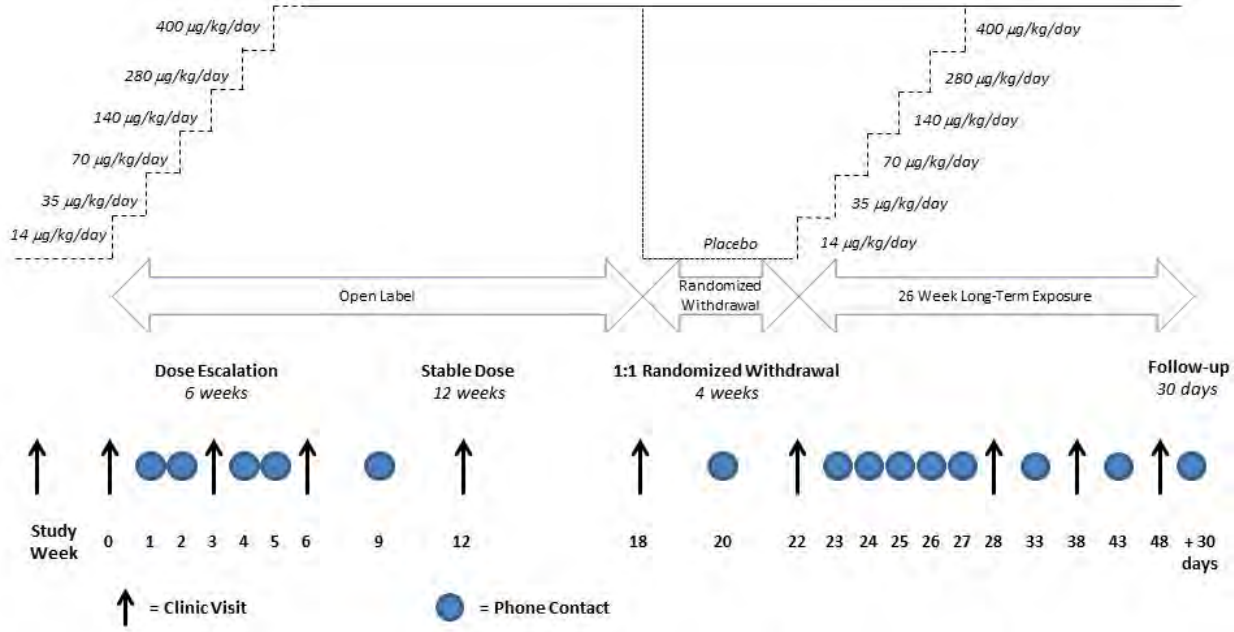
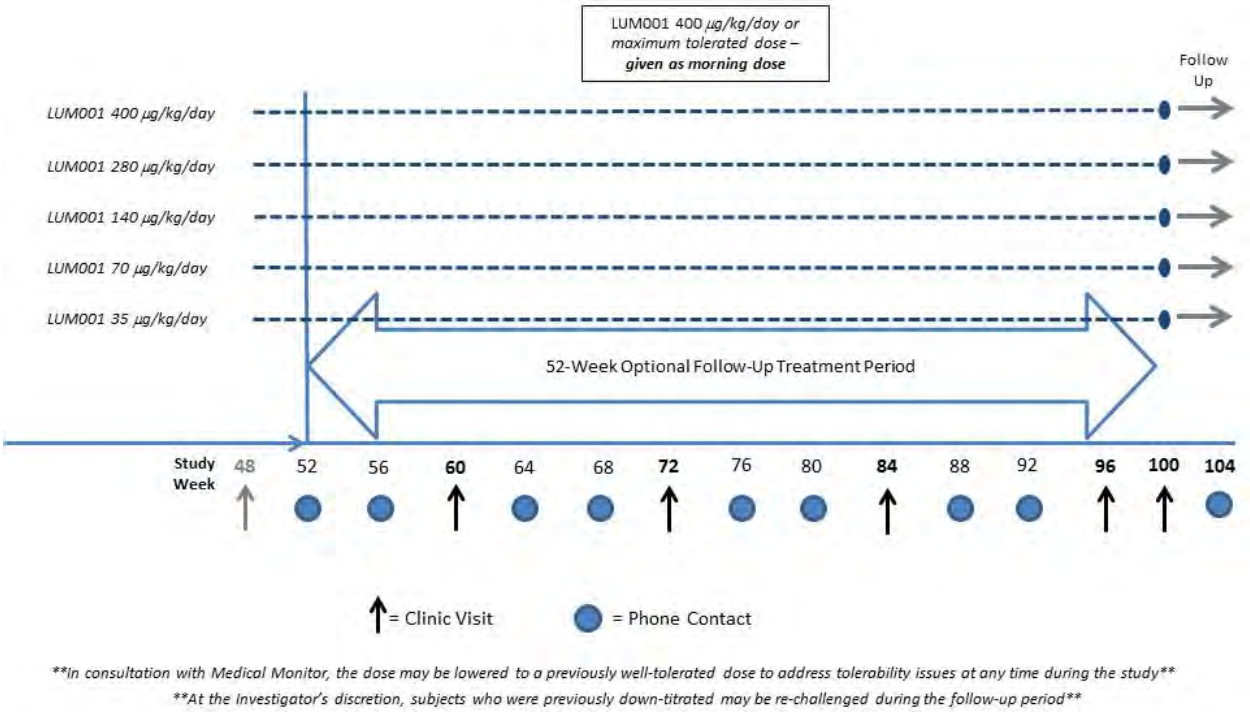


Figure 4: 52-week Optional Follow-up Treatment Scheme (<7 days from last LUM001 dose)

Applies to the following subject population:

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

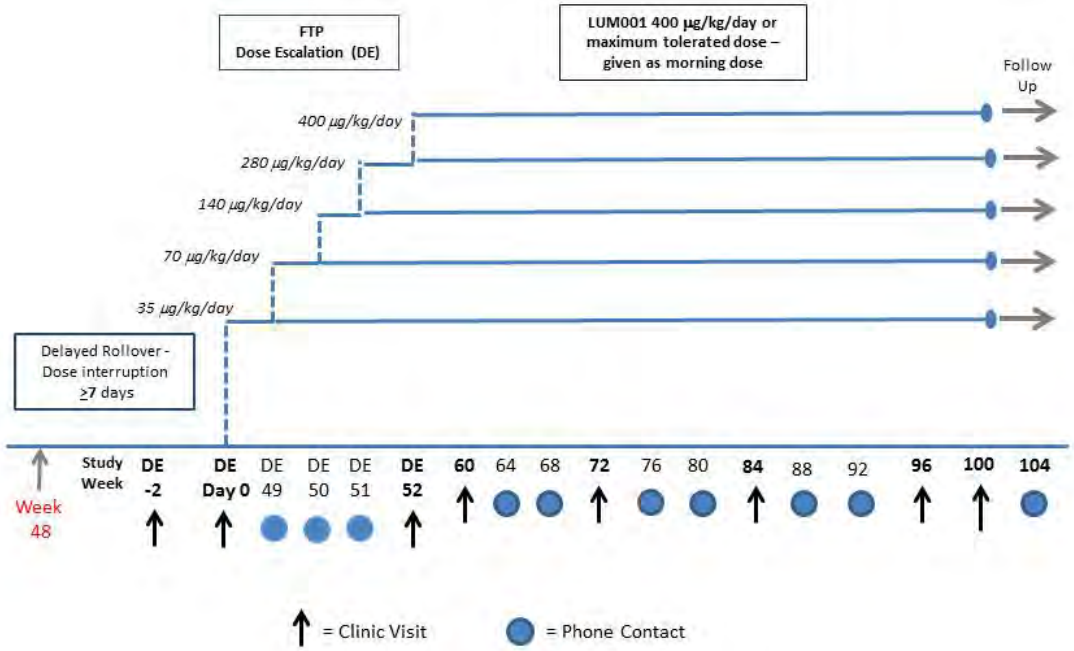


In consultation with Medical Monitor, the dose may be lowered to a previously well-tolerated dose to address tolerability issues at any time during the study
At the Investigator's discretion, subjects who were previously down-titrated may be re-challenged during the follow-up period

Figure 5: 52-week Optional Follow-up Treatment Scheme (≥7 days from last LUM001 dose)

Applies to the following subject population:

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

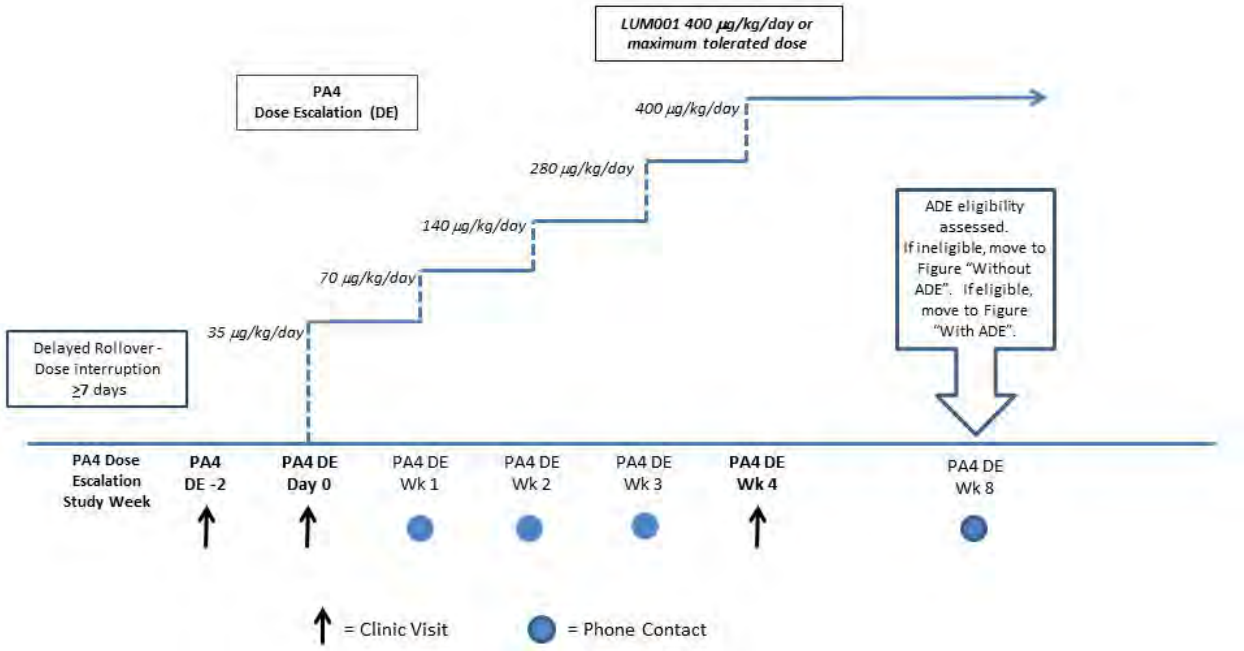


Abbreviations: DE=dose escalation; FTP=follow-up treatment period.

Figure 6: Long-term Optional Follow-up Treatment Scheme (≥7 days from Last LUM001 Dose between Protocol Amendment 3 and Protocol Amendment 4)

Applies to the following subject population:

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

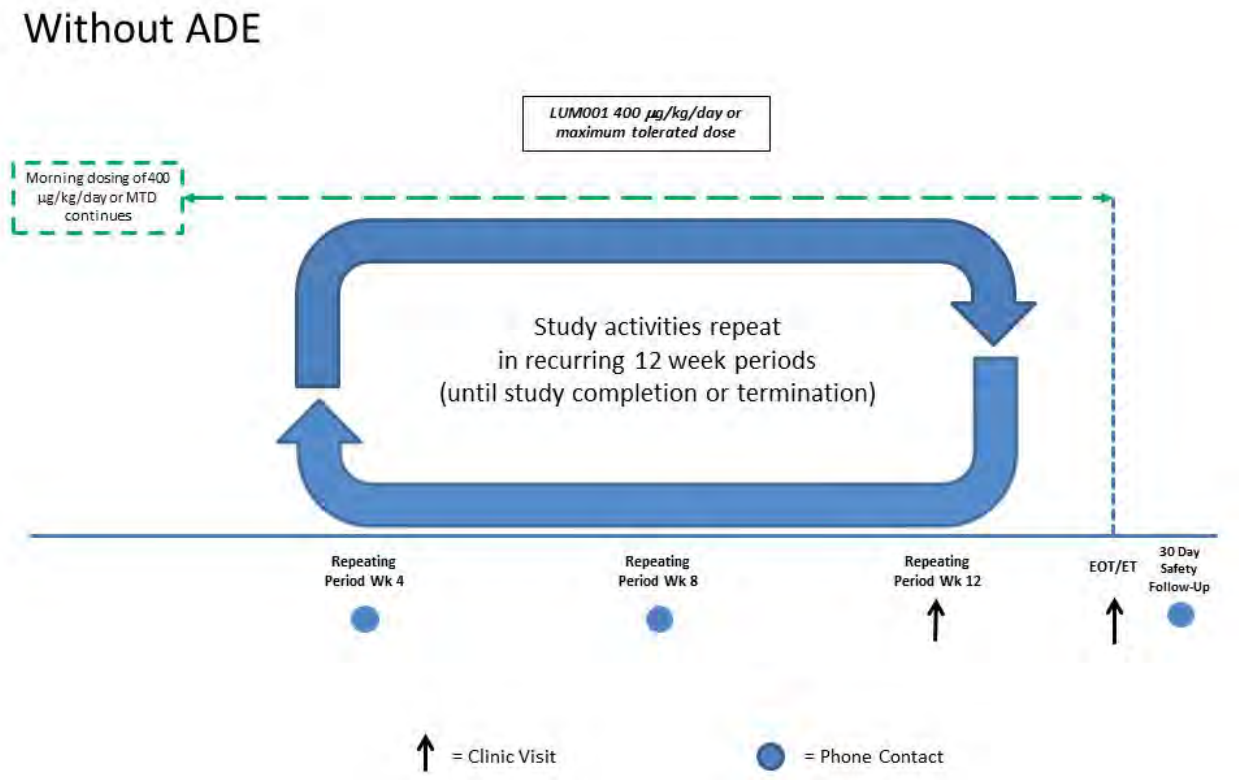


Abbreviations: ADE=afternoon dose escalation; DE=dose escalation; PA=protocol amendment; Wk=week.

Figure 7: Long-term Optional Follow-up Treatment Scheme, without Afternoon Dose Escalation (ADE)

Applies to the following subject population:

- Subjects deemed ineligible for ADE

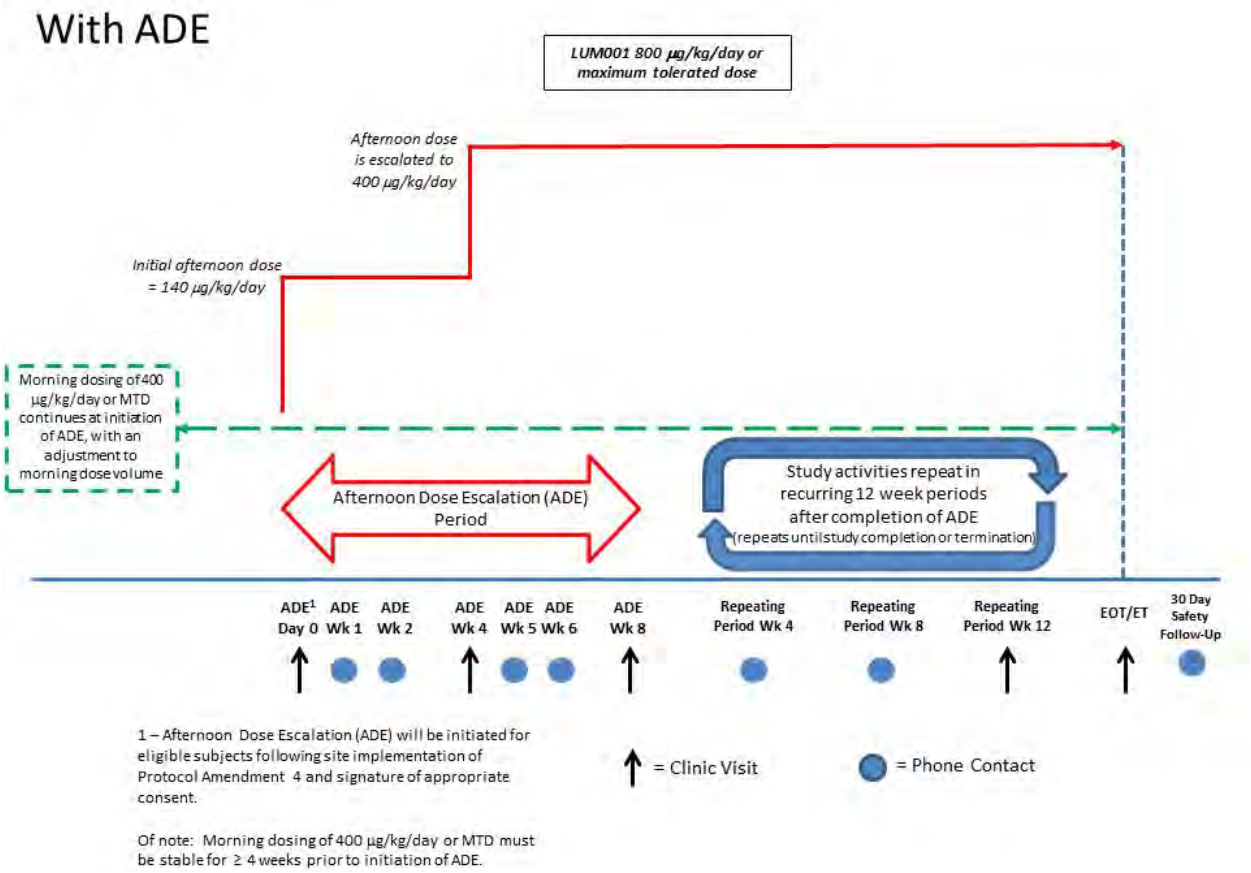


Abbreviations: EOT=end of treatment; ET=early termination; MTD=maximum tolerated dose; Wk=week.

Figure 8: Long-term Optional Follow-up Treatment Scheme under Protocol Amendment 4, with Afternoon Dose Escalation (ADE)

Applies to the following subject population:

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



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

5.5.1 Screening

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

5.5.2 Treatment

Study drug will be prepared for each individual subject by a central pharmacy based on the subject's weight at screening. Diluent will be added by the central pharmacy pharmacist prior to shipping study drug to the site. Study drug will be dispensed to subjects/caregivers. During the course of the study, it may be necessary to instruct the subject/caregiver to return to the site for an unscheduled dispensation of study drug. The appropriate amount of study drug will be dispensed at the Study Day 0 visit and daily dosing will begin on Study Day 1.

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

All subjects will receive LUM001, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day, during the initial open-label treatment period of the study. After completion of the 12-week stable dosing period, subjects will be randomized 1:1 to either a 4-week double-blind study drug withdrawal period during the study or will remain on study drug. Subjects will then enter a 26-week long-term stable dosing period and all subjects will receive LUM001, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day during the initial open-label treatment period of the study. Subjects will be considered for a 52-week optional treatment period, if eligible, receiving up to 400 µg/kg/day, or the highest tolerated dose below the 400 µg/kg/day dose. Subjects will then be considered for the long-term optional follow-up treatment, if eligible, receiving up to 800 µg/kg/day (given as twice daily doses of 400 µg/kg), or a maximum possible daily dose of 50 mg/day.

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

5.5.2.1 Dose Escalation Period

Initially, the LUM001 dose will be administered as a daily morning dose in either a 1.0 mL or 0.5 mL solution. The dose will be increased weekly over a 6-week period up to 400 µg/kg/day QD or a maximum daily dose of 20 mg/day QD as follows:

Week 1 Dose: 14 µg/kg/day QD
Week 2 Dose: 35 µg/kg/day QD
Week 3 Dose: 70 µg/kg/day QD
Week 4 Dose: 140 µg/kg/day QD
Week 5 Dose: 280 µg/kg/day QD
Week 6 Dose: 400 µg/kg/day QD (maximum daily dose of 20 mg QD)

Subjects should be administered study drug daily for at least 7 days at each dose level during the dose escalation period.

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

replacement study medication will be issued to the subject as quickly as possible. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose.

5.5.2.2 Stable Dosing Treatment Period

Subjects will continue dosing for another 12 weeks using the dose administered at Week 6, which may be 400 µg/kg/day or the highest tolerated dose below 400 µg/kg/day.

5.5.2.3 Double-blind Placebo-controlled Study Drug Withdrawal Period

At the Week 18 visit, eligible subjects will be randomized 1:1 to continue to receive study drug or a corresponding placebo for 4 weeks.

5.5.2.4 Long-term Exposure Period

Following the 4-week study drug randomized withdrawal period, subjects who received placebo will receive LUM001 dosed according to a dose escalation schedule that mirrors the initial escalation (ie, the LUM001 dose will be increased weekly over a 6-week period to the maximum tolerated dose up to 400 µg/kg/day or 20 mg/day or the highest tolerated dose below the 400 µg/kg/day dose). Subjects who were randomized to receive LUM001 during this period will continue to receive the same dose of LUM001 and, following Week 22, a simulated dose escalation will occur to maintain the blind in the randomized withdrawal period. Dosing with LUM001 will continue in a 26-week long-term exposure period to complete 48 weeks of study.

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

5.5.2.5 52-week Optional Follow-up Treatment Period

At Week 48, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the 52-week optional follow-up treatment period. The 3 following possible scenarios may occur:

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

- Subjects who are eligible to roll over into the optional follow-up treatment period with a LUM001 dosing interruption of ≥7 days will be dose escalated beginning at 35 µg/kg/day and up to a maximum of 400 µg/kg/day or highest tolerated dose (as detailed in Section 8.1.8.

- Subjects who do not wish to enter the follow-up treatment period will be contacted via telephone by the study site approximately 30 days after the last dose of study drug.

5.5.2.6 Long-term Optional Follow-up Treatment Period

Upon completion of the 52-week optional follow-up treatment period, and/or implementation of this amendment, whichever occurs first, subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over (or enter) the long-term optional treatment period. The 3 following possible scenarios may occur:

Scenario 1: Subjects eligible to roll over into the long-term optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 continuous days:

- Subjects with normal sBA level AND ItchRO(Obs) score <1.5 will be maintained at the same dose level and will continue morning dosing only.
- Subjects with sBA level above normal AND/OR ItchRO(Obs) score ≥1.5 will start BID dosing (afternoon dose escalation; ADE) as follows:
    - The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated.
    - The afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg.

Scenario 2: Subjects eligible to roll over into the long-term optional follow-up treatment period with a LUM001 interruption of ≥7 days:

- First, the morning dose is escalated up to 400 µg/kg/day or highest tolerated dose following a 5-week dose escalation beginning at 35 µg/kg/day.
- Once the morning dose of 400 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO(Obs) score will be evaluated.
    - Subjects with normal sBA AND ItchRO(Obs) score <1.5 after morning dose escalation will be maintained at the same dose level and will continue morning dosing only.
    - Subjects with sBA above normal AND/OR ItchRO(Obs) score ≥1.5 will begin BID dosing (ADE) as outlined as follows:
        - The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated.
        - The afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg.

The following parameters apply to both dosing scenarios outlined above:

- The afternoon dose will only be initiated once the subject has been treated on stable morning doses for at least 4 weeks.

- The sBA value used for determination of ADE eligibility will be the most recent available value collected within the prior 16 weeks. The ItchRO(Obs) score used for ADE eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 16 weeks.

- The maximum daily dose will be 400 µg/kg BID, ie, 800 µg/kg/day (up to a maximum possible daily dose of 50 mg/day).

Subjects will continue to receive study drug until they are eligible to enter another LUM001 study, or until LUM001 is available commercially, or until the sponsor stops the program or development in this indication, whichever occurs first.

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

Scenario 3: Subjects who do not consent to Protocol Amendment 4 will continue their treatment as outlined in Protocol Amendment 3.

5.5.3 Safety Follow-up Period

A safety follow-up phone call will be made by the study site 30 days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and any AEs noted during this phone call will be recorded. Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in the long-term optional follow-up treatment period under Protocol Amendment 4.

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

5.6 End of Study

For subjects who do not consent to the long-term optional follow-up treatment period, a subject is considered to have completed treatment if treatment was not permanently discontinued prior to the Week 48 visit. A follow-up phone contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.

The subject is considered to have completed treatment and study period for the corresponding follow-up treatment period (when consented under Protocol Amendment 3 or Protocol

Amendment 4) if study treatment was not discontinued prior to completing Week 96 for Protocol Amendment 3 or completing the EOT visit in Schedule J under Protocol Amendment 4. Temporary drug interruption is not considered treatment discontinuation. A follow-up contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.

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

6 SUBJECT ENROLLMENT

6.1 Screening

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

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

Subjects will be enrolled in the optional follow-up treatment period based on the investigator's determination of meeting eligibility criteria outlined in Section 7. A subject will be considered enrolled in the long-term optional follow-up period under Protocol Amendment 4 after the subject consents and the investigator has determined the subject meets study entry eligibility criteria per Protocol Amendment 4. However, any subject who consents to Protocol Amendment 4 and does not meet criteria per the investigator is considered a screen failure for the long-term optional follow-up period under Protocol Amendment 4. Screen failures are eligible for rescreening (Section 8.1.1).

6.2 Randomization

Subjects begin the study at Day 0 and are treated in an open-label fashion from Week 1 to Week 18. Subjects will then be randomized 1:1 to continue to receive study drug or a corresponding placebo for 4 weeks between Week 19 and Week 22 at the start of the double-blind, placebo-controlled study drug withdrawal period (Week 19 to Week 22). This randomization will be stratified by response criteria where response is defined as a ≥50% reduction in serum bile acids between Baseline and Week 12 or Week 18. Serum bile acid results will remain blinded after baseline testing.

During the double-blind, placebo-controlled, randomized drug withdrawal period, siblings will be assigned in a blinded manner to the same treatment arm.

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

6.3 Replacement of Subjects

A subject who withdraws from the study prior to completion of the stable dosing treatment period (Week 18) may be replaced at the discretion of the sponsor.

6.4 Unblinding of Treatment Assignment

Although subjects begin the study at Day 0 and are treated in an open-label fashion from Week 1 to Week 18, subjects will be randomized 1:1 to continue to receive study drug or a corresponding placebo for 4 weeks between Week 19 and Week 22 at the start of the double-blind, placebo-controlled study drug withdrawal period. The sponsor (or designee) will prepare the randomization list. All subjects, monitors, and study center personnel related to the study, except for the central pharmacist (or qualified designee) who prepares the study drug will be blinded to study treatment during the randomized withdrawal period (Weeks 19-22) and the long-term exposure period (Weeks 23-48) and to the subject's study drug withdrawal period treatment assignment.

After Week 48 the study will be unblinded to facilitate preparation of the interim analysis.

If in the event of an emergency situation when knowledge of the treatment assignment during the double-blind, randomized drug withdrawal period will impact the clinical management of the subject, the investigator will have the ability to unblind the treatment assignment for that subject. If a subject is unblinded by the investigator, the sponsor must be informed of the unblinding within 24 hrs. If the blinding is prematurely broken, it is the responsibility of the investigator to promptly document and explain any unblinding to the sponsor.

All subjects will receive LUM001, or LUM001 and placebo during this study. Breaking of the blind during the initial 48-week period of the study should not occur before all subjects either discontinue or complete Week 48, except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or when causality must be determined prior to submitting a regulatory safety report for a serious adverse event (SAE) (as defined in Section 11.2.3).

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

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

7 SUBJECT ELIGIBILITY

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

7.1 Inclusion Criteria

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

1. Male or female between the ages of 12 months and 18 years inclusive.
2. Diagnosis of ALGS based on the diagnostic criteria outlined in Section 16.3.
3. Evidence of cholestasis (one or more of the following):
    a. Total serum bile acid > 3x ULN for age.
    b. Conjugated 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. Females of childbearing potential must have a negative serum pregnancy test during Screening.
5. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug, must agree and use acceptable contraception during the trial, as described in Section 8.6.1.
6. Subject is expected to have a consistent caregiver(s) for the duration of the study.
7. Informed consent and assent (per IRB/IEC) as appropriate.
8. Access to phone for scheduled calls from study site.
9. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study.
10. Caregivers (and age appropriate subjects) must digitally accept the licensing agreement in the eDiary software.
11. 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 (maximum possible reports = 14 per week).
12. Average daily score >2 on the Itch Reported Outcome (ItchRO™) questionnaire (maximum possible daily score of 4) for two consecutive weeks in the screening period, prior to dosing. A daily score is the higher of the scores for the morning and evening ItchRO. The average daily score is the sum of all daily scores divided by the number of days the ItchRO was completed.

7.2 Exclusion Criteria

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

1. Chronic diarrhea requiring ongoing intravenous fluid or nutritional intervention.
2. Surgical interruption of the enterohepatic circulation.
3. Previous liver transplant.
4. Decompensated cirrhosis (ALT >15 x ULN, INR >1.5 [unresponsive to vitamin K therapy], albumin <3.0 g/dL, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy).
5. History or presence of other concomitant liver disease.
6. 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 (eg, inflammatory bowel disease).
7. History or presence of gallstones or kidney stones.
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. Recent medical history or current status that suggests that the subject may be unable to complete the study.
11. Any female who is pregnant or lactating or who is planning to become pregnant during the study period.
12. Known history of alcohol or substance abuse.
13. Administration of bile acid or lipid binding resins within 28 days prior to screening and throughout the trial.
14. Known hypersensitivity to LUM001 or any of its components.
15. Receipt of investigational drug, biologic, or medical device within 28 days prior to screening, or 5 half-lives of the study agent, whichever is longer.
16. History of non-adherence to medical regimens, unreliability, mental instability or incompetence that could compromise the validity of informed consent or lead to non-adherence with the study protocol based upon investigator judgment.
17. Any other conditions or abnormalities which, in the opinion of the investigator or medical monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study.
18. Subjects weighing over 50 kg at screening.

<u>Protocol Amendment 3: Eligible subjects for the 52-week optional follow-up treatment period:</u>

Subjects will be considered eligible for the 52-week optional follow-up treatment period if they have:

- Completed the protocol through the Week 48 visit with no safety concerns. Subjects who were discontinued due to safety reasons can be rechallenged if blood tests are back to relatively normal values for this patient population and subject does not meet any of the

protocol's stopping rules. The decision will be made by the investigator in consultation with the medical monitor.

- Subjects who have undergone a surgical disruption of the enterohepatic circulation will not be eligible to enter into the follow up treatment period.
- Subjects who were discontinued for other reasons will be considered for the 52-week optional follow-up treatment period on an individual basis. The decision will be made by the investigator in consultation with the medical monitor.

Protocol Amendment 4: Eligible subjects for the long-term optional follow-up treatment period:

Inclusion Criteria for subjects with LUM001dosing interruption <7 days, or ≥7 days:

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

1. The subject has either:
   - completed the protocol through the Week 48 visit with no major safety concerns

   OR
   - discontinued due to safety reasons judged unrelated to the study drug, and laboratory results have returned to levels acceptable for this patient population or individual and subject does not meet any of the protocol's stopping rules at the time of entry into the follow-up period. The decision will be made by the investigator in consultation with the medical monitor. [Subjects who were discontinued for other reasons will be considered on an individual basis.]
2. Females of childbearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at the time of entry into the long-term optional follow-up treatment period.
3. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug, must agree and use acceptable contraception during the trial, as described in Section 8.6.1.
4. Informed consent and assent (per IRB/EC) as appropriate.
5. Access to phone for scheduled calls from study site.
6. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study.

Exclusion Criteria for Subjects with LUM001 dosing interruption≥7 days:

All exclusion criteria mentioned in Section 7.2 apply upon entry into the long-term optional follow-up period, with the exception of exclusion criterion #18.

8 STUDY PROCEDURES

8.1 Study Schedule

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

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

Screening evaluations will be performed from Day -28 to Day -1. In the absence of documented JAGGED1 or NOTCH2 mutation prior to screening, genetic testing may be performed for JAGGED1 and/or NOTCH2 (Spinner et al., 2000). The appropriate genetic counseling will be provided to subjects and their legal caregivers at a study visit following the receipt of results of genetic testing. Results of genetic screen will not impact continued participation in the study.

After obtaining informed consent (and/or assent when appropriate), demographic data (gender, age, and race) will be collected and subjects will undergo a medical history and physical examination including body weight, height, and vital signs, compilation of concomitant medications, and have blood and urine samples taken for clinical laboratory testing. For subjects who do not have documentation of a JAGGED-1 or NOTCH2 mutation, a blood sample may be obtained for genotyping. The physician will provide an assessment of itch severity using the clinician scratch score during Screening. The eDiary for assessing pruritus with the Itch Reported Outcome (ItchRO) instrument will be dispensed and subjects and caregivers will undergo training during the Screening visit. The patient/ caregiver ItchROs (ItchRO [Pt], ItchRO [Obs]) will be completed twice daily during the Screening period to establish eligibility and a baseline score. Subjects 9 years of age and older will continue independent twice daily completion of their ItchRO. Subjects 5-8 years of age will continue twice daily completion of their ItchRO with the assistance of their caregivers, if needed. Caregivers will continue twice daily completion of their ItchRO. 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, (maximum possible reports = 14 per week). Subjects are required to discontinue bile acid resins for at least 28 days prior to screening and throughout the study. Females who are of childbearing potential will have a serum pregnancy test. Eligibility criteria will be reviewed to confirm a subject's eligibility 4-7 days prior to the Baseline Visit.

Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 28-day screening period, consideration may be given to rescreening at a later date. Screening procedures should be repeated at that time. Subject data pertaining to screening will be collected after the subject has been rescreened and determined to meet eligibility.

8.1.2 Dose Escalation Treatment Period (Day 0 to Week 6)

At the Baseline Visit (Day 0), subjects will be assessed to confirm continued study eligibility and undergo a physical examination including body weight, height, and vital signs, and have urine and blood samples taken for hematology, chemistry, fasting lipid panel, baseline levels of bile

acids and other cholestasis biochemical markers. Blood will also be collected for determination of baseline fat-soluble vitamins and a plasma LUM001 drug level. Compliance with ItchRO will be assessed. The Clinician Scratch Scale, Xanthoma Scale, and PedsQL questionnaires will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study medication for Weeks 1, 2, and 3 will be supplied at the Baseline Visit to eligible subjects. Subjects and caregivers will continue twice daily completion of their ItchRO throughout the Dose-Escalation Treatment Period. Subjects will return to the clinic at Weeks 3 and 6 and follow-up phone calls will be made at Weeks 1, 2, 4, and 5. On clinic visit days, safety and clinical laboratory evaluations will be performed, and a physical exam will be performed (including collection of vital signs, height and weight measurements). Clinician scratch scale, adherence to study medication, and ItchRO compliance will be assessed. Concomitant medications and any adverse events will be recorded. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study drug will be supplied at Weeks 3 and 6.

8.1.3 Stable Dosing Treatment Period (Week 7 to Week 18)

Each subject will continue dosing with study drug during a 12-week Stable Dosing Treatment Period using the dose administered at Week 6, which may be 400 µg/kg/day or the highest tolerated dose below 400 µg/kg/day. Subjects 9 years of age and older will continue independent twice daily completion of their ItchRO. Subjects 5-8 years of age will continue twice daily completion of their ItchRO with the assistance of their caregivers, if needed. Caregivers will continue twice daily completion of their ItchRO. Subjects will receive a follow-up phone call at Week 9 and return to the clinic at Weeks 12 and 18. At the Week 12 and 18 visits, safety and clinical laboratory evaluations will be performed, and a physical exam will be performed (including collection of vital signs, height and weight measurements). Blood samples will be taken for fasting lipid panel, serum bile acids, fat soluble vitamins, and other cholestasis biochemical markers. Blood sampling for study drug determination may also be performed. After the baseline pharmacokinetic analysis, blood sampling for an additional pharmacokinetic analysis will be done at one additional time point - at Week 12, 18, 38, or 48 – to be selected by the site/investigator (sample to be taken approximately 4 hours post-dosing). Clinician scratch scale, adherence to study medication, ItchRO compliance, and the PedsQL questionnaire will be assessed and concomitant medications and any adverse events will be recorded. In addition, at the Week 18 visit the Clinician Xanthoma Scale, Patient Impression of Change (PIC), Caregiver Impression of Change (CIC), and Caregiver Global Therapeutic Benefit (CGTB) assessments will be completed. At the Week 18, visit subjects will also be randomized 1:1 to either continue to receive study drug or a corresponding placebo between Week 19 and Week 22. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study drug will be supplied at Week 12 and study drug (or placebo) at Week 18.

8.1.4 Double-blind, Placebo-controlled Study Withdrawal Period (Week 19 to Week 22)

Age appropriate subjects and caregivers will continue twice daily completion of their ItchRO. Subjects will receive a follow-up phone call at Week 20 and return to the clinic at Week 22. At the Week 22 visit, safety and clinical laboratory evaluations will be performed, and a physical

exam will be performed (including collection of vital signs, height and weight measurements). Blood samples will be taken for fasting lipid panel, serum bile acids, fat soluble vitamins, and other cholestasis biochemical markers. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Study drug will be supplied at Week 22. Clinician Scratch Scale, adherence to study medication, ItchRO compliance, PIC, CIC, CGTB, and the PedsQL questionnaires will be assessed and concomitant medications and any adverse events will be recorded.

8.1.5 Long-term Exposure Period (Week 23 to Week 48)

Following the 4-week double-blind, study drug withdrawal period, subjects who received placebo will once again receive LUM001 according to the schedule where the dose is increased weekly over a 6-week period up to 400 μg/kg/day or a maximum daily dose of 20 mg/day. Following the 4-week study drug withdrawal period, subjects who were randomized to receive LUM001 will undergo a simulated dose escalation to maintain the blind in the randomized withdrawal period and continue to receive LUM001 during the long-term exposure period, at the same dose administered at Week 22.

Subjects and caregivers will continue twice daily completion of their ItchRO throughout the long-term exposure period to the Week 48 clinic visit. Subjects will return to the clinic at Weeks 28, 38, and 48. At these visits, safety and clinical laboratory evaluations will be performed, and a physical exam will be performed (including collection of vital signs, height and weight measurements). Blood samples will be taken for fat soluble vitamins, as well as possible pharmacokinetic blood sampling for study drug determination (if not done previously at Week 12 or 18). Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study medication. Clinician scratch scale, adherence to study medication, and ItchRO compliance will be assessed. Subjects/caregivers will receive follow-up phone calls at the end of Weeks 23-27, 33, and 43. Concomitant medications and adverse events will be recorded at all clinic visits and at scheduled telephone contacts.

At the investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the long-term exposure period. Additional study drug will be supplied at each clinic visit during the long-term exposure period.

8.1.6 Week 48

At Week 48, a physical exam (including collection of vital signs, height and weight measurements) will be performed. Blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids, other cholestasis biochemical markers, and possibly LUM001 drug level analysis. Females who are of childbearing potential will have a urine pregnancy test. The Clinician Scratch Scale, Clinician Xanthoma Scale, and PedsQL questionnaire will be completed. The PIC, the CIC, and the CGTB assessments will be completed. Concomitant medications and adverse events will be recorded. Study drug compliance will be assessed and all remaining study drug and study supplies will be collected. Study drug will be discontinued and eDiaries will be returned to the site at this visit.

Subjects will then be considered for a 52-week optional follow-up treatment, if eligible, to continue on their highest tolerated dose.

Subjects who withdraw from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week 48/Study Termination visit (Schedule of Procedures, 16.1).

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

Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo a physical examination, as well as have urine and blood samples taken for safety and clinical laboratory evaluations, lipid panel, bile acids, other cholestasis biochemical markers, fat soluble vitamins, and drug level. In addition the following assessments should be completed: the Clinician Scratch Scale, the Clinician Xanthoma Scale, the PedsQL, the PIC, the CIC, and the CGTB assessments, as defined for ET (see Schedule of Procedures, Section 16.1). For safety reasons, efforts must be made to follow subjects for at least 30 days following their last dose of study drug.

8.1.8 52-week Optional Follow-up Treatment Period

Subjects who are eligible to roll over into the 52-week optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level within the 52-week optional follow-up treatment period (Figure 4).

During this period, subjects will return to the clinic at Weeks 60, 72, 84, 96, and 100; telephone contacts will occur at Weeks 64, 68, 76, 80, 88, and 92.

Subjects with ≥7 days since last dose of LUM001 will be dose escalated up to 400 µg/kg/day or to the highest tolerated dose (see Figure 5). The dose escalation (DE) period will proceed as follows:

- Week DE-2 Clinic Visit: obtain consent, weight, and draw blood for laboratory analyses
- Week DE 0 Clinic Visit: PI evaluates laboratory results, study drug is dispensed, and subject begins at 35 µg/kg/day dose level (if no safety concerns)
- Week DE 49 Telephone Contact: subject escalates to 70 µg/kg/day dose level
- Week DE 50 Telephone Contact: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated
- Week DE 51 Telephone Contact: subject escalates to 280 µg/kg/day dose level if prior dose level was tolerated
- Week DE 52 Clinic Visit: laboratory tests and dose escalates to 400 µg/kg/day dose, if prior dose level was tolerated

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

8.1.9 Long-term Optional Follow-up Treatment Period

Upon completion of the additional 52-week optional follow-up treatment period and/or implementation of this amendment, whichever occurs first, subjects who are eligible to roll over onto the long-term optional follow-up treatment period will continue to receive study drug until the first of the following occurs:

i. The subjects are eligible to enter another LUM001 study

ii. LUM001 is available commercially, or

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

Once Protocol Amendment 4 is implemented at the site, a determination about Afternoon Dose Escalation (ADE) will be made.

Refer to Section 5.4 for schematics describing the flow of study visits within this period.

Subjects who are eligible to roll over from the 52-week optional follow up treatment period into the long-term optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days prior to implementation of Protocol Amendment 4 will be consented and evaluated for eligibility for ADE. Once a determination about ADE has been made, the subject will then either initiate the ADE (see Figure 8) or continue receiving the same dose of LUM001 once a day (Figure 7), depending on whether they meet criteria for initiating ADE.

Screening evaluations for subjects with ≥7 days since last dose of LUM001 prior to implementation of Protocol Amendment 4 will be performed from Day -14 to Day -1. After obtaining informed consent (and/or assent when appropriate), subjects will undergo a physical examination including body weight, height, and vital signs, and have blood and urine samples taken for clinical laboratory testing. Females who are of childbearing potential will have a serum pregnancy test. Eligibility criteria will be confirmed prior to the Baseline Visit. The Clinician Scratch Scale and Clinician Xanthoma Scale will be completed. Concomitant medications and any adverse events will be recorded.

Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 14-day screening period, consideration may be given to rescreening at a later date. Screening procedures should be repeated at that time. Subject data pertaining to screening will be collected after the subject has been rescreened and determined to meet eligibility.

Subjects with ≥7 days since last dose of LUM001 prior to implementation of Protocol Amendment 4 will be dose escalated up to 400 µg/kg/day or to the highest tolerated dose beginning at Dose Level 2 (35 µg/kg/day), as outlined in Figure 6.

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

- Protocol Amendment 4 DE Week -2 Clinic Visit: obtain consent, weight, and draw blood for laboratory analyses
- Protocol Amendment 4 DE Day 0 Clinic Visit: investigator evaluates laboratory results, study drug is dispensed, and subject begins at 35 µg/kg/day dose level (if no safety concerns)
- Protocol Amendment 4 DE Week 1 Telephone Contact: subject escalates to 70µg/kg/day dose level if prior dose level was tolerated
- Protocol Amendment 4 DE Week 2 Telephone Contact: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated
- Protocol Amendment 4 DE Week 3 Telephone Contact: subject escalates to 280 µg/kg/day dose, if prior dose level was tolerated
- Protocol Amendment 4 DE Week 4 Clinic Visit: laboratory tests and dose escalates to 400 µg/kg/day dose (maximum daily dose of 20 mg), if prior dose level was tolerated
- Protocol Amendment 4 DE Week 8 Telephone Contact: eligibility for ADE will be determined

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

- Repeating Period Week 4 Telephone Contact (ie, beginning 4 weeks after consent to Protocol Amendment 4): Collection of concomitant medications and any adverse events.
- Repeating Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.
- Repeating Period Week 12 Clinic Visit: Physical exam, body weight and height, vital signs, and blood samples for clinical laboratory testing including fasting lipid panel. Blood will also be collected for determination of baseline fat-soluble vitamins. Urine samples for clinical laboratory testing will be collected at every other visit. ItchRO compliance will be assessed, the electronic diary will be issued, the Clinician Scratch Scale and Clinician Xanthoma Scale will be administered, and the PedsQL questionnaire will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected.
- Subjects who do not qualify for ADE may be assessed at a later time point on a case by case basis following discussions between the investigator and medical monitor. Such re-

evaluations may only occur at the Week 12 visit of any Repeating Period beginning with RP2. If in the course of the ADE re-evaluation, a subject is found to qualify for ADE, then the subject will move into Schedule F or G, as outlined in Section 16.1. During the follow-up treatment period, subjects will return to the clinic every 3 months.

Subjects eligible for ADE, (ie, who have sBA level above normal AND/OR ItchRO [Obs] score ≥1.5), will begin BID dosing (ADE) as follows (see Figure 8):

- On ADE Day 0, morning dosing will continue at 400 µg/kg or the maximum tolerated dose. However, the volume of the morning dose will be reduced by half. Of note: Morning dosing must have been stable for ≥4 weeks prior to initiation of ADE.
- On ADE Day 0, the afternoon dose will be initiated at 140 µg/kg/day and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose then will be escalated up to 400 µg/kg (ie, up to a maximum 800 µg/kg/day or maximum tolerated dose).

The following procedures will occur during the ADE period:

- ADE Day 0 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The Clinician Scratch Scale, Clinician Xanthoma Scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected.
- ADE Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.
- ADE Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The Clinician Scratch Scale, Clinician Xanthoma Scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected.
- ADE Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.
- ADE Week 8 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The Clinician Scratch Scale, Clinician

Xanthoma Scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed upon completion of other study procedures. Concomitant medications and any adverse events will be collected.

Thereafter, subjects will have study activities repeated in repeating 12-week periods as described above, until study completion or termination (see Figure 8)

If any subject experiences intolerance, the investigator, in consultation with the medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period; later attempts to escalate the dose are permitted. At the investigator's discretion and in consultation with the medical monitor, subjects who were previously down-titrated may be rechallenged during the follow-up treatment period. If the subject is on a twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose.

Safety and clinical laboratory evaluations and a physical exam (including collection of vital signs, height and weight measurements) will be completed at each clinic visit. In addition, the Clinician Scratch Scale, Clinician Xanthoma Scale, and PedsQL will be administered and study drug compliance will be assessed (PedsQL will not be performed at certain clinic visits - please refer to schedule of procedures). The PIC, CIC, and CGTB assessments will be completed at Weeks 84, 96, 100, and the End of Treatment (EOT) / ET visit. Palatability data will be collected at each clinic visit during the long-term optional follow up treatment period (including the EOT/ET visit), with the exception of the PA4 DE, and ADE visits. Plasma samples will be obtained for LUM001 pharmacokinetics at the ADE Day 0, ADE Week 4, and ADE Week 8 visits, and at the 3 scheduled clinic visits following completion of the ADE period. Subjects/caregivers will receive follow-up phone calls at Weeks 64, 68, 76, 80, 88, 92, as well as those outlined within the DE, PA4 DE, and repeating 12-week periods. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.

Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, 84, and 96 clinic visits, at PA4 DE Week 4, and at every clinic visit within the repeating 12-week periods. Electronic diaries will be provided to subjects and caregivers at these visits and re-training on the use of the diary will occur, as appropriate.

At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the long-term exposure period.

With the exception of the EOT/ET visit, additional study drug will be supplied at each clinic visit during the follow-up treatment period. Unused study drug will be collected at every visit.

Subjects will be encouraged to complete all study activities and visits. Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo safety and clinical laboratory evaluations, including pharmacokinetic sampling of LUM001, determination of serum bile acids, other cholestasis biochemical markers, fat soluble vitamins,

and AFP. In addition the following assessments should be completed: the Clinician Scratch Scale, Clinician Xanthoma Scale, the PedsQL, the PIC, the CIC, the CGTB, and the palatability questionnaire, as defined for ET (see Schedule of Procedures, Section 16.1). For subjects who complete the study, the assessments performed at the EOT visit will be identical to the assessments performed at the ET visit.

8.1.10 End of Treatment or Early Termination

Any subject who completes or withdraws from the study should undergo all procedures specified for the EOT/ET visit (see Schedule J). The following assessments are to be completed at the EOT/ET visit: safety and clinical laboratory evaluations, including determination of serum bile acids, lipid panel, other cholestasis biochemical markers, fat soluble vitamins and AFP. Female subjects who are of childbearing potential will have a urine pregnancy test. Study drug compliance will be assessed. Concomitant medications and adverse events will be collected. In addition, the following assessments should be completed: the Clinician Scratch Scale, Clinician Xanthoma Scale, the PedsQL, the PIC, the CIC, and the CGTB assessments, as defined for the ET visit (see Schedule of Procedures, Section 16.1).

8.1.11 Safety Follow-up Period

A safety follow-up phone call will be made 30 days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded.

8.2 Genetic Testing

JAGGED1 and NOTCH2 mutations can be predictive of ALGS. For ALGS subjects who meet clinical diagnostic criteria for ALGS (see Section 16.3) but do not have documentation of a JAGGED1 or NOTCH2 mutation, the clinical diagnosis of ALGS may be confirmed by genotyping. Genetic counseling, as appropriate, will be provided to subjects and their legal caregivers. Subjects for whom prior genotyping was performed may need to have an optional repeat analysis performed if the original information collected at screening was insufficient for complete documentation of the diagnosis of ALGS including the type of mutation recorded. For those participants for which the type of the mutation cannot be documented, genetic testing may be conducted and the results recorded.

8.3 Physical Examination, Weight and Height, Vital Signs

A physician investigator will conduct a physical examination on each subject at screening and at every study clinic visit. In addition, body weight, height, and vital signs, including body temperature, blood pressure, respiration and pulse, will be determined at every study clinic visit.

8.4 Laboratory Assessments

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

The investigator is responsible for reviewing and signing all laboratory reports. The clinical significance of each value outside of the reference range will be assessed and documented as either not clinically significant (NCS) or clinically significant (CS). See Section 11.4.3 regarding laboratory abnormalities.

8.5 Pruritus and Quality of Life Assessments

8.5.1 Itch Reported Outcome (ItchRO™)

Pruritus will be assessed using the Itch caregiver and patient reported outcome measures (ItchRO) administered as a twice daily electronic diary. Caregivers for all subjects will complete the Observer instrument: ItchRO(Obs)™. Children ≥9 years of age will independently complete the patient instrument: ItchRO(Pt)™. Children between the ages of 5 and 8 years will complete the patient instrument with the assistance of their caregiver: ItchRO(Pt), if needed. Age at screening will be used as the age for the determination of the appropriate ItchRO instrument to be used for the study and this same instrument will be used for the duration of the study (regardless of subsequent birthdays after the screening visit). The primary measure of pruritus will be made using the ItchRO(Obs).

Subjects and caregivers will be trained in the use of the electronic diary during the screening visit. Beginning with the screening period, pruritus will be assessed and recorded twice daily by caregivers and subjects (ItchRO), as described in Section 16.4.

To be eligible for study entry, caregivers must complete at least 10 eDiary reports (morning and/or evening) during each of two consecutive weeks of the screening period and have an average daily score of >2 for 2 consecutive weeks prior to study start. 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. Subjects are required to discontinue bile acid resins for at least 28 days prior to screening and throughout the study.

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 48 clinic visit (or sooner if the subject has withdrawn from the study before the Week 48 visit). For subjects who enter the 52-week and long-term optional follow-up treatment periods, completion of the diary will occur as outlined in the Schedule of Procedures in Section 16.1.

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing 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 report is not completed within the allowed reporting window, whichever report has been completed will represent the daily score. In the event that a subject/caregiver failed to complete both the morning and evening reports, the daily score for that day will be treated as missing data. The handling of missing data on the daily ItchRO score will be outlined in the SAP for the study.

8.5.2 Clinician Scratch Scale

A clinician's assessment of pruritus made by the principal investigator or appropriate designee using the clinician scratch scale (Section 16.5) will be recorded at screening, Day 0 (baseline), Weeks 3, 6, 12, 18, 22, 28, 38, and 48. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the clinician scratch scale will also be administered at clinic visits as outlined in the Schedule of Procedures in Section 16.1.

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

8.5.3 Clinician Xanthoma Scale

A clinician's assessment of xanthomatosis will be made by the principal investigator or appropriate designee using the Clinician Xanthoma Scale (Section 16.6). This assessment will be completed at Baseline (Day 0) and at Weeks 18, and 48. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the Clinician Xanthoma Scale will be recorded as outlined in the Schedule of Procedures in Section 16.1.

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

8.5.4 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL™ is a questionnaire that will be administered to subjects and/or caregivers at the Week 0 (baseline), 18, 22, and 48. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the PedsQL will be administered as outlined in the Schedule of Procedures in Section 16.1. For subjects with interruptions in LUM001 dosing of ≥7 days, the PedsQL will also be administered at DE Day 0. The PedsQL is a validated, modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescents (Varni et al., 2001). In addition to the core generic PedsQL module, the multidimensional fatigue and family impact questionnaire will also be administered at the Week 0 (baseline), 18, 22, and Week 48 using the age-appropriate module (see Section 16.7). Age at baseline will be used as the age for the determination of the appropriate module to be used for the study and this same module will be used for the duration of the study (regardless of subsequent birthdays after the baseline visit). For subjects who enter the 52-week and long-term optional follow-up treatment periods, the multidimensional fatigue and family impact questionnaire will be administered as outlined in the Schedule of Procedures in Section 16.1.

8.5.5 Patient Impression of Change

The PIC is designed to assess the subject's perception of his/her itching after various points of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The PIC will be completed, by subjects who were 9 years of age or older at the Week 18, 22, and 48 visits. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the PIC will be completed by subjects who were 9 years of age or older at clinic visits as outlined in the Schedule of Procedures in Section 16.1.

8.5.6 Caregiver Impression of Change

The CIC is designed to assess the caregiver's perception of the subject's itch related symptoms and xanthoma severity after various points 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 18, 22, and 48 visits. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the CIC will be completed as outlined in the Schedule of Procedures in Section 16.1.

8.5.7 Caregiver Global Therapeutic Benefit

The 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 18, 22, and 48 visits. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the CGTB will be completed as outlined in the Schedule of Procedures in Section 16.1.

8.5.8 Palatability

A palatability questionnaire (see Section 16.12) will be completed by the subject and/or caregiver (dependent on age) at clinic visits at time points as outlined in the Schedule of Procedures in Section 16.1.

8.6 Restriction on the Lifestyle of Subjects

8.6.1 Contraception Requirements

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

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

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

Acceptable methods of contraception are:

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

Male Contraception:

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

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

8.6.2 Fasting Requirements

On study days in which blood samples are collected for the lipid panel and/or cholestasis biomarkers, all subjects will be required to fast for at least 4 hours (only water is permitted) before blood sample collection. On these visit days study drug should be administered as usual (1 mL, 5 mL, or 0.25 qAM, ac), in the morning 30 minutes before breakfast. After breakfast only water should be consumed until the scheduled clinic visit.

9 STUDY DRUG

9.1 Study Drug Description

9.1.1 LUM001

LUM001 is a powder that is to be dissolved with an appropriate diluent in order to administer the study drug as an oral solution. The compositions of LUM001 study drug 1.0 mL, 0.5 mL, and 0.25 mL oral solutions are described, respectively, in Table 4, Table 5, and Table 6.

Table 4: Composition of LUM001 1.0 mL Oral Solution

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

q.s = quantity sufficient

Table 5: Composition of LUM001 0.5 mL Oral Solution

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

q.s = quantity sufficient

Table 6: Composition of LUM001 0.25 mL Oral Solution

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

q.s = quantity sufficient

9.1.2 Placebo

The matching placebo contains the diluent with no active ingredient. The compositions of placebo 1.0 mL, 0.5 mL, and 0.25 mL study drug oral solutions are described, respectively, in Table 7, Table 8, and Table 9.

Table 7: Composition of Placebo 1.0 mL Oral Solution

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

q.s = quantity sufficient

Table 8: Composition of Placebo 0.5 mL Oral Solution

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

q.s = quantity sufficient

Table 9: Composition of Placebo 0.25 mL Oral Solution

Component	Function	Quantity per 0.5 mL
Propylene Glycol	Co-solvent	62.5 mg
Sucralose	Sweetener	1.875 mg
Grape Flavoring Agent	Taste Masking Agent	1.25 mg
Water	Vehicle	q.s. to 0.25 mL

q.s = quantity sufficient

9.2 Packaging and Labeling

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

9.3 Drug Accountability

Study staff is required to document the receipt, dispensing and return/destruction of study drug supplies provided by the sponsor.

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

10 TREATMENT OF SUBJECTS

10.1 Study Drug Administration

The dose of study drug (LUM001 or placebo) in this study is based on weight. The subject's weight determined at the screening visit will be used to calculate the administered dose of study drug for the first 22 weeks of the study. During the study, the study drug may be adjusted if there is a change of ≥10% in weight since the screening visit or if there is a change of ≥10% in weight since the last weight-based medication adjustment to maintain the target dose (µg/kg/day). The dose may also be down-titrated, at the investigator's discretion and in consultation with the medical monitor, for subjects experiencing intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) to a given dose. If the subject is on twice daily dosing regimen, dose reduction should first be attempted with the afternoon dose. Subjects who were previously down-titrated may be rechallenged during the long-term exposure period.

Study drug will be prepared for each subject by a central pharmacy based on the subject's weight at screening. Grape flavored diluent will be added by the central pharmacy pharmacist prior to shipping study drug to the site. Once study drug has been added to the diluent the resulting solution is stable at temperatures ranging from 4-8^{o}C to room temperature for at least 12 months.

Subjects will receive a grape-flavored solution containing LUM001. Each subject dose will be administered orally once a day (QD) or twice a day (BID) using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the doses should be taken approximately at the same time each day for the duration of the treatment period. See Section 5.5.2 for information regarding dosing during the treatment periods, respectively.

QD Dosing Regimen

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

BID Dosing Regimen

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

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

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

10.2 Treatment Compliance

Compliance with treatment dosing will be monitored and recorded by the study center staff. Subjects and/or caregivers will be asked to complete a paper drug dosing diary indicating when they took their study medication and when they ate breakfast and, for subjects who receive a BID regimen, when they ate dinner (evening meal).

10.3 Concomitant Medications

A concomitant medication is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered during participation in the study (the period from the first day of screening through the last contact.

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

All medications (other than study drug) taken by subjects during the course of the study will be recorded and reviewed by the principal investigator (PI)/investigator's designee. Concomitant medication will be coded using the World Health Organization (WHO) Drug Dictionary (release date 01 Sep 2008, or more recent version if available). AEs related to administration of these medications must also be documented.

Subjects are required to discontinue bile acid resins for at least 28 days prior to screening and for duration of the study. The dosage and dosing regimen of concomitant drug therapy other than that specified by the protocol should not change during the first 22 weeks of study, with the exception of weight-based dose adjustments and vitamin supplementation. No new medications used to treat pruritus may be added during the first 22 weeks of the study. All modifications to a subject's concomitant drug therapy, including weight-based dose adjustments and vitamin supplementation regimen must be carefully documented in the relevant case report forms. If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the investigator or investigator's designee and sponsor to continue or discontinue the subject.

10.4 Other Protocol-required Drugs

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

10.5 Safety Monitoring Rules

10.5.1 General Monitoring Rules

In the evaluation of adverse events and the potential relationship to study drug it is important to note that due to their liver disease many patients with ALGS have abnormal liver enzyme levels (eg ALT, ALP) and total bilirubin at baseline. If an individual subject exhibits a CTCAE Grade 3 treatment emergent laboratory abnormality, with the exception of the specific rules outlined

below (Sections 10.5.2), dosing can be suspended or continued as per the investigator's judgment and following discussion with the medical monitor. If suspended the investigator and medical monitor will evaluate the subject's safety data and make a decision to either restart dosing at the same level, restart dosing at a lower dose level, or discontinue dosing.

To ensure subject safety, if 6 or more subjects at a dose level lower, suspend or stop study medication or exhibit treatment emergent toxicity of CTCAE Grade 3 or greater in the same system organ class (SOC), with the exception of the specific rules outlined below, further dosing of subjects at that dose level and any higher dose levels will be halted until a safety assessment is completed. Study visits and completion of the ItchRO diaries, for all randomized subjects, will continue during the assessment period. After review a decision will be made whether to restart dosing at the same dose level, restart dosing at a lower dose level, or discontinue the subjects from the study. The Data Monitoring Committee (DMC) will be notified of any SAE as specified in the DMC charter.

10.5.2 Safety Monitoring Rules

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

Confirmation Guidance: At any time during the study, the initial clinical laboratory results exceeding the safety monitoring criteria presented below **must be confirmed** by performing measurements on new specimens. Of note: the INR re-test should be conducted by the central laboratory, but may also be conducted at a local laboratory on an as needed basis. All new specimen collections should take place as soon as possible, ideally within 48 to 72 hours of the notification of the laboratory result. It may be difficult for some subjects who live far from the study site to return to the study site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to study investigators and medical monitors immediately, and the data should be included in the case reports.

Stopping Rule Guidance: Subject dosing must be suspended until the retest results are available. If any of the stopping criteria described below (see Section 10.5.2.2 and Section 10.5.2.5) is confirmed, the physician investigator (PI) in consultation with the medical monitor (or appropriately qualified designee) will permanently discontinue the subject from further treatment with study drug (LUM001 or placebo). The subject will be evaluated as outlined below and will be encouraged to complete the ET study procedures (Week 48 visit). Subjects who do not meet the stopping rules based on retest may continue dosing and the investigator and the medical monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. The investigator should also assess the need to capture an AE, its severity according to the CTCAE directives and potential causality. These assessments should also include an evaluation of whether criteria for an SAE are fulfilled (see Section 11.2.3), in particular whether the event should be considered as an important medical event, ie, an event that would have met one of the other seriousness criteria in the absence of appropriate medical interventions.

10.5.2.1 Safety Monitoring for Liver Chemistry Tests

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

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

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

Baseline Total Bilirubin	Total Bilirubin
Total Bilirubin 1-10 mg/dL	3 mg increase
Total Bilirubin >10 mg/dL	5 mg increase

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

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

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

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

10.5.2.2 Stopping Rules for Liver Chemistry Elevations

In the event of confirmed laboratory results exceeding the following criteria, **and the event is without an alternative explanation as discussed with the medical monitor,** discontinuation of dosing of a subject with study drug (LUM001 or placebo) will be considered if:

Baseline Tests	Change Observed
ALT (any level)	ALT ≥ 20 x ULN
Total Bilirubin 1-10 mg/dL	5 mg increase **and** a 2 x increase over baseline level
Total Bilirubin >10 mg/dL	2 x increase over baseline level

10.5.2.3 Safety Monitoring for Triglycerides

In the event of a confirmed laboratory result for fasting total triglyceride >500 mg/dL, the investigator and the medical monitor may consider a temporary interruption of study drug. Dosing may resume when the triglyceride level returns to <300 mg/dL or to the subject's baseline level.

10.5.2.4 Safety Monitoring for Fat Soluble Vitamins

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

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

10.5.2.5 Monitoring/Stopping Rules for Coagulation Panel Results

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

10.6 Adjustment of Dose

Gastrointestinal intolerance, as evidenced by diarrhea/loose stools, abdominal pain/cramping and nausea, is expected to be the most frequent manifestation of a lack of tolerability to study drug. If an individual subject exhibits a treatment emergent CTCAE Grade 2 or greater drug-related GI

toxicity, study drug dose may be lowered to a previously well tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose. This decision should be made in consultation with the medical monitor. A requirement for intravenous fluids as treatment for diarrhea will lead to discontinuation of study drug.

10.7 Withdrawal of Subjects from the Study

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

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

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

For safety reasons, efforts must be made to follow subjects for at least 28 days following their last dose of study drug. If a subject withdraws due to an AE, the investigator should arrange for the subject to have follow-up visit(s) until the AE has resolved or stabilized.

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

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

11 SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

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

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

11.1 Regulatory Requirements

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

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

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

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

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

11.2 Definitions

11.2.1 Adverse Event

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

An adverse event does not include the following:

- Continuous persistent disease/symptom present before the start of study drug, which does not unexpectedly progress, or change in severity following drug administration.

- Disease being studied and/or signs and symptoms associated with the disease, such as jaundice or itching, or abnormalities in liver enzymes already present during the screening period or at the baseline visit.
- Treatment failure or lack of efficacy.

11.2.2 Adverse Reaction and Suspected Adverse Reaction

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

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

11.2.3 Serious Adverse Event (SAE)

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

- Results in death.
- Is life-threatening: that is, poses an immediate risk of death at the time of the event.
- An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE.
- Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization. Admission to the hospital is the criterion that defines "serious," not the duration of hospital stay.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at

home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.3 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (ie, before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. In addition, AEs that occur while the subject is not enrolled in the study during a gap period will be collected as medical history unless the AE started within 30 days of last dose. Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. The investigator should always group signs and symptoms into a single term that constitutes a single unifying diagnosis if possible.

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

11.3.1 Serious Adverse Events

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

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

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

11.3.2 Non-serious Adverse Events

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

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

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

11.3.3.1 Relationship to the Study Drug

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

Related: There is clear evidence that the event is related to the use of study drug (eg, confirmation by positive rechallenge test).

Possible: The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and study drug administration.

Unlikely/Remote: An event for which an alternative explanation is more likely (eg, concomitant medications or ongoing medical conditions) or the temporal relationship to study drug administration and/or exposure suggests that a causal relationship is unlikely (for reporting purposes, Unlikely/Remote will be grouped together with Not Related).

Not Related: The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the investigator believes no relationship exists between the event and study drug.

11.3.3.2 Severity

The Common Terminology Criteria for Adverse Events (CTCAE) grade of the event should be reported according to CTCAE Version 4.0 (Section 16.11). If the CTCAE does not have a grading for a particular adverse event, the severity of the event should be reported based on the following:

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

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

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

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

11.3.3.3 Action Taken with Study Drug

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

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

11.3.3.4 Treatment Given for Adverse Event

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

11.3.3.5 Outcome of the Adverse Event

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

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

If the event is 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).

11.4 Procedures for Handling Special Situations

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

- Serious adverse event (SAE; see Section 11.3.1)

- Pregnancy
- Dosing errors
- Treatment unblinding for any reason (see Section 6.4)

11.4.1 Pregnancy Reporting

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

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

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

11.4.2 Dosing Errors

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

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

Should an overdose occur, the investigator or designee should refer to the Guidance to investigator's section of the investigator's brochure and contact the sponsor or designee within 24 hours.

11.4.3 Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment (eg, bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia). Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the investigator until the parameter returns to its baseline value or until agreement is reached between the investigator and medical

monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the investigator should not be deemed NCS on the laboratory sheet.

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

12 STATISTICAL CONSIDERATIONS

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

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

12.1 Sample Size Considerations

Alagille syndrome is a rare disease. The planned sample size of 30 evaluable ALGS subjects is based on practical considerations, rather than a desired power for a pre-specified difference.

12.2 Populations

12.2.1 Safety Population

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

12.2.2 Efficacy Populations

The main population for efficacy will be the modified intention-to-treat population (MITT), defined as all subjects who were enrolled, received study medication through Week 18, and had a reduction from baseline in serum bile acids of ≥50% at the Week 12 or Week 18 measurement. Subjects will be analyzed by assigned treatment**.**

The intention-to-treat (ITT) Population includes all subjects who were enrolled and received at least one dose of the study medication. Subjects will be analyzed by assigned treatment.

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

12.2.3 Siblings

The enrollment of siblings is allowed. During the double-blind, placebo-controlled, randomized drug withdrawal period, siblings will be assigned in a blinded manner to the same treatment arm. The data from all enrolled participants (including siblings) will be used for the safety analysis. For the efficacy analysis, data from only one of the siblings will be used. The choice of which subject's data to use in the efficacy analysis will be done in a random fashion before the LUM001-304 study is unblinded. Details of the analysis methods will be outlined in the SAP.

12.2.4 Demographic and Baseline Characteristics

12.2.4.1 Subject Disposition

Subject disposition will be summarized descriptively. The number and percentage of subjects enrolled, completed, and withdrawing, along with reasons for withdrawal, will be tabulated overall, and by study phase and treatment group. For purposes of analysis, there will be 3 study phases: Dose escalation/stable dose (Weeks 0-18), Randomized Withdrawal (Weeks 19-22) and Long-Term Exposure (Weeks 23-48 and 23-100).

The number of subjects in each analysis population will be reported. Line listings will be prepared for all subjects not following the planned dosing schedule, showing all doses and dose changes occurring.

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

12.2.4.2 Baseline Data

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

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

Demographic and baseline characteristics will be summarized descriptively overall, by dose group (as appropriate), responder group and treatment group.

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

Medical history information will be presented in listings.

12.2.5 Efficacy Analyses

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

12.2.5.1 Efficacy Variables

The primary efficacy endpoint will be the mean change from Week 18 to 22 of fasting serum bile acid levels in subjects who previously responded to LUM001 treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18. A sensitivity analysis will also be

conducted using subjects who experienced a reduction from baseline in serum bile acids of ≥50% at the Week 48 measurement.

Secondary efficacy endpoints include mean change from Week 18 to Week 22 in liver enzymes (ALP, ALT, and bilirubin [total and direct]) and pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO), in subjects who previously responded to LUM001 treatment, as defined by a reduction in ItchRO scale >1 point from baseline to Week 12 or Week 18. Secondary efficacy endpoints also include mean change from baseline to Week 18 in fasting serum bile acid levels, liver enzymes (ALP, ALT, and bilirubin [total and direct]) and pruritus as measured by ItchRO (Observer ItchRO/Patient ItchRO).

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

For this instrument the caregiver and/or subject will indicate the itch severity in the morning and in the evening each day for the duration of the study (baseline to Week 48). The daily score will be assessed as outlined in Section 16.4 and will have a range from 0-4, with the higher score indicating increasing itch severity. A daily score is defined as the higher of the scores from the morning and evening ItchRO, representing the most severe itch over the 24 hour period. For the change from baseline calculation in average daily ItchRO score, baseline is defined as the average daily ItchRO score in the week consisting of the 7 days immediately prior to Day 0. The average daily score will be the average of the daily scores over a defined study week consisting of the 7 days prior to the visit.

In addition, an analysis for a daily score defined as an average of morning and evening scores will be conducted.

If a caregiver is not compliant with the ItchRO(Obs) during the week prior to a study visit, the average daily score from the most recent, previous compliant week will be used in a Last Observation Carried Forward format. On study compliance for the ItchRO(Obs) will be defined as having at least 4 of the 7 daily ItchRO(Obs) scores for a 7-day period. Similar methods will be used for the ItchRO(Pt). Missing data imputation will not be done for other efficacy endpoints.

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

The following additional efficacy evaluations will be assessed:

- Change from baseline to Weeks 18, 22, 48 and then every 12 weeks in:
    - Fasting serum bile acid levels

  - Liver enzymes (ALT, ALP) and bilirubin (total and direct)
  - Pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO)
  - Other biochemical markers of cholestasis [total cholesterol, low-density lipoprotein cholesterol (LDL-C)]
  - Bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)]
- Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 in:
  - Pruritus response rates as measured by ItchRO (Observer ItchRO/patient ItchRO)
  - Clinician scratch scale
- Change from baseline for PedsQL at Week 18, 22, 48, 60, 72, 84, 96, and 100 and change from Week 18 to Week 22
- PIC at Week 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- CIC at Week 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- CGTB assessment at Weeks 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22
- Change from Baseline (Day 0) to Week 48 in xanthomas, as measured by Clinician Xanthoma Scale

Additional assessments of efficacy variables will occur during the 52-week and long-term optional treatment periods in 12-week intervals. Any of the above evaluations may also occur at clinic visits during the DE, PA4 DE, and ADE periods. Additional exploration of evaluations will be specified in the statistical analysis plan.

A number of sensitivity analyses will be performed to assess the robustness of the results as well as consider the time course of the efficacy assessments. Details of these analyses will be outlined in the SAP for the study.

12.2.5.2 Primary Efficacy Analysis

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

The difference between treatment groups in change from Week 18 to Week 22 in serum bile acid will be evaluated using an ANCOVA model with treatment group as a factor, and Week 18 serum bile acid as a covariate. Treatment group differences within responder groups as well as the potential interaction between responder group and treatment group will also be examined where possible.

12.2.5.3 Secondary, Exploratory and Other Efficacy Analyses

Secondary and exploratory efficacy variables that are continuous measures will be analyzed similarly to the primary efficacy analyses. Where sample size allows, treatment effects over time will be examined using methods appropriate for repeated observations.

Exploratory efficacy measures that are categorical will be analyzed using the chi-square test or Fisher's Exact test as appropriate based on sample sizes. Additionally, the Cochran-Mantel-Haenszel test will be used to adjust for response group. Exploratory efficacy measures will be summarized by frequencies and percents, overall, and by phase and treatment group. This includes the responder definition for pruritus, which will be outlined in the SAP. P-values from the secondary and exploratory efficacy analyses will be considered nominal.

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

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

12.2.6 Safety Analyses

Safety analyses will be performed on the Safety Population.

12.2.6.1 Safety Assessments

The following assessments will be used to monitor safety:

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

12.2.7 Planned Method of Analysis

Safety data, including AEs, clinical laboratory tests, vital signs, physical examinations, and concomitant medication usage will be summarized descriptively overall, by phase (Section 12.2.4.1) and by treatment group for the Safety Population. Summaries may also be provided by dose group if appropriate. Individual subject listings will be prepared for all safety data.

12.2.8 Safety Analysis

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

12.2.8.1 Adverse Events

Frequencies (number and percentage) of subjects with one or more treatment emergent AEs will be summarized by dose group and/or treatment group, by system organ class and preferred term

according to the Medical Dictionary for Regulatory Activities (MedDRA™) terminology. All treatment emergent AEs, all treatment emergent AEs potentially related to study drug, all treatment emergent SAEs and all treatment emergent SAEs potentially related to study drug will be summarized. Specific AEs of special interest, particularly GI related AEs, will be outlined in the SAP and summarized. AEs will be summarized over the entire study and then separately for the dose escalation/stable dose periods (weeks 0-18), randomized withdrawal, and long-term exposure periods of the study.

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

12.2.8.2 Laboratory Tests

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

A separate listing will present laboratory values of all subjects who change from normal to abnormal or from abnormal to normal during the course of the study, where normal ranges for this population are outlined in the SAP. Changes within a treatment group for selected safety measures will be assessed at Weeks 3, 6, 12, 18, 22, 28, 38, 48, 60, 72, 84, 96 and at additional time points during the 52-week and long-term optional treatment periods and final study evaluation visit using methods to be specified in the SAP prior to unblinding the data.

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

12.2.8.3 Physical Exams, Vital Signs and Weight/Height Measurements

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

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

12.2.8.4 Concomitant Medications

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

using counts and percentages. Medications started prior to the first dose of study medication will be indicated in the data listing. A separate listing for medications taken for pruritus will be given that clearly indicates the phase of the study.

12.2.8.5 Study Drug Exposure

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

12.2.8.6 Serum Alpha-fetoprotein

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

12.2.9 Palatability Analyses

Palatability data will be collected at each clinic visit in the follow up treatment period, with the exception of the DE, PA4 DE, and ADE visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age). Data will be listed for individual subjects and summarized using descriptive statistics by study visit. Assessment of change over time will be evaluated. Baseline will be defined as the first recorded evaluation.

12.2.10 Interim Analyses

There will be an interim analysis (IA) conducted after all subjects complete or discontinue the study after Week 48 to guide the future of the program. At the IA the study will be unblinded.

12.2.11 Additional Analyses

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

13 INVESTIGATOR'S REGULATORY OBLIGATIONS

13.1 Informed Consent

The written informed consent/assent documents should be prepared in the languages of the potential patient population, based on an English template version provided by the sponsor or designee.

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

Subjects and/or their legally acceptable representative(s) will be required to read, sign, and date an IEC approved informed consent/assent form (ICF/IAF) summarizing the discussion at screening. Since this is a pediatric study, in addition to the written informed consent, the assent of the child must also be obtained. The person who conducted the informed consent discussion (not necessarily an investigator) should also sign and date the ICF/IAF. The original signed ICF/IAF should be retained in accordance with institutional policy. Subjects and/or their legally acceptable representative(s) will be given a copy of their ICF/ 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/IAF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF/IAF in this central study folder if not done so during the performance of the study.

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

13.2 Study Personnel

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

13.3 Ethical Conduct of the Study

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

13.4 Independent Ethics Committee/Institutional Review Board

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

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

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

13.5 Confidentiality

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

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

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

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

14 ADMINISTRATIVE AND LEGAL OBLIGATIONS

14.1 Pre-study Documentation Required

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

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

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

14.2 Protocol Amendments

Protocol amendments must be made only with the prior approval of the sponsor or designee. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent/assent documents. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the study. The investigator must send a copy of the approval letter from the IEC/IRB to the sponsor or designee. Amendments to the protocol will not be implemented until written IEC/IRB approval has been received.

14.3 Study Termination

Both the sponsor or designee and the investigator reserve the right to terminate the study at the investigator's site, according to the terms of the study contract. The investigator/sponsor or designee should notify the IEC/IRB in writing of the study's completion or ET and send a copy of the notification to the sponsor or designee.

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

14.4 Study Documentation and Storage

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

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

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

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

14.5 Study Monitoring

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

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

study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

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

14.6 Language

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

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

14.7 Compensation for Injury

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

15 REFERENCES

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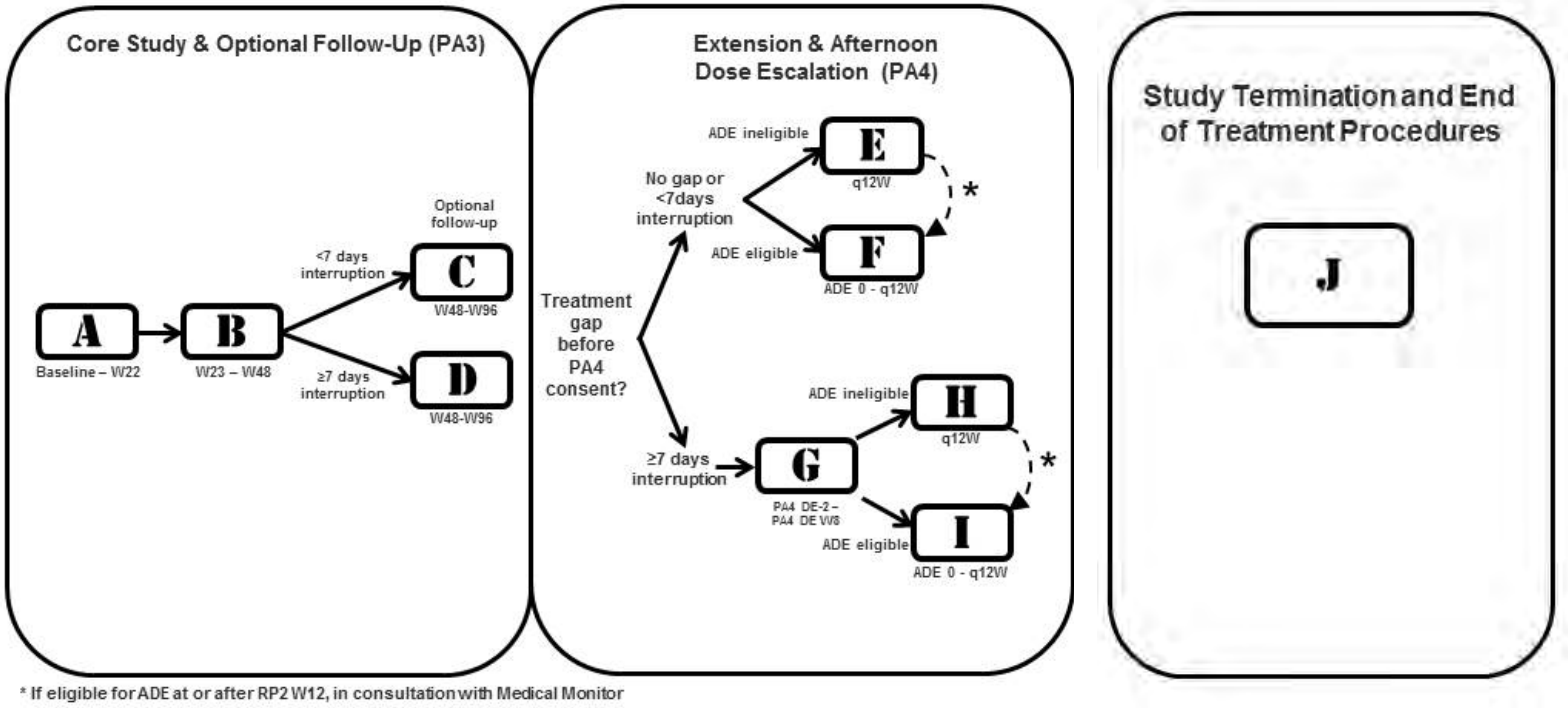
16 APPENDICES

16.1 Schedule of Procedures

Overall Scheme and Corresponding Schedule of Procedures

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

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



16.1.1 Schedule of Procedures A-D: Study Entry – Week 96

Schedule of Procedures A – Screening – Week 22

Study Period	Screening	Baseline	Treatment Period										
			Dose Escalation[i]						Stable Dose			Randomized Withdrawal	
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**18**	**20**	**22**
Study Day	**Day -28 to -1**	**Day 0**	**7**	**14**	**21**	**28**	**35**	**42**	**63**	**84**	**126**	**140**	**154**
Window (in days)			**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**
Informed Consent	X												
Eligibility Assessment/ Medical History	X	X											
Demographics	X												
Physical Exam	X	X			X			X		X	X		X
Body Weight & Height	X	X			X			X		X	X		X
Randomization to Placebo vs. LUM001											X		
Vital Signs[a]	X	X			X			X		X	X		X
CBC with Differential[b]	X	X			X			X		X	X		X
Coagulation[b]	X	X			X			X		X	X		X
Chemistry Panel[b]	X	X			X			X		X	X		X
Lipid Panel[b,c]		X								X	X		X
Cholestasis Biomarkers[b,c]		X								X	X		X
Total Serum bile acids[c]	X[k]	X								X	X		X
Fat Soluble Vitamins[b,c]		X								X	X		X
JAGGED1/NOTCH2 Genotyping[d] (if needed)	X												
Plasma Sample for LUM001		X[j]								X[j]	X[j]		
Urinalysis[b]	X	X[g]			X[g]			X[g]		X	X		X
Serum or Urine Pregnancy Test (if indicated)[e]	X	X			X			X		X	X		X
Subject eDiary/Caregiver eDiary (ItchRO)	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Clinician Scratch Scale	X	X			X			X		X	X		X
Clinician Xanthoma Scale		X									X		
PedsQL		X									X		X
Patient/Caregiver Impression of Change											X		X

Schedule of Procedures A – Screening – Week 22

Study Period	Screening	Baseline	Treatment Period										
			Dose Escalation[i]						Stable Dose			Randomized Withdrawal	
Study Week			**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**18**	**20**	**22**
Study Day	**Day -28 to -1**	**Day 0**	**7**	**14**	**21**	**28**	**35**	**42**	**63**	**84**	**126**	**140**	**154**
Window (in days)			**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**
Caregiver Global Therapeutic Benefit											X		X
Enrollment		X											
Study Drug Supplied		X			X			X		X	X		X
Review Study Diaries & Assess Compliance		X			X			X		X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[f]			X	X		X	X		X			X	

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[c] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[d] Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation in support of the diagnosis of ALGS.
[e] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Subjects must be available to receive a phone call from study staff.
[g] At the indicated visits during the treatment period, oxalate will be part of the urinalysis.
[h] During screening and throughout the study, the eDiary (ItchRO) will be completed twice daily (AM & PM). Compliance will be assessed at each visit/phone contact.
[i] Subjects should be dosed for at least 7 days at each dose level.
[j] Pharmacokinetic analysis will be done at Baseline, and then approximately 4 hours post-dosing at one additional time point – at Week 12, 18, 38, or 48 (to be selected by site/investigator).
[k] Subjects are NOT required to fast prior to sample collection at the screening visit.

Clinic Visit
Phone Contact

Schedule of Procedures B – Long-term Exposure: Week 23–Week 48

Study Period	Treatment Period (cont'd)										Follow Up
	Long-Term Exposure										
Study Week	23	24	25	26	27	28	33	38	43	Week 48 (or Early Termination[f])	
Study Day	161	168	175	182	189	196	231	266	301	336	30 days after final dose
Window (in days)	(±2)	(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)	(±14)	(±5)
Physical Exam						X		X		X	
Body Weight & Height						X		X		X	
Vital Signs[a]						X		X		X	
CBC with Differential[b]						X		X		X	
Coagulation[b]						X		X		X	
Chemistry Panel[b]						X		X		X	
Lipid Panel[b,c]										X	
Total Serum bile acids[c]										X	
Cholestasis Biomarkers[b,c]										X	
Fat Soluble Vitamins[b,c]						X		X		X	
Plasma Sample for LUM001								X[i]		X[i]	
Urinalysis[b]						X		X		X[g]	
Urine Pregnancy Test (if indicated)[d]						X		X		X	
Clinician Scratch Scale						X		X		X	
Clinician Xanthoma Scale										X	
Subject eDiary/Caregiver eDiary (ItchRO)	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
PedsQL										X	
Patient & Caregiver Impression of Change										X	
Caregiver Global Therapeutic Benefit										X	
Study Drug Supplied						X		X		X[j]	
Review Study Diaries & Assess Compliance						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[e]	X	X	X	X	X		X		X		X

Schedule of Procedures B – Long-term Exposure: Week 23–Week 48

Study Period	Treatment Period (cont'd) Long-Term Exposure										Follow Up
Study Week	23	24	25	26	27	28	33	38	43	Week 48 (or Early Termination[f])	
Study Day	161	168	175	182	189	196	231	266	301	336	30 days after final dose
Window (in days)	(±2)	(±2)	(±2)	(±2)	(±2)	(±5)	(±5)	(±5)	(±5)	(±14)	(±5)

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[c] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[d] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[e] Subjects must be available to receive a phone call from study staff.
[f] Subjects who withdraw early should complete all evaluations at this visit.
[g] At the indicated visits during the treatment period, oxalate will be part of the urinalysis.
[h] During screening and throughout the study, the eDiary (ItchRO) will be completed twice daily (AM and PM). Compliance will be assessed at each visit/phone contact.
[i] Pharmacokinetic analysis will be done at Baseline, and then approximately 4 hours post-dosing at one additional time point – at Week 12, 18, 38, or 48 (to be selected by site/investigator).
[j] For subjects entering optional Follow-up Treatment Period, once corresponding consent is signed.

Clinic Visit
Phone Contact

Schedule of Procedures C – 52-week Optional Follow-up Treatment Period (FTP): Week 48-96 for Those Subjects <7 Days from the Last Dose of LUM001. Includes evaluation of eligibility for BID dosing regimen.

Study Period	52-week FTP											
Study Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**
Window (in days)	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Informed Consent/Assent for PA4[g]			X			X			X			X
Afternoon Dose Escalation (ADE) eligibility assessment followed by shift in visit schedule[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Physical Exam			X			X			X			X
Body Weight & Height			X			X			X			X
Vital Signs[a]			X			X			X			X
CBC with Differential[b]			X			X			X			X
Coagulation[b]			X			X			X			X
Chemistry Panel[b]			X			X			X			X
Lipid Panel[b,c]			X			X			X			X
Cholestasis Biomarkers[b,c]			X			X			X			X
Fat Soluble Vitamins[b,c]			X			X			X			X
Optional Genotyping[d]			X									
Urinalysis[b]			X			X			X			X
Urine Pregnancy Test (if indicated)[e]			X			X			X			X
Clinician Scratch Scale			X			X			X			X
Clinician Xanthoma Scale			X			X			X			X
Subject eDiary/Caregiver eDiary (ItchRO)			X[i]	X[i] to Week 62		X[i]	X[i] to Week 74		X[i]	X[i] to Week 86		X[i]
PedsQL			X			X			X			X
Patient & Caregiver Impression of Change									X			X
Caregiver Global Therapeutic Benefit									X			X
Study Drug Supplied			X			X			X			X
Review Study Diaries & Assess Compliance			X			X			X			X

Schedule of Procedures C – 52-week Optional Follow-up Treatment Period (FTP): Week 48-96 for Those Subjects <7 Days from the Last Dose of LUM001. Includes evaluation of eligibility for BID dosing regimen.

Study Period	52-week FTP											
Study Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**
Window (in days)	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Phone contact[f]	X	X		X	X		X	X		X	X	

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation.
[c] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[d] Genotyping sample will be drawn at Week 60 or at the time of re-consent for the optional follow-up treatment period; sample will be used to provide a full characterization and documentation of the mutation type in support of the diagnosis of ALGS.
[e] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Subjects must be available to receive a phone call from study staff.
[g] Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent patient for Protocol Amendment 4 at the next clinic visit.
[h] Once the Protocol Amendment 4 consent/assent has been signed, site will assess subject eligibility for Protocol Amendment 4 and ADE. Depending on the outcome of ADE eligibility assessment, subject will move into either Schedule of Procedures E or F. Of note: It is possible that subject will not necessarily complete up through Week 96 before they move to Schedule of Procedures E or F. ADE eligibility assessments may occur any time between Week 52 and Week 100.
[i] During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 60, Week 72, and Week 84 visits.

Clinic Visit
Phone Contact

Schedule of Procedures D – 52-week Optional Follow-up Treatment Period: DE -2 – Week 96 for Those Subjects ≥7 Days from the Last Dose of LUM001. Includes evaluation of eligibility for BID dosing regimen.

Study Period	Treatment Period (cont'd)															
	FTP Dose Escalation (DE)						FTP									
FTP Study Week	**DE -2**	**DE 0**	**DE 49**	**DE 50**	**DE 51**	**DE 52**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**
DE Study Day	-14	0	343 [a]	350 [a]	357 [a]	364 [a]	420 [a]	448 [a]	476 [a]	504 [a]	532 [a]	560 [a]	588 [a]	616 [a]	644 [a]	672 [a]
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Informed Consent/Assent for study re-entry under PA3	X															
Eligibility Assessment for study re-entry	X															
Informed Consent/Assent for PA4[h]							X			X			X			X
Afternoon Dose Escalation (ADE) eligibility assessment followed by shift in visit schedule[i]							X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
Physical Exam	X	X				X	X			X			X			X
Body Weight & Height	X	X				X	X			X			X			X
Vital Signs[b]	X	X				X	X			X			X			X
CBC with Differential[c]	X	X				X	X			X			X			X
Coagulation[c]	X	X				X	X			X			X			X
Chemistry Panel[c]	X	X				X	X			X			X			X
Lipid Panel[c,d]	X	X				X	X			X			X			X
Cholestasis Biomarkers[c,d]	X	X				X	X			X			X			X
Fat Soluble Vitamins[c,d]	X	X				X	X			X			X			X
Optional Genotyping[e]	X															
Urinalysis[c]	X	X				X	X			X			X			X
Urine Pregnancy Test[f]	X	X				X	X			X			X			X

Schedule of Procedures D – 52-week Optional Follow-up Treatment Period: DE -2 – Week 96 for Those Subjects ≥7 Days from the Last Dose of LUM001. Includes evaluation of eligibility for BID dosing regimen.

Study Period	Treatment Period (cont'd)															
	FTP Dose Escalation (DE)						FTP									
FTP Study Week	**DE -2**	**DE 0**	**DE 49**	**DE 50**	**DE 51**	**DE 52**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**
DE Study Day	-14	0	343 [a]	350 [a]	357 [a]	364 [a]	420 [a]	448 [a]	476 [a]	504 [a]	532 [a]	560 [a]	588 [a]	616 [a]	644 [a]	672 [a]
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**
Clinician Scratch Scale	X	X				X	X			X			X			X
Clinician Xanthoma Scale		X				X	X			X			X			X
Subject eDiary/Caregiver eDiary							X[j]	X[j] to Week 62		X[j]	X[j] to Week 74		X[a]	X[j] to Week 86		X[a]
PedsQL		X					X			X			X			X
Patient & Caregiver Impression of Change													X			X
Caregiver Global Therapeutic Benefit													X			X
Study Drug Supplied		X				X	X			X			X			
Review Study Diaries & Assess Compliance						X	X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact[g]			X	X	X			X	X		X	X		X	X	

[a] Calculation of Study Day includes subject's participation through the first 48 weeks.
[b] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[c] See Section 16.2 for detailed list of laboratory analytes. Blood samples for analysis of fat soluble vitamins should be drawn prior to administration of vitamin d supplementation.
[d] Subjects are required to fast at least 4 hrs (only water permitted prior to collection).
[e] Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation type in support of the diagnosis of ALGS. Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] For females of childbearing potential, result must be reviewed prior to dispensing study drug.
[g] Subjects must be available to receive a phone call from study staff.
[h] Once necessary approvals are received for Protocol Amendment 4 and associated consent/assent documents are available, site will consent/assent subject for Protocol Amendment 4 at the next clinic visit.

Schedule of Procedures D – 52-week Optional Follow-up Treatment Period: DE -2 – Week 96 for Those Subjects ≥7 Days from the Last Dose of LUM001. Includes evaluation of eligibility for BID dosing regimen.

	Treatment Period (cont'd)															
Study Period	**FTP Dose Escalation (DE)**						**FTP**									
FTP Study Week	**DE -2**	**DE 0**	**DE 49**	**DE 50**	**DE 51**	**DE 52**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**
DE Study Day	-14	0	343 [a]	350 [a]	357 [a]	364 [a]	420 [a]	448 [a]	476 [a]	504 [a]	532 [a]	560 [a]	588 [a]	616 [a]	644 [a]	672 [a]
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**	**(±7)**	**(±7)**	**(±14)**

[i] Once the Protocol Amendment 4 consent/assent has been signed, site will assess subject eligibility for Protocol Amendment 4 and ADE. Depending on the outcome of ADE eligibility assessment, subject will move into either Schedule of Procedures E or F. Of note: It is possible that subject will not necessarily complete up through Week 96 before they move to Schedule of Procedures E or F. ADE eligibility assessments may occur any time between Week 60 and Week 100.

[j] During the Follow-up Treatment Period, daily completion of the study diary for 2 consecutive weeks following Week 68, Week 96, and Week 120 visits.

Clinic Visit
Phone Contact

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

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

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

	Below study activities repeat in repeating 12-week periods[h]		
Repeating Period Week (RPx)	**RPx Week 4**	**RPx Week 8**	**RPx Week 12**
Scheduling Considerations	**4 weeks after consent under PA4**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
Physical Exam			X
Body Weight & Height			X
Vital Signs[a]			X
CBC with Differential[b]			X
Coagulation[b]			X
Chemistry Panel[b]			X
Lipid Panel[b,c]			X
Cholestasis Biomarkers[b,c]			X
Fat Soluble Vitamins[b,c,d]			X
Urinalysis[b]			X[j]
AFP Sample			X[i]
Serum or Urine Pregnancy Test (if indicated)[e]			X
Clinician Scratch Scale			X
Clinician Xanthoma Scale			X
Caregiver ItchRO/ Patient ItchRO			X (collected for 2 week period following this visit)

	Below study activities repeat in repeating 12-week periods[h]		
Repeating Period Week (RPx)	**RPx Week 4**	**RPx Week 8**	**RPx Week 12**
Scheduling Considerations	**4 weeks after consent under PA4**		
Window (in days)	**(±7)**	**(±7)**	**(±14)**
PedsQL			X
Palatability Questionnaire			X
Study Drug Supplied[f]			X
Assess Compliance			X
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Follow-up Phone Contact[g]	X	X	

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

Clinic Visit
Phone Contact

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

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

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

Study Period	**Follow-up Treatment Period Afternoon Dose Escalation (ADE)**							**Study activities repeat in repeating 12-week periods after completion of the ADE period[h]**		
Study Week	**ADE Day 0**	**ADE Week 1**	**ADE Week 2**	**ADE Week 4**	**ADE Week 5**	**ADE Week 6**	**ADE Week 8**	**Week 4**	**Week 8**	**Week 12**
Scheduling Considerations	**To be scheduled as soon as ADE eligibility is confirmed and materials are on-site**							**The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.**		
Window (in days)	**N/A – see above**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±7)**	**(±7)**	**(±14)**
Urinalysis[b]	X			X			X			X[k]
AFP Sample										X[i]
Plasma Sample for LUM001[j]	X			X			X			X[j]
Serum or Urine Pregnancy Test (if indicated)[e]	X			X			X			X
Clinician Scratch Scale	X			X			X			X
Clinician Xanthoma Scale	X			X			X			X
Caregiver ItchRO/ Patient ItchRO										X (collected for 2 week period following this visit)
PedsQL	X			X			X			X
Palatability Questionnaire										X
Study Drug Supplied[f]	X			X			X			X
Assess Compliance	X			X			X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X

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

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

Clinic Visit
Phone Contact

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

Schedule of Procedures G – Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, applicable as follows:

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

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

Study Period	**Protocol Amendment 4 Follow-up Treatment Period Dose Escalation (DE)**						
PA4 DE Study Week	**PA4 DE -2**	**PA4 DE Day 0**	**PA4 DE Week 1**	**PA4 DE Week 2**	**PA4 DE Week 3**	**PA4 DE Week 4**	**PA4 DE Week 8**
Scheduling Considerations	**-14**	**0**					
Window (in days)	**(±14)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±14)**
Fat Soluble Vitamins[b,c,d]	X	X				X	
Urinalysis[b]	X	X				X	
Serum or Urine Pregnancy Test (if indicated)[e]	X	X				X	
Clinician Scratch Scale	X	X				X	
Clinician Xanthoma Scale	X	X				X	
Caregiver ItchRO/ Patient ItchRO						X (collected for 2 week period following this visit)	
PedsQL		X					
Study Drug Supplied[f]		X				X	
Assess Compliance						X	
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Follow-up Phone Contact[g]			X	X	X		X

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.

Clinic Visit
Phone Contact

Schedule of Procedures H – Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject ineligible for ADE

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

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

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

Clinic Visit
Phone Contact

Schedule of Procedures I – Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject eligible for ADE

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

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

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

[a] Blood pressure (BP), heart rate (HR), temperature, respiration rate.
[b] See Section 16.2 for detailed list of laboratory analytes.
[c] Subjects are required to fast at least 4 hrs (only water permitted) prior to collection.
[d] Blood samples must be drawn before administration of vitamin supplementation.
[e] Females of childbearing potential, result must be reviewed prior to dispensing study drug.
[f] Study drug may be dispensed at unscheduled clinic visits.
[g] Subjects must be available to receive a phone call from study staff.
[h] Study visits will continue in the same pattern until the first of the following occur: (i) subjects are eligible to enter another LUM001 study, or (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.
[i] Sample will be drawn at every other clinic visit starting with RP1 Week 129.
[j] Pharmacokinetic sample will additionally be collected at the three scheduled clinic visits following completion of the afternoon dose escalation period.
[k] At indicated visits during treatment period, oxalate will be part of the UA.

Clinic Visit
Phone Contact

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

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

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

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

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

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

Clinic Visit
Phone Contact

16.2 List of Laboratory Analytes

Screening Tests
JAGGED1/NOTCH2 Genotyping (if indicated)
Serum βhCG (if indicated)

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

Coagulation
aPTT (sec)
PT (sec)
INR

Clinical Chemistry
Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Phosphorus
Glucose
BUN
Creatinine
Uric Acid
Total bilirubin
Direct bilirubin
Alkaline phosphatase (ALP)
AST (SGOT)
ALT (SGPT)
GGT

Lipid Panel[a]
Total cholesterol
LDL-C (direct)
HDL-C
Triglycerides (TG)

Cholestasis Biomarkers[1]
Serum bile acids
7α hydroxy-4-cholesten-3-one (C4)

Fat Soluble Vitamins[b]
25-hydroxy vitamin D
Retinol
Retinol binding protein
Tocopherol (α)

Marker of hepatocellular carcinoma
alpha-fetoprotein (AFP)

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

LUM001 Drug Levels
LUM001 in plasma

[a] Other biomarkers [eg, autotaxin, lysophosphatidic acid (LPA), FGF-19, FGF-21] may be measured at the discretion of the sponsor, samples will be collected and appropriately stored for subsequent analysis, as needed.

[b] Blood samples for the analysis of fat soluble vitamins should be drawn prior to administration of vitamin supplementation and approximately 4 hours after food or formula.

[c] Will be performed on abnormal findings unless otherwise specified.

[d] At the specified time points on the Schedule of Procedures (Section 16.1), oxalate will be part of the urinalysis.

16.3 Alagille Syndrome Diagnostic Criteria

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

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

[a] Family history = ALGS present in a first degree relative.
[b] Identified = JAGGED1 or NOTCH2 mutation identified in clinical laboratory.
[c] Not identified = Not identified on screening, or not screened for.

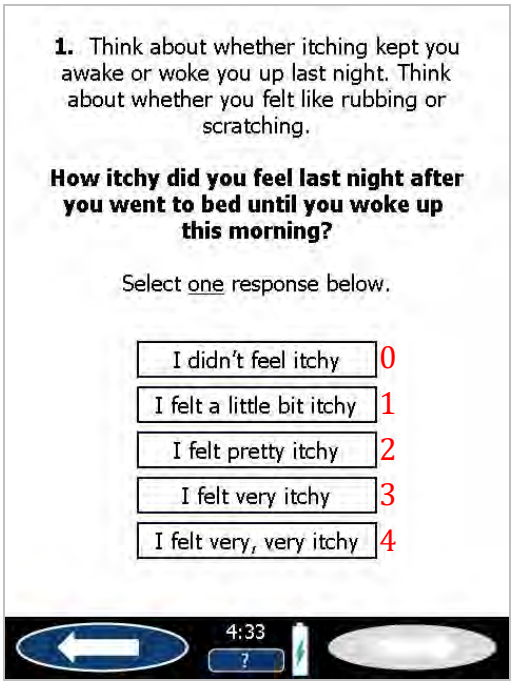
16.4 Itch Reported Outcome Instrument (ItchRO™)

Many of the ALGS subjects in this study are expected to be between the ages of 2 and 10, necessitating reliance upon an observer-reported outcome instrument (ObsRO) to evaluate a pruritus endpoint.

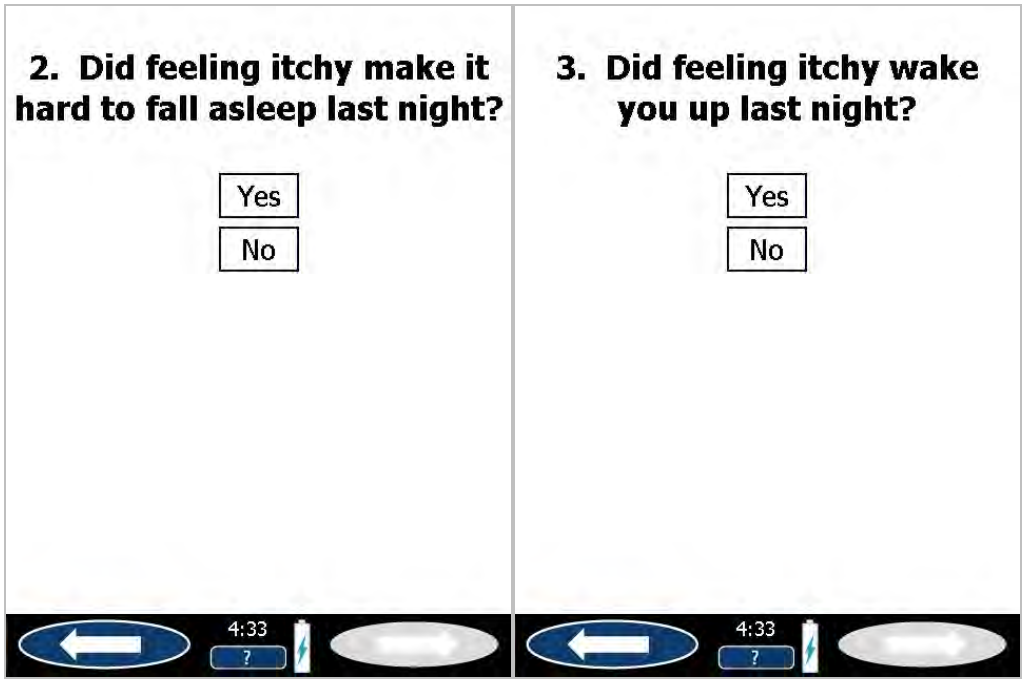
The ItchRO instrument is being developed both as a patient reported outcome (PRO) instrument for pediatric subjects (9 years of age and older) and an ObsRO for caregivers/parents. The ItchRO will be completed using an electronic diary (eDiary) twice daily (morning and evening) for both the PRO and ObsRO.

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

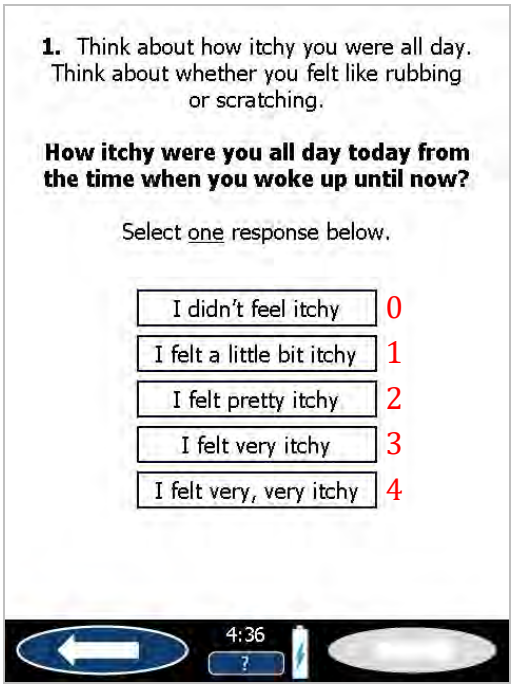
A screen shot from the ItchRO(Pt) **morning report** is show below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Pt) morning report score is 0 and the maximum score is 4.



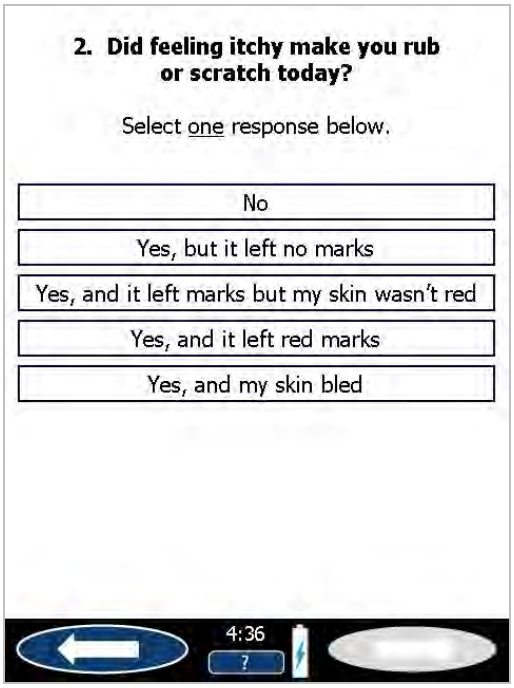
If the patient selects "I didn't feel itchy at all" the diary is complete, if not the following screens will be shown on the eDiary:



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

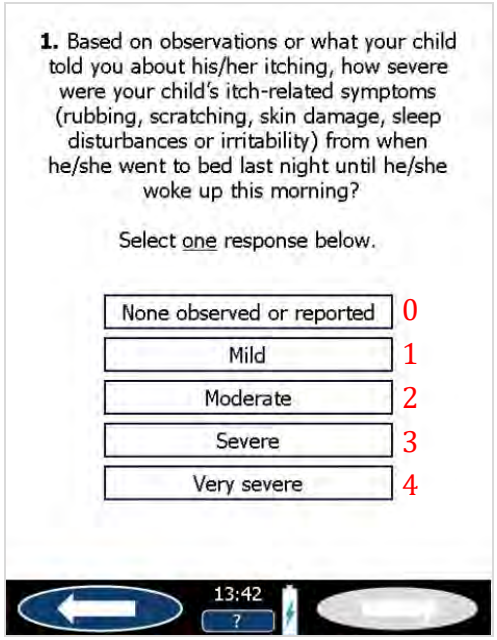


If the patient selects "I didn't feel itchy" the diary is complete, if not the following screen will be shown on the eDiary:



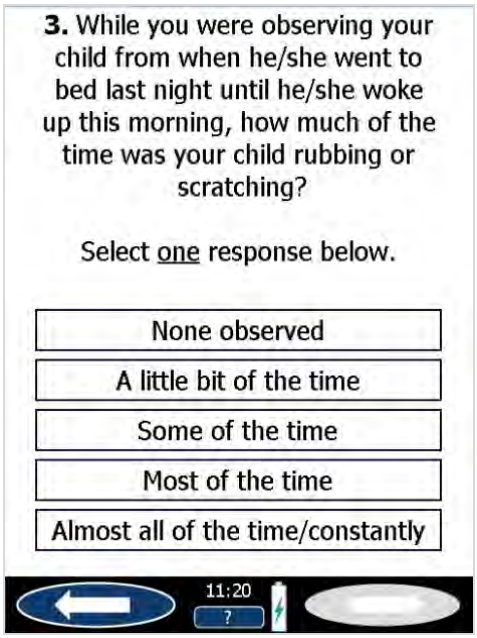
16.4.2 Observer Itch Reported Outcome Instrument, ItchRO(Obs)™

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

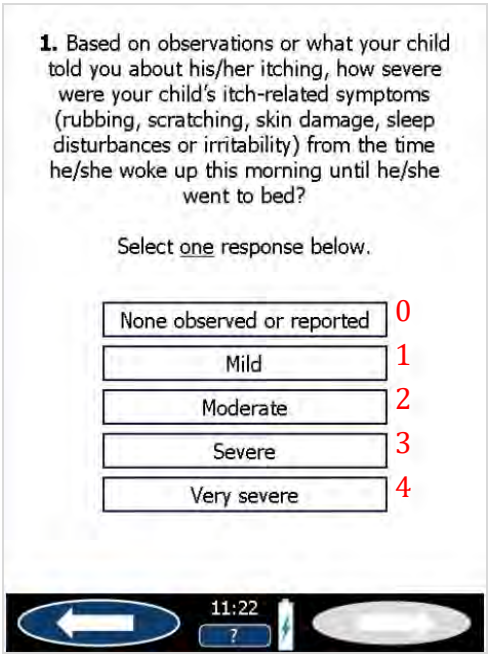


If the caregiver selects "None observed or reported" the diary is complete, if not the following screen will be shown on the eDiary:

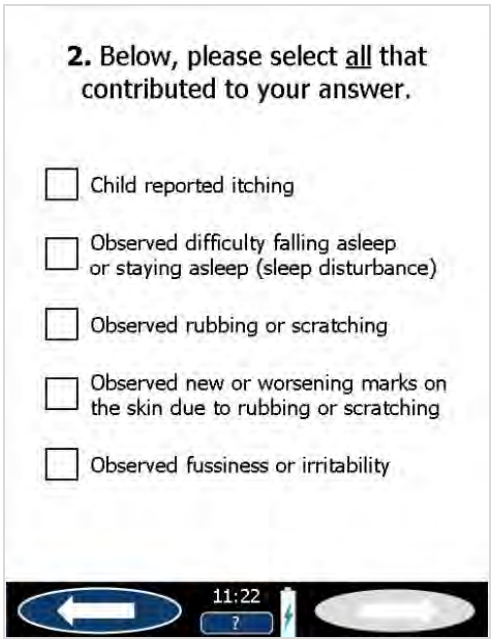
All caregivers will also be required to answer the following question on the ItchRO(Obs) **morning report**:



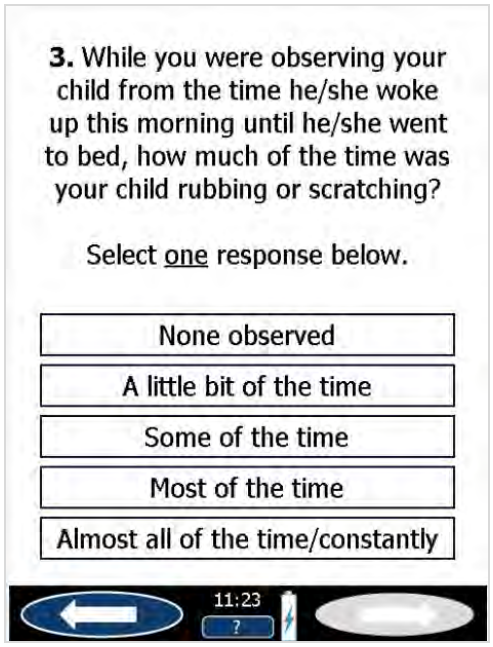
A screen shot from the ItchRO(Obs) **evening report** is shown below. The score associated with each response option is indicated in red text (these will not be shown on the eDiary). The minimum ItchRO(Obs) evening report score is 0 and the maximum score is 4.



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



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



16.5 Clinician Scratch Scale

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

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

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

16.6 Clinician Xanthoma Scale

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

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

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

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

16.7 Pediatric Quality of Life Inventory (PedsQL™)

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

Pediatric HRQoL measurement instruments must be sensitive to cognitive development and must include both child self-report and parent proxy-report. Accordingly, the PedsQL consists of developmentally appropriate forms for children ages 1-12 months and 13-24 months, and 2-4, 5-7, 8-12, and 13-18 years. Pediatric self-report is measured in children and adolescents ages 5-18 years, and parent proxy-report of child HRQOL is measured for children and adolescents ages 2-18 years. Subjects will continue to fill out the same questionnaire used at baseline for continuity of data collection, regardless of subsequent birthdays after the baseline visit.

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

16.7.1 Parent Report for Infants (1 to 12 months)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 1-12 months)

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

PedsQL 3

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

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

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

16.7.2 Parent Report for Infants (13 to 24 months)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Infant Scales

PARENT REPORT for INFANTS (ages 13-24 months)

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

PedsQL 3

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

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

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

16.7.3 Parent Report for Toddlers (ages 2-4)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

Please complete this section if your child attends school or daycare

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

16.7.5 Parent Report for Children (ages 8-12)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

16.7.6 Parent Report for Teenagers (ages 13-18)

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

Instructions for interviewer:

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

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

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

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

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

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

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

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

PedsQL 2

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

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

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

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

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

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

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

PedsQL 3

How much of a problem is this for you?

Not at all 

Sometimes 

A lot 

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0 - Language (Country)

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID# _____

Date: _____

PedsQL™
Multidimensional Fatigue Scale

Standard Version

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

Instructions for interviewer:

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

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

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

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

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

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

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

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

PedsQL 2

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

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

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

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

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

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

PedsQL 3

How much of a problem is this for you?

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

ID# _____

Date: _____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

ID# _____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Standard Version

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

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

16.7.17 Family Impact Module v 2.0

ID#_____

Date:_____

PedsQL™
Family Impact Module

Version 2.0

PARENT REPORT

DIRECTIONS

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

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

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

PedsQL 2

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

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

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

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

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

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

PedsQL 3

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

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

DIRECTIONS

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

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

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

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

16.8 Patient Impression of Change (PIC)

The Patient Impression of Change (PIC) is designed to assess the subject's perception of his/her itching at the end of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The PIC will be completed by subjects who were 9 years of age or older at the Week 18, 22 and 48 visits. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the CIC will be completed as outlined in the Schedule of Procedures in Section 16.1.

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

PIC

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

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

16.9 Caregiver Impression of Change (CIC)

The Caregiver Impression of Change (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 18, 22 and 48 visits. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the CIC will be completed as outlined in the Schedule of Procedures in Section 16.1.

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

CIC

How would you rate the change in your child's itch related symptoms since the start of the study?

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

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

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

16.10 Caregiver Global Therapeutic Benefit (CGTB)

The Caregiver Global Therapeutic Benefit (CGTB) questionnaire is designed to assess the caregiver's perception of the treatment benefits on the subject's itching compared to the side effects experienced with study drug. The CGTB will be completed by all caregivers at the Week 18, 22 and 48 visits. For subjects who enter the 52-week and long-term optional follow-up treatment periods, the CIC will be completed as outlined in the Schedule of Procedures in Section 16.1.

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

CGTB

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

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

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

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

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

CONTENTS

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.					
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node.					
Spleen disorder	Incidental findings (e.g., Howell-Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the spleen.					
Thrombotic thrombocytopenic purpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Cardiac disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in aortic valve function or structure.					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the pumping function of the heart.					
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles.					
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by pathological irregularities in the cardiac conduction system.					
Constrictive pericarditis	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by a thickened and fibrotic pericardial sac; these fibrotic changes impede normal myocardial function by restricting myocardial muscle action.					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

Cardiac disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in mitral valve function or structure.					
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.					
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.					
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

Cardiac disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in pulmonary valve function or structure.					
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.					
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
Definition: A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall.					
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.					
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in tricuspid valve function or structure.					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His.					
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Congenital, familial and genetic disorders					
	Grade				
Adverse Event	1	2	3	4	5
Congenital, familial and genetic disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Ear and labyrinth disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear.					
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation, swelling and redness to the outer ear and ear canal.					
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the external ear region.					
Hearing impaired	Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 8 kHz in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz and above in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	Adults: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); non-servicable hearing. Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.					
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear.					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, and vision problems.					
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Endocrine disorders					
	Grade				
Adverse Event	1	2	3	4	5
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder characterized by unusually late sexual maturity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands.					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.					
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal male.					
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Eye disorders					
	Grade				
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; topical intervention indicated (e.g., antibiotics); limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
Corneal ulcer	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Limiting self care ADL; declining vision (worse than 20/40 but better than 20/200)	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber.					
Dry eye	Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva.					
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle.					
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the eye.					
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by impaired eyelid function.					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light.					
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens.					
Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficits; multiple topical or oral agents indicated; limiting instrumental ADL	EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow.					
Keratitis	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Decline in vision (worse than 20/40 but better than 20/200); limiting self care ADL	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the cornea of the eye.					
Night blindness	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an inability to see clearly in dim light.					

Eye disorders					
	Grade				
Adverse Event	1	2	3	4	5
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).					
Papilledema	Asymptomatic; no visual field defects	Symptomatic decline in vision; visual field defect present sparing the central 20 degrees	Marked visual field defect (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by swelling around the optic disc.					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of light.					
Retinal detachment	Asymptomatic	Exudative and visual acuity 20/40 or better	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium.					
Retinal tear	-	Laser therapy or pneumopexy indicated	Vitroretinal surgical repair indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.					
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects vision.					
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder involving the retina.					
Scleral disorder	Asymptomatic; clinical or diagnostic observations only	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better).	Symptomatic, limiting self care ADL; marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by involvement of the sclera of the eye.					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye.					
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by blood extravasation into the vitreous humor.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct.					
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterized by swelling of the abdomen.					
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region.					
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin.					
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region.					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the anus.					
Anal necrosis	-	-	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the anal region.					
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the anal region.					
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the anal canal.					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity.					
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cecum.					
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
Definition: A disorder characterized by inflammation of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site.					
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon.					
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the colon.					
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the colon.					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.					
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-
Definition: A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous.					
Diarrhea	Increase of <=4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site.					
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the duodenum.					
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum.					
Duodenal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall.					
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the duodenum.					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms, intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing.					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines.					
Enterovesical fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; noninvasive intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine.					
Esophageal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site.					
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the esophageal wall.					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the esophagus.					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal wall.					
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from esophageal varices.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site.					
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the gastric wall.					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastric wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the stomach.					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site.					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region.					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss; refractory to medical intervention; unable to maintain nutrition orally	-	-
Definition: A disorder characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine.					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to ailment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region.					
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the hemorrhoids.					
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the ileum and another organ or anatomic site.					
Ileal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ileal wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Ileal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the ileum.					
Ileal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall.					
Ileal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the ileum.					
Ileal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.					
Ileus	-	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
Jejunal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site.					
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the jejunal wall.					
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the jejunal wall.					
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the jejunum.					
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Lower gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus).					
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea.					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the oral mucosal.					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the stomach.					
Oral cavity fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site.					
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mouth.					
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.					
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the pancreatic duct.					
Pancreatic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pancreas and another organ or anatomic site.					
Pancreatic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pancreas.					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pancreas.					
Pancreatitis	-	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by inflammation of the pancreas.					
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
Definition: A disorder in the gingival tissue around the teeth.					
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the peritoneum.					
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum.					
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site.					
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus.					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the rectum.					
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the rectal wall.					
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region.					
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall.					
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum.					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the retroperitoneal area.					
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the salivary duct.					
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site.					
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the small intestine.					
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents.					
Small intestinal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the small intestine wall.					
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the small intestine.					
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the small intestine.					
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the stomach.					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the tooth.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the cecum.					
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach).					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

General disorders and administration site conditions					
	Grade				
Adverse Event	1	2	3	4	5
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Death neonatal	-	-	-	-	Death
Definition: A disorder characterized by cessation of life occurring during the first 28 days of life.					
Death NOS	-	-	-	-	Death
Definition: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues.					
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.					
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.					
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face.					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal.					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough.					
Gait disturbance	Mild change in gait (e.g., wide-based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	-	-
Definition: A disorder characterized by walking difficulties.					
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

General disorders and administration site conditions					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Infusion site extravasation	-	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling.					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms.					
Neck edema	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck.					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by discomfort in the chest unrelated to a heart disorder.					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony.					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Hepatobiliary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct.					
Biliary fistula	-	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site.					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones.					
Gallbladder fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Symptomatic or severely altered GI function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder.					
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder.					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall.					
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma.					
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region.					
Perforation bile duct	-	-	Radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					

Hepatobiliary disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein.					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the abdominal cavity.					
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving an artery.					
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the biliary tract.					
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bladder.					
Bone infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bones.					
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the breast.					
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bronchi.					
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process that arises secondary to catheter use.					
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an infectious process involving the cecum.					
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the conjunctiva. Clinical manifestations include pink or red color in the eyes.					
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cornea.					
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a cranial nerve.					
Device related infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the duodenum.					
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain and spinal cord tissues.					
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines.					
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the esophagus.					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye.					
Gallbladder infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gallbladder.					
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gums.					
Hepatic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the liver.					
Hepatitis viral	Asymptomatic, treatment not indicated	-	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma.					
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skeletal muscles.					
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammatory process involving the larynx.					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the lips.					
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lungs.					
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lymph nodes.					
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mediastinum.					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord.					
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a mucosal surface.					
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the nail.					
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
Otitis media	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the middle ear.					
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pancreas.					
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.					
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pelvic cavity.					
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the penis.					
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peritoneum.					
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the throat.					
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein.					
Pleural infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pleura.					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the prostate gland.					
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	-	-	-
Definition: A disorder characterized by an infectious process involving the nasal mucosal.					
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the salivary gland.					
Scrotal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock.					
Sinusitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses.					
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skin.					
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
Soft tissue infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving soft tissues.					
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an infectious process involving the spleen.					
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a stoma (surgically created opening on the surface of the body).					
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a tooth.					
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the trachea.					
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).					
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urethra.					
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra.					
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial tissues.					
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vagina.					
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vulva.					
Wound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the wound.					
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Ankle fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot.					
Aortic injury	-	-	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta.					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery.					
Biliary anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures).					
Bladder anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures).					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.					
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment.					
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.					
Esophageal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures).					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury.					
Fallopian tube anastomotic leak	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures).					
Fallopian tube perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A finding of rupture of the fallopian tube wall.					
Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of a necrotic process occurring in the gastrointestinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-surgical intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken.					
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery.					
Injury to inferior vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava.					
Injury to jugular vein	-	-	Symptomatic limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein.					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the superior vena cava.					
Intestinal stoma leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from an intestinal stoma (surgically created opening on the surface of the body)					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of blockage of the normal flow of the contents of the intestinal stoma.					
Intestinal stoma site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood leakage from the intestinal stoma.					
Intraoperative arterial injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to an artery during a surgical procedure.					
Intraoperative breast injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A finding of damage to the breast parenchyma during a surgical procedure.					
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the heart during a surgical procedure.					
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection of injured organ/structure indicated; disabling (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the ear during a surgical procedure.					
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the endocrine gland during a surgical procedure.					
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the gastrointestinal system during a surgical procedure.					
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the head and neck during a surgical procedure.					
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure.					
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the hepatic parenchyma and/or biliary tract during a surgical procedure.					
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the musculoskeletal system during a surgical procedure.					
Intraoperative neurological injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the nervous system during a surgical procedure.					
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the eye during a surgical procedure.					
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the kidney during a surgical procedure.					
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A finding of damage to the reproductive organs during a surgical procedure.					
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the respiratory system during a surgical procedure.					
Intraoperative skin injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the skin during a surgical procedure.					
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the spleen during a surgical procedure.					
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the urinary system during a surgical procedure.					
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to a vein during a surgical procedure.					
Kidney anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a kidney anastomosis (surgical connection of two separate anatomic structures).					
Large intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large intestine.					
Pancreatic anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures).					
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures).					
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding occurring after a surgical procedure.					
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of a previously undocumented problem that occurs after a thoracic procedure.					
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A finding of protrusion of the intestinal stoma (surgically created opening on the surface of the body) above the abdominal surface.					
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of displacement of the urostomy.					
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.					
Rectal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a rectal anastomosis (surgical connection of two separate anatomic structures).					
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective radiologic or operative intervention indicated	-	-
Definition: A finding of tumor-like collection of serum in the tissues.					
Small intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small bowel.					
Spermatic cord anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures).					
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Definition: A finding of traumatic injury to the spine in which the continuity of a vertebral bone is broken.					
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the gastrointestinal stoma (surgically created opening on the surface of the body).					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure.					
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding from the trachea.					
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor; radiologic or endoscopic intervention indicated (e.g., stent, laser); limiting self care ADL	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of blockage of the lumen of the trachea.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood leakage from the tracheostomy site.					
Ureteric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures).					
Urethral anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a urethral anastomosis (surgical connection of two separate anatomic structures).					
Urostomy leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from a urostomy.					
Urostomy obstruction	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A finding of blockage of the urostomy.					
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding from the urostomy site.					
Urostomy stenosis	-	Symptomatic but no hydronephrosis, no sepsis or no renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the opening of a urostomy.					
Uterine anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a uterine anastomosis (surgical connection of two separate anatomic structures).					
Uterine perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the uterine wall.					
Vaginal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures).					
Vas deferens anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures).					
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated; disabling	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to a vein.					
Wound complication	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound; local care indicated	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of development of a new problem at the site of an existing wound.					
Wound dehiscence	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	Fascial disruption or dehiscence without evisceration; primary wound closure or revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation of the approximated margins of a surgical wound.					
Wrist fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of traumatic injury to the wrist joint in which the continuity of a wrist bone is broken.					
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen.					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g. , >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.					
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin I in a biological specimen.					
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin T in a biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen.					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen.					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.					

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.					
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen.					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds.					
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.					
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.					
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.					
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches.					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite.					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inability to properly metabolize glucose.					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.					
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.					
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues.					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g. tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the abdominal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving a joint.					
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the back region.					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the bones.					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the buttocks.					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the chest wall region.					
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-
Definition: A disorder characterized by non-neoplastic overgrowth of bone.					
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the deep connective tissues.					
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation on the lateral side of the body in the region below the ribs and above the hip.					
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL	Weakness limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites.					
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-
Definition: A disorder characterized by of stature that is smaller than normal as expected for age.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Head soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the head.					
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated; disabling	-	-
Definition: A disorder characterized by excessive fluid in a joint, usually as a result of joint inflammation.					
Joint range of motion decreased	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a decrease in joint flexibility of any joint.					
Joint range of motion decreased cervical spine	Mild restriction of rotation or flexion between 60 - 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	-	-
Definition: A disorder characterized by a decrease in flexibility of a cervical spine joint.					
Joint range of motion decreased lumbar spine	Stiffness; difficulty bending to the floor to pick up a very light object but able to do athletic activity	Pain with range of motion (ROM) in lumbar spine; requires a reaching aid to pick up a very light object from the floor	<50% lumbar spine flexion; associated with symptoms of ankylosis or fused over multiple segments with no L-spine flexion (e.g., unable to reach to floor to pick up a very light object)	-	-
Definition: A disorder characterized by a decrease in flexibility of a lumbar spine joint.					
Kyphosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine.					
Lordosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the lumbar portion of the spine.					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body.					
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the lower limb muscles.					
Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body.					
Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles.					
Muscle weakness upper limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the upper limb muscles.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	-	-
Definition: A disorder characterized by of a malformation of the musculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.					
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving the skeletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the neck area.					
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the neck.					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible.					
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis.					
Scoliosis	<20 degrees; clinically undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a malformed, lateral curvature of the spine.					
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the lower extremity.					
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Superficial soft tissue fibrosis	Mild induration; able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration; able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the superficial soft tissues.					
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately ailment or hydrate orally	-	-
Definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication.					
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	Severe length discrepancy >5 cm; limiting self care ADL; disabling; operative intervention indicated	-	-
Definition: A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities.					
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
	Grade				
Adverse Event	1	2	3	4	5
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematopoietic cell production by the bone marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis.					
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).					
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).					
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.					
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.					
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function.					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					

Nervous system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond.					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.					
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.					
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Definition: A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the facial muscles.					
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the facial nerve (seventh cranial nerve).					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.					
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized by characterized by excessive sleepiness during the daytime.					

Nervous system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).					
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.					
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the olfactory nerve (first cranial nerve).					

Nervous system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral motor nerves.					
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by paralysis of the recurrent laryngeal nerve.					
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.					
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.					
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness.					
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death
Definition: A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Nervous system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.					
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).					
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Pregnancy, puerperium and perinatal conditions					
	Grade				
Adverse Event	1	2	3	4	5
Fetal death	-	-	-	-	Fetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.					
Fetal growth retardation	-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-
Definition: A disorder characterized by inhibition of fetal growth resulting in the inability of the fetus to achieve its potential weight.					
Premature delivery	Delivery of a liveborn infant at >34 to 37 weeks gestation	Delivery of a liveborn infant at >28 to 34 weeks gestation	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-
Definition: A disorder characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation.					
Unintended pregnancy	-	-	Unintended pregnancy	-	-
Definition: A disorder characterized by an unexpected pregnancy at the time of conception.					
Pregnancy, puerperium and perinatal conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Psychiatric disorders					
	Grade				
Adverse Event	1	2	3	4	5
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death
Definition: A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-being which is disproportionate to events and stimuli.					
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by a false sensory perception in the absence of an external stimulus.					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characterized by difficulty in falling asleep and/or remaining asleep.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized by a decrease in sexual desire.					
Libido increased	Mild increase in sexual interest not adversely affecting relationship	Moderate increase in sexual interest adversely affecting relationship	Severe increase in sexual interest leading to dangerous behavior	-	-
Definition: A disorder characterized by an increase in sexual desire.					
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behavior and elevation of mood.					
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

Psychiatric disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking.					
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences; threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be still.					
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own life.					
Suicide attempt	-	-	Suicide attempt or gesture without intent to die which may not require hospitalization	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own life.					
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death

Renal and urinary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract.					
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine.					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death
Definition: A disorder characterized by the formation of crystals in the pelvis of the kidney.					
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

Renal and urinary disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the kidney.					
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by inability to control the flow of urine from the bladder.					
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate.					
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract.					
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized by a change in the color of the urine.					
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the breast region.					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.					
Fallopian tube obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube.					
Fallopian tube stenosis	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A disorder characterized by a narrowing of the fallopian tube lumen.					
Female genital tract fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors.					
Genital edema	Mild swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals.					
Gynecomastia	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males.					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by the presence of blood in a fallopian tube.					
Irregular menstruation	Intermittent menses with skipped menses for no more than 1 to 3 months	Intermittent menses with skipped menses for more than 4 to 6 months	Persistent amenorrhea for more than 6 months	-	-
Definition: A disorder characterized by irregular cycle or duration of menses.					
Lactation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-
Definition: A disorder characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males.					
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormally heavy vaginal bleeding during menses.					
Nipple deformity	Asymptomatic, asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-
Definition: A disorder characterized by a malformation of the nipple.					
Oligospermia	Sperm concentration >48 million/mL or motility >68%	Sperm concentration 13 - 48 million/mL or motility 32 - 68%	Sperm concentration <13 million/mL or motility <32%	-	-
Definition: A disorder characterized by a decrease in the number of spermatozoa in the semen.					
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the ovary.					
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by tearing or disruption of the ovarian tissue.					
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle.					
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the strength of the muscles of the pelvic floor.					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pelvis.					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the penis.					
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the area between the genital organs and the anus.					
Premature menopause	-	-	Present	-	-
Definition: A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, night sweats, mood swings and a decrease in sex drive.					
Prostatic hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by bleeding from the prostate gland.					
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).					
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the scrotal area.					
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the spermatic cord.					
Spermatic cord obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents of the spermatic cord.					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the testis.					
Testicular hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the testis.					
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the testis.					
Uterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the uterus and another organ or anatomic site.					
Uterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the uterus.					
Uterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the uterine outlet.					
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the vagina and another organ or anatomic site.					
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the vagina.					
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the vagina.					
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the vaginal wall.					
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterized by a narrowing of the vaginal canal.					
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					
Reproductive system and breast disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by inhalation of solids or liquids into the lungs.					
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by the collapse of part or the entire lung.					
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL, endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site.					
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube.					
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated, limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by milky pleural effusion (abnormal collection of fluid) resulting from accumulation of lymph fluid in the pleural cavity.					
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the nose.					
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder characterized by harsh and raspy voice arising from or spreading to the larynx.					
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <98%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
Laryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the larynx and another organ or anatomic site.					
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the larynx.					
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the laryngeal airway.					
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx.					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the pharynx.					
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a necrotic process occurring in the pharynx.					
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pharyngolaryngeal region.					
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung.					
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure.					
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure.					
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site.					
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder.					
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characterized by involvement of the paranasal sinuses.					
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the involuntary expulsion of air from the nose.					
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characterized by of marked discomfort in the throat.					
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a high pitched breathing sound due to laryngeal or upper airway obstruction.					
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site.					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-
Definition: A disorder characterized by a change in the sound and/or speed of the voice.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.					
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location.					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.					
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center).					
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area.					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-
Definition: A disorder characterized by shrinking of adipose tissue.					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen)					
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Generalized involving sites other than palms, soles, or axillae; associated with electrolyte/hemodynamic imbalance	-	-
Definition: A disorder characterized by excessive perspiration.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails.					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin.					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face.					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin covering the top and the back of the head.					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition.					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment.					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin.					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes.					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.					
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Social circumstances					
	Grade				
Adverse Event	1	2	3	4	5
Menopause	Menopause occurring at age 46 - 53 years of age	Menopause occurring at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-
Definition: A disorder characterized by the permanent cessation of menses, usually defined by 12 consecutive months of amenorrhea in a woman over 45 years of age.					
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Surgical and medical procedures					
	Grade				
Adverse Event	1	2	3	4	5
Surgical and medical procedures - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Vascular disorders					
	Grade				
Adverse Event	1	2	3	4	5
Capillary leak syndrome	-	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure.					
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characterized by episodic reddening of the face.					
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel.					
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling.					
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
Definition: A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mm Hg.					
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.					
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity					
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by excessive fluid collection in tissues that causes swelling.					
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characterized by a cystic lesion containing lymph.					
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (>=24 hrs) and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by impaired circulation to an extremity.					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					

Vascular disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi-modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characterized by obstruction of the blood flow in the superior vena cava. Signs and symptoms include swelling and cyanosis of the face, neck, and upper arms, cough, orthopnea and headache.					
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.					
Vasculitis	Asymptomatic; intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia, urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel.					
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by a decrease in blood supply due to narrowing or blockage of a visceral (mesenteric) artery.					
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

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16.12 Palatability Questionnaire

LUM001 304 Palatability Questionnaire
Caregiver Only

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

Questionnaire to be completed by:

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

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

Yes	Not sure	No
		

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

Yes	Not sure	No

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

Very Easy	Easy	Neither Easy or Difficult	Difficult	Very Difficult
				

Version 1.0, 01 Dec 2016

LUM001 304 Palatability Questionnaire

Child Only or Child and Caregiver

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

Questionnaire to be completed by:

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

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

Very Good	Good	Nor good or bad	Bad	Very Bad
				

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

Very Good	Good	Nor good or bad	Bad	Very Bad
				

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

Yes	Not sure	No
		

Version 1.0, 01 Dec 2016

16.13 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	20 Mar 2014	
Amendment 1	06 Mar 2015	Global
Amendment 2	08 May 2015	Global
Amendment 3	13 Nov 2015	Global
Amendment 4	28 Mar 2017	Global
Amendment 5	06 Nov 2017	Global

16.13.1 Protocol Amendment 5 Summary of Changes

Protocol Number: LUM001-304

Protocol Title: LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BL**I**ND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN API**C**AL S**O**DIUM-DEPE**N**DENT B**I**LE A**C**ID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Amendment: **5**

Date: 06 Nov 2017

The LUM001-304 protocol is being amended to change the study design going forward to an open label study, beyond what was previously described in Protocol Amendment 4. As all subjects have now either reached Week 48 or discontinued prior to Week 48, the interim analysis will be performed and the study will be unblinded.

In addition, in the Appendices, Study Schedule I and J have been updated to include clinician xanthoma scale.

The following changes have been made to the Protocol Amendment 4 (28 March 2017). Note that correction of typographical and grammatical errors are not captured in the below table.

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

<table>
<tr><th>Section</th><th>Description of Change</th></tr>
<tr><td>Synopsis, Statistical considerations
Interim Analysis</td><td><u>Interim Analysis</u>

There will be an interim analysis (IA) conducted after all subjects complete or discontinue the study after Week 48 to guide the future of the program. At the IA the study will be unblinded. <s>The IA may result in an interim report or publications. The IA will be conducted internally by an unblinded sponsor team as outlined in the unblinded study plan charter. The unblinded sponsor team will not be involved in the day to day clinical study activities..</s></td></tr>
<tr><td>Subject Enrollment
6.4 Unblinding of Treatment Assignment</td><td>After Week 48 the study will be unblinded to facilitate preparation of the interim analysis. <s>A designated statistician will securely maintain an unblinded randomization schema.</s>

All subjects will receive LUM001, or LUM001 and placebo during this study. Breaking of the blind during the initial 48-week period of the study should not occur before all subjects either discontinue or complete Week 48, except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or when causality must be determined prior to submitting a regulatory safety report for a serious adverse event (SAE) (as defined in Section 11.2.3).</td></tr>
<tr><td>Statistical Considerations
Section 12.2.10
Interim Analyses</td><td>There will be an interim analysis (IA) conducted after all subjects complete or discontinue the study after Week 48 to guide the future of the program. At the IA the study will be unblinded. <s>The IA may result in an interim report or publications. The IA will be conducted internally by an unblinded sponsor team as outlined in the unblinded study plan charter. The unblinded sponsor team will not be involved in the day to day clinical study activities..</s></td></tr>
<tr><td>16 Appendices
16.1.3 Schedule of Procedures I – Long-Term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject eligible for ADE</td><td>Insertion of clinician xanthoma scale
<table>
<tr><th>Study Period</th><th colspan="7">Follow-up Treatment Period
Afternoon Dose Escalation (ADE)</th><th colspan="3">Study activities repeating in repeating 12-week periods after completion of the ADE period[3]</th></tr>
<tr><th>FTP Study Week</th><th>ADE Day 0</th><th>ADE Week 1</th><th>ADE Week 2</th><th>ADE Week 4</th><th>ADE Week 5</th><th>ADE Week 6</th><th>ADE Week 8</th><th>Week 4</th><th>Week 8</th><th>Week 12</th></tr>
<tr><td>Scheduling Considerations</td><td>To be scheduled as soon as ADE eligibility is confirmed and materials are on-site</td><td></td><td></td><td></td><td></td><td></td><td></td><td>The initial Week 4 contact will be scheduled 4 weeks following ADE Week 8.</td><td></td><td></td></tr>
<tr><td>Window (in days)</td><td>N/A – see above</td><td>(±2)</td><td>(±2)</td><td>(±2)</td><td></td><td>(±2)</td><td>(±2)</td><td>(±7)</td><td>(±7)</td><td>(±14)</td></tr>
<tr><td>Clinician Xanthoma Scale</td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Caregiver ItchRO/ Patient ItchRO</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>X (collected for 2 week period following this visit)</td></tr>
<tr><td>PedsQL</td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Palatability Questionnaire</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Study Drug Supplied[4]</td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Assess Compliance</td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Concomitant Medications</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Adverse Events</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Follow-up Phone Contact[5]</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td></tr>
</table></td></tr>
<tr><td>16 Appendices
16.1.4 Schedule of Procedures J – Study Termination and End of Treatment</td><td>Insertion of clinician xanthoma scale</td></tr>
</table>

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

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

16.13.2 Protocol Amendment 4 Summary of Changes

Protocol Number: LUM001-304

Protocol Title: LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BL**I**ND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN API**C**AL S**O**DIUM-DEPE**N**DENT B**I**LE A**C**ID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Amendment: **4**

Date: 28 Mar 2017

The changes below were made to Protocol Amendment 3.

The following table provides a summary list of changes that were included in Protocol Amendment 3 (*new text indicated in bold; deleted text indicated in strikethrough)*:

Section	Description of Change
Cover page, Sponsor; Title Page, Sponsor; Sponsor Signature Page Sponsor Protocol Signature page, Sponsor	**Changed from:** Lumena Pharmaceuticals, Inc. 12531 High Bluff Drive, Suite 110 San Diego, CA 92130 USA **To:** Lumena Pharmaceuticals LLC* **300 Shire Way** **Lexington, MA 02421** USA ***Lumena Pharmaceuticals LLC is an indirect wholly-owned subsidiary of Shire North American Group, Inc**
Title Page , Medical Lead; Protocol Signature page, Sponsor (Shire) Approval	**Changed from:** **Medical Lead:** ~~Beatriz Caballero, MD~~ Shire~~ Human Genetic Therapies,Inc.~~ Zahlerweg 10 6300 Zug Switzerland ~~Phone: +41(0) 41 288 42 30~~ ~~Email: beaballero@shire.com~~ **To:** **Medical Lead:** **Thomas Jaecklin, MD** Shire Zahlerweg 10 6300 Zug Switzerland **Phone: +41(0) 79 850 77 18** **Email: thomas.jaecklin@shire.com**
Emergency Contact Information	Inserted new page containing emergency contact information for reporting of serious adverse events (SAEs) to be aligned with Shire protocol template.
Product Quality Complaints	Inserted new page containing product quality complaint information for reporting of investigational product quality complaints to be aligned with Shire protocol template.
Synopsis, Objectives; Section 3, Study Objectives	Objectives of **Long-term** Optional Follow-up Treatment Period (After Week 48): • To offer eligible subjects in the LUM001-304 study continued study treatment after Week 48 until the first of the following occurs: ~~(i) up to 52 weeks of additional treatment (Week 100) or (ii) in the event that a new study opens to enrollment~~ **(i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication.** • **To explore twice a day (BID) dosing regimen and higher daily dosing of LUM001.**

Section	Description of Change
	• **To assess the level of alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma.** • **To assess palatability of the LUM001 formulation.**
Synopsis, Study Design; Section 5.1, Study Design	The study is divided into ~~5~~**6** parts: ….a 12-week **open-label** stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, a 26-week long-term stable dosing period at doses up to 400 µg/kg/day, ~~and an~~ a 52-week optional follow-up treatment period, **and a long-term optional follow-up treatment period** for eligible subjects who choose to stay on treatment with LUM001. **During this long-term optional follow-up treatment period, subjects may have their dose of LUM001 increased to a maximum of 800 µg/kg/day (400 µg/kg BID), based on efficacy (sBA level and ItchRO [Obs] score) and safety assessment.** Subjects' participation in the **long-term** optional follow-up treatment period will continue until the first of the following occur: ~~(i) up to 52 weeks of additional treatment (Week 100) or (ii) in the event that a new study opens to enrollment~~ **(i) the subjects are eligible to enter another LUM001 study, (ii) LUM001 is available commercially, or (iii) the sponsor stops the program or development in this indication. Subjects who do not consent to Protocol Amendment 4 will continue their treatment as outlined in Protocol Amendment 3.**
Synopsis, Inclusion Criteria; Section 7.1, Inclusion Criteria	5. **Males and females of child-bearing potential who are** sexually active ~~females~~, **or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug,** must ~~be prepared to~~ **agree and** use ~~an effective method (≤ 1% failure rate) of~~ **acceptable** contraception during the trial. Effective methods of contraception are ~~considered to be~~ **described in Section 8.6.1.** ~~a. Hormonal (e.g., contraceptive pill, patch, intramuscular implant or injection); or~~ ~~b. Barrier method, e.g., (a) condom (male or female) or (b) diaphragm, with spermicide; or~~ ~~c. Intrauterine device (IUD).~~
Synopsis, Inclusion Criteria; Section 7.2, Exclusion Criteria	**Protocol Amendment 4: Eligible Subjects for the long-term optional follow-up treatment period:** **Inclusion Criteria for subjects with LUM001 dosing interruption <7 days, or ≥7 days**: **Subjects will be considered eligible for the long-term optional follow-up treatment period if they meet the following criteria:** **1. The subject has either:** o **completed the protocol through the Week 48 visit with no major safety concerns.** **OR** o **discontinued due to safety reasons judged unrelated to the study drug, and laboratory results have returned to levels acceptable for this patient population or individual and subject does not meet any of the protocol's stopping rules at the time of**

Section	Description of Change
	entry into the follow-up period. The decision will be made by the investigator in consultation with the sponsor medical monitor. [Subjects who were discontinued for other reasons will be considered on an individual basis.] **2. Females of childbearing potential must have a negative urine or serum pregnancy test (β-hCG) at the time of entry into the long-term optional follow-up treatment period.** **3. Males and females of child-bearing potential who are sexually active, or are not currently sexually active during the study, but become sexually active during the period of the study and 30 days following the last dose of study drug, must agree and use acceptable contraception during the trial.** **4. Informed consent and assent (per IRB/EC) as appropriate.** **5. Access to phone for scheduled calls from study site.** **6. Caregivers (and age appropriate subjects) must be willing and able to use an eDiary device during the study.** **<u>Exclusion Criteria for Subjects with LUM001 dosing interruption≥7 days :</u>** **All exclusion criteria mentioned for the core study apply upon entry into the long-term optional follow-up period, with the exception of exclusion criterion #18.**
Synopsis, Treatment Groups; Section 5.5.2, Treatment;	**Subjects will be considered for a 52-week optional treatment period, if eligible, receiving up to 400 µg/kg/day, or the highest tolerated dose below the 400 µg/kg/day dose**. Subjects will then be considered for **the long-term** optional ~~52-week~~ follow-up treatment, if eligible, ~~to continue on their highest tolerated dose~~ **receiving up to 800 µg/kg/day (given as twice daily doses of 400 µg/kg), or to a maximum possible daily dose of 50 mg/day.**
Synopsis, Study Drug Dosage and Administration; Section 10.1, Study Drug Administration	**Study Drug Administration** Subjects ~~who weigh 10 kg or more at screening~~ will receive ~~1.0 mL~~ **a** grape-flavored solution containing LUM001 ~~or placebo. Subjects who weigh less than 10 kg at screening will receive 0.5 mL grape-flavored solution containing LUM001. The volume~~ administered~~, either 1.0 mL or 0.5 mL will not change during~~ **orally once a day (QD) or twice a day (BID) using the** ~~the course of the study. Each daily~~ **syringe provided. The first** dose ~~will~~ **should** be ~~administered in the morning~~ **taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the dose should be taken** approximately at the same time ~~every day~~ **each day for the duration of the treatment period.** **QD Dosing Regimen** **For QD dosing, the required dose will be delivered in 0.5 mL volume for subjects who weigh less than 10 kg and in 1.0 mL for subjects who weigh 10 kg or more.**

Section	Description of Change
Section 5.5.2.1, Dose Escalation Period	**BID Dosing Regimen** **For BID dosing, the required dose is delivered in half the dosing volume: 0.25 mL BID for subjects who weigh less than 10 kg and 0.50 mL BID for subjects who weigh 10 kg or more.** **For subjects weighing less than 10 kg at study entry, once a weight of 10 kg is reached while in the study, the subject will be moved from 0.5 mL maximum daily dosing volume (0.25 mL BID) to 1.0 mL maximum daily dosing volume (0.50 mL BID).** **Study Drug Dosage** Initially, the LUM0001 dose will be **administered as a daily morning dose in either a 1.0 mL or 0.5 mL solution. The dose will be** increased weekly over a 6-week period up to 400 µg/kg/day **QD** or a maximum daily dose of 20 mg/day **QD** as follows…
Section 5.5.2.4, Long-term Exposure Period	Following the 4-week study drug randomized withdrawal period, subjects who received placebo will receive LUM001 dosed according to a dose escalation schedule that mirrors the initial escalation (ie the LUM001 dose will be increased weekly over a 6-week period **to the maximum tolerated dose** up to 400 µg/kg/day or ~~a maximum daily dose of~~ 20 mg/day or the highest tolerated dose below the 400 µg/kg/day dose).
Section 5.5.2.5, 52-week Optional Follow-up Treatment Period	**Optional Follow-up Treatment Period** At Week 48, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the ~~52-week~~, **optional** follow-up treatment period. The 3 following possible scenarios may occur: … • Subjects who are eligible to roll over into the optional follow-up treatment period with a LUM001 dosing interruption of ≥7 days will be dose escalated **beginning at 35 µg/kg/day and** up to **a maximum of** 400 µg/kg/day or highest tolerated dose ~~following a 5-week dose escalation beginning at 35 µg/kg/day~~. • Subjects who do not wish to enter the follow-up treatment period will be contacted via telephone by the study site approximately ~~28~~**30** days after the last dose of study drug. ~~During the study, the study drug may be adjusted if there is a change of ≥10% in weight since the screening visit or if there is a change of ≥10% in weight since the last weight based medication adjustment to maintain the target dose (µg/kg/day).~~
Section 5.5.2.6, Long-term Optional Follow-up Treatment Period	**Long-term Optional Follow-up Treatment Period** **Upon completion of the 52-week follow-up treatment period and/or implementation of this amendment, whichever occurs first, subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over (or enter) into the long-term optional,**

Section	Description of Change
	follow-up treatment period. The 3 following possible scenarios may occur: **Scenario 1: Subjects eligible to roll over into the long-term optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days:** • **Subjects with normal sBA level AND ItchRO(Obs) score <1.5 will be maintained at the same dose level and will continue morning dosing only.** • **Subjects with sBA level above normal AND/OR ItchRO(Obs) score ≥1.5 will start BID dosing (afternoon dose escalation; ADE) as follows:** o **The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated.** o **The afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg.** **Scenario 2: Subjects eligible to roll over into the long-term optional follow-up treatment period with a LUM001 interruption of ≥7 days:** • **First, the morning dose is escalated up to 400 µg/kg/day or highest tolerated dose following a 5-week dose escalation beginning at 35 µg/kg/day.** • **Once the morning dose of 400 µg/kg or maximum tolerated dose is achieved, sBA and ItchRO(Obs) score will be evaluated.** o **Subjects with normal sBA AND ItchRO(Obs) score <1.5 after morning dose escalation will be maintained at the same dose level and will continue morning dosing only.** o **Subjects with sBA above normal AND/OR ItchRO(Obs) score ≥1.5 will begin BID dosing (ADE) as follows:** ▪ **The morning dose will be continued at the same dose level, but the volume of the morning dose will be reduced by half at the same time that the afternoon dose is initiated.** ▪ **The afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg.** **The following parameters apply to both dosing scenarios outlined above:** • **The afternoon dose will only be initiated once the subject has been treated on stable morning doses for at least 4 weeks.** • **The sBA value used for determination of ADE eligibility will be the most recent available value collected within the**

Section	Description of Change
	prior 16 weeks. The ItchRO(Obs) score used for ADE eligibility will be derived from the most recent available 7-day interval of ItchRO(Obs) collected within the prior 16 weeks. • **The maximum daily dose will be 400 µg/kg BID, ie, 800 µg/kg/day (up to a maximum possible daily dose of 50 mg/day).** **Scenario 3: Subjects who do not consent to Protocol Amendment 4 will continue their treatment as outlined in Protocol Amendment 3.**
Synopsis, Rationale for Dose and Schedule Selection	**During the study, the study drug may be adjusted if there is a change of ≥10% in body weight since the screening visit or if there is a change of ≥10% in weight since the last weight based medication adjustment to maintain the target dose.** **If a subject experiences intolerance due to gastrointestinal symptoms (eg, diarrhea, abdominal pain, cramping) at any time during the study, the physician investigator in consultation with the sponsor medical monitor may lower the dose to a previously tolerated dose; later attempts to escalate the dose are permitted. If the subject is on a BID dosing regimen, dose lowering should first be attempted with the afternoon dose** **…** ~~The dose may be down-titrated, at the investigator's discretion and in consultation with the Sponsor Medical Monitor, for subjects experiencing intolerance to a given dose.~~ **Under Protocol Amendment 4, an afternoon dose is introduced for eligible subjects in the long-term optional follow up treatment period. LUM001 doses will be escalated over a period of 4-8 weeks up to a maximum dose of 400 µg/kg BID (or maximum tolerated dose). The afternoon dose is only initiated and escalated in subjects with elevated sBA and/or ItchRO(Obs) ≥1.5 on the maximum (or maximum tolerated) morning dose.** **This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001. Twice daily dosing is used in this study based on the findings of a healthy volunteers study in adult males (Study SHP625-101), which demonstrated that bile acid levels in feces increase with escalating doses and twice-daily regimen of LUM001 (up to 100 mg QD and 50 mg BID). In this study, subjects who were randomized to LUM001 treatment, received 1 of 4 doses of LUM001 (10, 20, 50, 100 mg) during 7 days. No titration was used in this study. There was a dose-dependent increase in total fecal BA excretion. In addition, BID dosing (ie, 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (ie, 100 mg QD). It is therefore hypothesized that twice-daily dosing has the potential to allow for more complete target engagement throughout the day at the level of the distal ileum.** **The higher dosing level is also supported by favorable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (post-natal day, PND21 through PND63). As expected**

Section	Description of Change
	for a drug intentionally designed to be minimally absorbed, systemic LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies in adult rats. No adverse effects were observed on postnatal growth and development of offspring at the highest doses tested (200 mg/kg/day in males, 1000 mg/kg/day in females). This study was initiated in juvenile animals at PND21, which from a whole animal development perspective, is typically representative of a 2-year old child. However, given the fact that LUM001 is a minimally absorbed drug, of particular importance is the age at which the GI tract is considered functionally mature. In humans this is considered to have occurred by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs during the first 3 weeks of life. Therefore, results from this study can be used to support the dosing levels proposed here for children 12 months of age and older.
Synopsis, Study Visit Schedule and Procedures; Section 5.5	Clarified titles of study design schemes and updated figures to reflect the addition of the extended follow-up treatment period beyond what was previously described in Protocol Amendment 3.
Synopsis only	~~For an individual subject, the study participation period will consist of a screening period of up to 4 weeks, a 48-week treatment period (a 6-week open-label, dose escalation period, a 12-week open-label stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, and a 26-week long-term exposure period), and a follow-up period of up to 4 weeks. Subjects who complete 48 weeks of treatment and those subjects who were previously treated with LUM001 may be eligible to receive treatment for up to 52 weeks during the optional follow-up treatment period.~~
Synopsis, Study Visit Schedule and Procedures; Section 8.1.1, Screening Period (Day -28 to -1)	Screening Period (Day -28 to Day -1): …. For subjects who do not have documentation of a JAGGED-1 or **NOTCH2** mutation, a blood sample ~~will~~ **may** be obtained for genotyping.
Synopsis, Study Visit Schedule and Procedures; Section 8.1.9, Long-term Optional Follow-up Treatment Period	In addition the following assessments should be completed: ~~the ItchRO (Pt and Obs),~~ the clinician scratch scale, the clinician xanthoma scale, the PedsQL, the ~~Patient Impression of Change~~ (PIC), the CIC, the ~~Caregiver Impression of Change,~~ the CGTB, ~~Caregiver Global Therapeutic Benefit assessments,~~ and the **palatability questionnaire**, as defined for **ET** ~~Early Termination. Efforts must be made to follow.~~ **For** subjects ~~for at least 4 weeks following their last dose of~~ **who complete the** study ~~drug~~, **an EOT visit will be completed; the assessments performed at this visit will be identical to the assessments performed at the ET visit.**
Section 8.1.8 (only, not synopsis), 52-week Optional Follow-up Treatment Period	**52-week** Optional Follow-up Treatment Period ~~post Week 48 to Week 100)~~: Subjects who are eligible to roll over ~~onto~~ **into** the **52-week optional** follow-up treatment **period with no LUM001 dosing interruption or an interruption of <7days will be maintained at the same dose level within the 52-week optional follow-up treatment period (Figure 4).**

Section	Description of Change
Synopsis, Study Visit Schedule and Procedures;	~~will continue to receive study drug at the dose they were receiving at Week 48 for up to 52 weeks of additional treatment or in the event that a new study opens to enrollment, whatever occurs first.~~ ~~Subjects who are eligible to roll over into the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level.~~ During ~~the~~ **this** ~~follow-up treatment~~ period, subjects will return to the clinic at Weeks 60, 72, 84, 96, and 100; ~~and~~ telephone contacts ~~to~~ **will** occur at Weeks ~~52, 56,~~ 64, 68, 76, 80, 88, and 92. **Long-term Optional Follow-up Treatment Period** **Upon completion of the additional 52-week follow up treatment period and/or implementation of this amendment, whichever occurs first, subjects who are eligible to roll over onto the long-term optional follow-up treatment period will continue to receive study drug until the first of the following occurs:** **i. The subjects are eligible to enter another LUM001 study,** **ii. LUM001 is commercially available, or** **iii. The sponsor stops the program or development of this indication.** **Once Protocol Amendment 4 is implemented at the site, a determination about ADE will be made.** **Subjects who are eligible to roll over from the 52-week follow-up treatment period into the long-term optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days prior to implementation of Protocol Amendment 4 will be consented and evaluated for eligibility for ADE. Once a determination about ADE has been made, the subject will then either initiate the ADE (Synopsis Figure 6) or continue receiving the same dose of LUM001 once a day (Synopsis Figure 5), depending on whether they meet criteria for initiating ADE.**
Section 8.1.9 (only, not synopsis), Long-term Optional Follow-up Treatment Period	**Screening evaluations for subjects with ≥7 days since last dose of LUM001 prior to implementation of Protocol Amendment 4 will be performed from Day -14 to Day -1. After obtaining informed consent (and/or assent when appropriate), subjects will undergo a physical examination including body weight, height, and vital signs, and have blood and urine samples taken for clinical laboratory testing. Females who are of childbearing potential will have a serum pregnancy test. Eligibility criteria will be confirmed prior to the Baseline Visit. The clinician scratch scale and clinician xanthoma scale will be completed. Concomitant medications and any adverse events will be recorded.** **Rescreening: If a subject is unable to complete the screening procedures and meet eligibility criteria within the 14-day screening period, consideration may be given to rescreening at a later date. Screening procedures should be repeated at that time. Subject data pertaining to screening will be collected after the subject has been rescreened and determined to meet eligibility.**

Section	Description of Change
Synopsis, Study Visit Schedule and Procedures; Section 8.1.9, Long-term Optional Follow-up Treatment Period	**Subjects with ≥7 days since last dose of LUM001 prior to implementation of Protocol Amendment 4 will be dose escalated up to 400 µg/kg/day or to the highest tolerated dose beginning at Dose Level 2 (35 µg/kg/day), as outlined in Synopsis Figure 4 (or Figure 6 for body of protocol).** **The dose escalation (DE) period will proceed as follows:** • **Protocol Amendment 4 DE-2 Clinic Visit: obtain consent, weight, and draw blood for laboratory analyses** • **Protocol Amendment 4 DE Day 0 Clinic Visit: investigator evaluates laboratory results, study drug is dispensed, and subject begins at 35 µg/kg/day dose level (if no safety concerns)** • **Protocol Amendment 4 DE Week 1 Telephone Contact: subject escalates to 70 µg/kg/day dose level** • **Protocol Amendment 4 DE Week 2 Telephone Contact: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated** • **Protocol Amendment 4 DE Week 3 Telephone Contact: subject escalates to 280 µg/kg/day dose level if prior dose level was tolerated** • **Protocol Amendment 4 DE Week 4 Clinic Visit: laboratory tests and dose escalates to 400 µg/kg/day dose (maximum daily dose of 20 mg), if prior dose level was tolerated** • **Protocol Amendment 4 DE Week 8 Telephone Contact: eligibility for ADE will be determined.** **Subjects not eligible for ADE (subjects with normal sBA level AND ItchRO(Obs) score <1.5), will be maintained at the same dose level and will continue morning dosing only. Subjects will have study activities repeated in repeating 12-week periods as follows, until study completion or termination:** • **Repeating Period Week 4 Telephone Contact (ie, beginning 4 weeks after consent to Protocol Amendment 4): Collection of concomitant medications and any adverse events.** • **Repeating Period Week 8 Telephone Contact: Collection of concomitant medications and any adverse events.** • **Repeating Period Week 12 Clinic Visit: Physical exam, body weight and height, vital signs, and blood samples for clinical laboratory testing including fasting lipid panel. Blood will also be collected for determination of baseline fat-soluble vitamins. Urine samples for clinical laboratory testing will be collected at every other visit. ItchRO compliance will be assessed, the electronic diary will be issued, the clinician scratch scale and clinician xanthoma scale will be administered, and the PedsQL questionnaire will be administered. Additionally, a palatability questionnaire will be completed. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will**

Section	Description of Change
	be assessed and study drug will be dispensed. Concomitant medications and adverse events will be collected. • **Subjects who do not qualify for ADE may be assessed at a later time point on a case by case basis following discussions between the investigator and medical monitor. Such re-evaluations may only occur at the Week 12 visit of any Repeating Period beginning with RP2. If in the course of the ADE re-evaluation, a subject is found to qualify for ADE, then the subject will move into Schedule F or G, as outlined in Section 16.1. During the follow-up treatment period, subjects will return to the clinic every 3 months.** **Subjects eligible for ADE,(ie, who have sBA level above normal AND/OR ItchRO(Obs) score ≥1.5), will begin BID dosing (afternoon dose escalation; ADE) as follows (see Figure 8):** • **On ADE Day 0, morning dosing will continue at 400 µg/kg or the maximum tolerated dose. However, the volume of the morning dose will be reduced by half. Of note: Morning dosing must have been stable for ≥4 weeks prior to initiation of ADE.** • **On ADE Day 0, the afternoon dose will be initiated at dose level 140 µg/kg and will continue at this dose for a period of 4 weeks. If this dose level is tolerated, the afternoon dose will then be escalated to 400 µg/kg.** **The following procedures will occur during the ADE period:** • **ADE Day 0 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and any adverse events will be collected.** • **ADE Week 1 and Week 2 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.** • **ADE Week 4 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be**

Section	Description of Change
	assessed and study drug will be dispensed. Concomitant medications and any adverse events will be collected. • **ADE Week 5 and Week 6 Telephone Contact: Collection of concomitant medications and any adverse events. Subject/caregiver will be reminded of dosing instructions.** • **ADE Week 8 Clinic Visit: Physical exam, body weight and height, vital signs, and blood and urine samples for clinical laboratory testing, including fasting lipid panel. Blood will also be collected for determination of fat-soluble vitamins. Plasma sample will be obtained for LUM001 pharmacokinetics. The clinician scratch scale, clinician xanthoma scale, and the PedsQL questionnaire will be administered. Female subjects who are of childbearing potential will have a urine pregnancy test prior to dispensing study drug. Study drug compliance will be assessed and study drug will be dispensed. Concomitant medications and any adverse events will be collected.** **If any subject experiences intolerance, the investigator, in consultation with the sponsor medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period; later attempts to escalate the dose are permitted. At the investigator's discretion, and in consultation with the sponsor medical monitor subjects who were previously down titrated may be rechallenged during the follow-up treatment period. If the subject is on a twice daily dosing regimen, dose lowering should be first attempted with the afternoon dose**. Safety and clinical laboratory evaluations…, and PedsQL will be administered and study drug compliance will be assessed (PedsQL will not be performed at ~~DE-2 or DE52)~~**.certain clinic visits – please refer to schedule of procedures).** The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 84, 96, ~~and 100. Subjects/caregivers will receive follow-up phone calls at Weeks 64, 68, 76, 80, 88, and 92.~~**100, and the End of Treatment (EOT)/Early Termination (ET) visit. Palatability data will be collected at each clinic visit during the long-term optional follow up treatment period (including the EOT/ET visit), with the exception of the PA4 DE, and ADE visits. Plasma samples will be obtained for LUM001 pharmacokinetics at the ADE Day 0, ADE Week 4, and ADE Week 8 visits, and at the 3 scheduled clinic visits following completion of the ADE period.** Subjects/caregivers will receive follow-up phone calls at Weeks 64, 68, 76, 80, 88, **92, as well as those outlined within the PA4 DE, ADE, and repeating 12-week periods.** Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, 84, ~~and~~ 96 clinic visits, **at PA4 DE Week 4, and every clinic visit within the repeating 12-week periods.** With the exception of the ~~Week 96 and Week 100~~ **EOT/ET** visit ~~(Study~~

Section	Description of Change
	~~Termination)~~,… Subjects will be encouraged to complete all study activities and visits. Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo safety and clinical laboratory evaluations, including **pharmacokinetic sampling of LUM001**, determination of serum bile acids, other cholestasis biochemical markers, fat soluble vitamins, and ~~plasma drug level.~~**AFP**. In addition the following assessments should be completed: ~~the ItchRO (Pt and Obs),~~ the clinician scratch scale, clinician xanthoma scale, the PedsQL, the ~~Patient Impression of Change~~**PIC, the CIC,** the Caregiver Impression of Change **CGTB**, and the ~~Caregiver Global Therapeutic Benefit~~ **palatability questionnaire**, as defined for Early Termination. ~~Efforts must be made to follow~~ **(ET). For** subjects ~~for at least 4 weeks following their last dose of~~ **who complete the** study ~~drug.~~ , **an EOT visit will be completed; the assessments performed at this visit will be identical to the assessments performed at the ET visit.** ~~At~~ **Following** completion of the Follow-up Treatment Period **or early discontinuation:** a safety follow-up phone call will be made **4** ~~weeks~~**30 days** after the last dose of study drug ~~(Week 100).~~
Synopsis, Safety and Tolerability;	**Alpha-fetoprotein (AFP), a marker of hepatocellular carcinoma, will be measured every 6 months throughout the optional extension period.**
Synopsis, Study Visit Schedule and Procedures; Section 8.1.9, Long-term Optional Follow-up Treatment Period	**Plasma samples will be obtained for LUM001 pharmacokinetics at the ADE Day 0, ADE Week 4, and ADE Week 8 visits, and at the 3 scheduled clinic visits following completion of the ADE period.**
Synopsis, Safety Evaluations	The following assessments will be used to evaluate safety: • Adverse events (AEs) and serious adverse events (SAEs). • Clinical laboratory results, including alpha-fetoprotein (AFP) as a screening for hepatocellular carcinoma. • Vital signs. • Physical exam findings, including body weight and height. • Concomitant medication usage.
Synopsis, Efficacy Evaluations; Section 12.2.5.1, Efficacy Variables	The primary efficacy ~~evaluation~~ **endpoint** will be the mean change ~~in~~ **from Week 18 to 22** of fasting serum bile acid levels ~~from Week 18 to Week 22 for those who~~ **in subjects who previously** responded to LUM001 treatment, ~~which is~~ **as** defined ~~as subjects who had~~ **by** a ~~>50%~~ reduction ~~serum bile acid levels~~ **sBA>70%** from baseline to Week 12 **or Week 18**. **A sensitivity analysis will also be conducted using subjects who experienced a reduction from baseline in serum bile acids of ≥50% at the Week 48 measurement.** … o Pruritus as measured by ItchRO (Observer ItchRO/patient ItchRO~~)~~**.) in subjects who previously responded to LUM001 treatment, as defined by a reduction in ItchRO scale >1 point from baseline to Week 12 or Week 18.** … o Change from baseline to Weeks 18, 22 48, and ~~4~~8 **then every**

Section	Description of Change
	12 weeks in: ~~Evaluations will be the mean~~ Change from Baseline (Day ~~0) to Week 18, prior to randomization, and the change from Week 18 to Week 48 and Week 18 to Week 100 in:~~ • ~~Biochemical markers of cholestasis and liver disease [alanine aminotransferase (ALT), alkaline phosphate (ALP), gamma-glutamyltransferase (GGT) and bilirubin (total and direct)].~~ • ~~Pruritus as measured by the electronic diary ItchRO instruments (ItchRO(Obs), caregiver instrument/ItchRO(Pt) patient instrument).~~ • ~~The change from Baseline (Day~~ 0) to Week 48 in xanthomas, as measured by clinician xanthoma scale ~~will also be evaluated.~~ Additional assessments of efficacy variables will occur during the ~~52-week~~ optional treatment period. ~~For subjects entering the 52-week optional treatment period with ≥7 days since last dose of LUM001,~~ **in 12 weekly intervals.** Any of the above evaluations may also occur at clinic visits during the DE ~~period~~, **PA4 DE, and ADE periods.**
Synopsis, Palatability Data; Section 12.2.9, Palatability Analyses Section 16.12, Palatability Questionnaire	**Palatability data will be collected at each clinic visit in the follow up treatment period, with the exception of the DE, PA4 DE, and ADE visits. A palatability questionnaire will be completed by the subject and/or caregiver (dependent on age). Assessment of change over time will be evaluated. Baseline will be defined as the first recorded evaluation.** Added palatability questionnaire
Section 8.5.8, Palatability	**A palatability questionnaire (see Section 16.12) will be completed by the subject and/or caregiver (dependent on age) at clinic visits at time points as outlines in the Schedule of Procedure in Section 16.1**
Synopsis, Statistical Considerations Section 12.2.10, Statistical Considerations	Safety measures including AEs, clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively by study period and over the entire study duration (Weeks 0-~~48).~~ **EOT Visit)**. **Interim Analysis** **There will be an interim analysis (IA) conducted after all subjects complete or discontinue the study after Week 48 to guide the future of the program. The IA may result in an interim report or publication. The IA will be conducted internally by an unblinded sponsor team as outlined in the unblinded study plan charter. The unblinded sponsor team will not be involved in the day-to-day clinical study activities.**
Section 4.4.1.3, Toxicology	~~The results from this study were very favorable.~~ As expected for a drug intentionally designed ~~to work in the intestinal lumen and~~ to be minimally absorbed, LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies with adult rats.
Section 4.5, Rationale for Dose and	*Updated Sample Daily Exposure (mg/day) in Pediatric Subjects table.*

Section	Description of Change
Schedule of Administration	~~In the current study, safety and efficacy of LUM001 will be assessed in children with ALGS and cholestatic liver disease, 12 months of age and older. The highest dose is equivalent to less than the well tolerated 1 mg dose used in Study 014 (~ 17 µg/kg, 60 kg body weight), where only two subjects reported moderate or severe GI-associated AEs during 14 days. On a weight basis, 23 subjects received a dose approximately ≥14 µg/kg/day. The highest starting dose in Study 014 was 168 µg/kg/day. To reduce the risk of loose stools and diarrhea in subjects in study LUM001-304, the LUM001 dose will be escalated over an up to 6-week period; dosing will start at 14 µg/kg/day, and will then be increased at 7-day intervals to 35 µg/kg/day, 70 µg/kg/day, 140 µg/kg/day, 280 µg/kg/day, and 400 µg/kg/day (equivalent to 20 mg daily dose in a 50 kg subject).~~ **The doses explored in the current study (up to 400 µg/kg/day BID) in subjects with ALGS are supported by the safety profile observed in completed and ongoing clinical studies of LUM001. Twice daily dosing is used in this study based on the findings of a healthy volunteers study in adult males (Study SHP625-101), which demonstrated that bile acid levels in feces increase with escalating doses and twice-daily regimen of LUM001 (up to 100 mg QD and 50 mg BID, respectively). In this study, subjects who were randomized to LUM001 treatment, received 1 of 4 doses of LUM001 (10, 20, 50, 100 mg) during 7 days. No titration was used in this study. There was a dose-dependent increase in total fecal BA excretion. In addition, BID dosing (i.e. 50 mg BID) led to a further increase in fecal BA excretion as compared to QD dosing (i.e. 100 mg QD). It is therefore hypothesized that higher doses and twice-daily dosing both have the potential to allow for more complete target engagement throughout the day at the level of the distal ileum.** **The higher dosing level is also supported by favourable results from a juvenile toxicity study conducted in rats administered LUM001 for 43 days (PND21 through PND63). As expected for a drug intentionally designed to be minimally absorbed, systemic LUM001 exposure was very low and consistent with levels that were previously determined in several oral gavage studies in adult rats. No adverse effects were observed on postnatal growth and development of offspring at the highest doses tested (200 mg/kg/day in males, 1000 mg/kg/day in females). This study was initiated in juvenile animals at PND21, which from a whole animal development perspective, is typically representative of a 2-year old child. However, given the fact that LUM001 is a minimally absorbed drug, of particular importance is the age at which the GI tract is considered functionally mature. In humans this is considered to have occurred by 12 months of age; likewise, postnatal maturation of the GI tract in rats occurs during the first 3 weeks of life. Therefore, results from this study can be used to support the dosing levels proposed here for children 12 months of age and older.**
Section 5.1, Study Design	~~At Week 48, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the 52-week, optional follow-up treatment period. The 3 following possible scenarios~~

Section	Description of Change
	~~may occur:~~ • ~~For subjects who are eligible to roll over into the follow-up treatment period, those with <7 days since the last dose of LUM001 will be maintained at the highest tolerated dose at Week 48.~~ • ~~For subjects who are eligible to roll over into the follow-up treatment period, those with ≥7 days since the last dose of LUM001 will be dose escalated up to 400 µg/kg/day or highest tolerated dose following a 5-week dose escalation beginning at 35 µg/kg/day.~~ • ~~For subjects who do not wish to enter the follow-up treatment period, or are not eligible to enter the follow-up treatment period, a safety follow-up phone call will be made by the study site 28 days after the last dose of study drug~~
Section 5.5, Overall Study Duration and Follow-up	For an individual subject, the ~~duration of the~~ study, ~~including subject~~ **participation period will consist of a** screening, **period of up to 4 weeks, a 48-week** treatment **period (including a 6-week, open-label, dose escalation period, a 12-week open-label stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period,** ~~safety~~ **a 26-week long-term exposure period) as well as a 52-week optional follow-up treatment period,** and **a long-term optional treatment period. A** safety follow-up ~~is expected to~~ **phone call will** be ~~approximately 56 weeks.~~ **made by the study site 30 days after the last dose of study drug.**
Section 5.5.2, Treatment	Study drug will be dispensed to subjects/caregivers ~~at the study~~. **During the course of the study, it may be necessary to instruct the subject/caregiver to return to the** site~~.~~ **for an unscheduled dispensation of study drug.** ~~Subjects who weigh 10 kg or more at screening will receive a 1.0 mL grape-flavored solution per day containing LUM001 Subjects who weigh less than 10 kg at screening will receive a 0.5 mL grape-flavored solution per day containing LUM001. The daily volume administered will not change during the course of the study. Dosing will occur over a 48-week treatment period. Each daily dose will be administered in the morning at least 30 minutes before breakfast (qAM, ac). Study drug should be administered approximately at the same time every day.~~ **Subjects will receive a grape-flavored solution containing LUM001 administered orally once a day (QD) or twice a day (BID) using the syringe provided. The first dose should be taken at least 30 minutes prior to the first meal of the day and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (main evening meal). The doses will not be administered q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the dose should be taken approximately at the same time each day for the duration of the treatment period.** **All subjects will receive LUM001, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day during the initial open-label**

Section	Description of Change
	treatment period of the study. After completion of the 12-week stable dosing period, subjects will be randomized 1:1 to either a 4-week double-blind study drug withdrawal period during the study or will remain on study drug. Subjects will then enter a 26-week long-term stable dosing period and all subjects will receive LUM001, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day during the initial open-label treatment period of the study. Subjects will then be considered for an optional follow-up treatment, if eligible, to continue on their highest tolerated dose receiving up to 800 µg/kg/day (given as twice daily doses of 400 µg/kg), or a maximum possible daily dose of 50 mg/day.
Section 5.5.2.1, Dose Escalation Period	Initially, the LUM001 dose will be **administered as a daily morning dose in either a 1.0 mL or 0.5 mL solution. The dose will be** increased weekly over a 6-week period up to 400 g/kg/day **QD** or a maximum daily dose of 20 mg/day **QD** as follows
Section 5.5.2.4, Long-term Exposure Period	**During the long-term exposure period, the dose may be adjusted to account for a change of ≥10% in weight since the screening visit (e.g. the amount of drug dosed may be increased to reflect the subject's weight increase).**
Section 5.5.2.6, Long-term Optional Follow-up Treatment Period	Subjects who are eligible to roll over into the **optional** follow-up treatment period~~, those with <7 days since the last dose of~~ **will continue treatment under dosing scenarios based on whether their** LUM001 ~~will be maintained at the highest tolerated dose at Week 48~~ **dosing will continue 1) without interruption/interruption of <7 continuous days, or 2) with interruption ≥7 days. Eligibility for BID dosing will be determined based on efficacy as measured by sBA level and ItchRO score. The 2 following dosing scenarios may occur.**
Section 5.5.3, Safety Follow-up Period	A safety follow-up phone call will be made by the study site ~~28~~**30** days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. **Concomitant medications and any AEs noted during this phone call will be recorded. Subjects who complete the study or who discontinued early due to reasons other than safety may be eligible for participation in the optional follow-up treatment period under Protocol Amendment 4.** ~~If any subject experiences intolerance, the investigator, in consultation with the Sponsor Medical Monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period. At the investigator's discretion, and in consultation with the Sponsor Medical Monitor, subjects who were previously down titrated may be re-challenged during the follow-up treatment period. During the follow-up treatment period, subjects will return to the clinic at Weeks 60, 72, 84, 96, and 100.~~ ~~Safety and clinical laboratory evaluations and a physical exam (including collection of vital signs, height and weight measurements) will be completed at each clinic visit. In addition, the clinician scratch scale, clinician xanthoma scale, and PedsQL (clinician xanthoma scale and Peds QL will not be evaluated at DE-2 and DE-52) will be administered and study drug compliance will be assessed. The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 84, 96, and 100. Subjects/caregivers will receive follow-up phone calls at Weeks 64, 68, 76, 80, 88, and 92. Concomitant medications and any~~

Section	Description of Change
	~~AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.~~ ~~Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, 84, and 96 clinic visits. Electronic diaries will be provided to subjects and caregivers at these visits and re-training on the use of the diary will occur, as appropriate.~~ ~~At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the long-term exposure period.~~ ~~With the exception of the Week 96 and Week 100 visit (Study Termination),~~ Additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used ~~and unused~~ study drug will be collected at ~~every~~ **each clinic** visit **and dosing compliance will be assessed**.
Section 5.6, End of Study	**For subjects who do not consent to the long-term optional follow-up treatment period, a subject is considered to have completed treatment if treatment was not permanently discontinued prior to the Week 48 visit. A follow-up phone contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.** **The subject is considered to have completed treatment and study period for the corresponding follow-up treatment period (when consented under Protocol Amendment 3 or Protocol Amendment 4) if study treatment was not discontinued prior to completing Week 96 for Protocol Amendment 3 or completing the EOT visit in Schedule J under Protocol Amendment 4. Temporary drug interruption is not considered treatment discontinuation. A follow-up contact is required for all subjects should the final visit occur earlier than 30 days from the final dose.** The end of study for the purposes of regulatory reporting is the point at which the last contact with the last subject during the protocol-specified scheduled follow-up period is made.
Section 6.1, Screening	**Subjects will be enrolled in the optional follow-up treatment period based on the investigator's determination of meeting eligibility criteria outlined in Section 7. A subject will be considered enrolled in the long-term optional follow-up period under Protocol Amendment 4 after the subject consents and the investigator has determined the subject meets study entry eligibility criteria per Protocol Amendment 4. However, any subject who consents to Protocol Amendment 4 and does not meet criteria per the investigator is considered a screen failure for the long-term optional follow-up period under Protocol Amendment 4. Screen failures are eligible for rescreening (Section 8.1.1).**
Section 8.1.1, Screening Period (Day -28 to Day -1)	In the absence of documented JAGGED1 or NOTCH2 mutation prior to screening, genetic testing may be performed for JAGGED1 **and/or NOTCH2** (Spinner et al., 2000). … For subjects who do not have documentation of a JAGGED-1 **or NOTCH2** mutation, a blood sample may be obtained for genotyping. … <u>Rescreening:</u> … **Subject data pertaining to screening will be collected after the subject has been rescreened and determined to**

Section	Description of Change
	meet eligibility.
Section 8.1.10, End of Treatment of Early Termination	Any ~~subject~~ **subject** who **completes or** withdraws from the study ~~prior to completion of all treatment period clinic visits~~ should undergo **all procedures specified for the EOT/ET visit (see Schedule J). The following assessments are to be completed at the EOT/ET visit:** safety and clinical laboratory evaluations, including determination of serum bile acids, lipid panel, other cholestasis biochemical markers, fat soluble vitamins, ~~and plasma drug level. In addition~~ and **AFP**. **Female subjects who are of childbearing potential will have a urine pregnancy test. Study drug compliance will be assessed. Concomitant medications and adverse events will be collected**. In addition, the following assessments … ~~Efforts must be made to follow subjects for at least 4 weeks following their last dose of study drug.~~
Section 8.1.11, Safety Follow-up Period	**A safety follow-up phone call will be made 30 days after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded.**
Section 8.5.1, Itch Reported Outcome (ItchRO™); Section 8.5.2, Clinician Scratch Scale; Section 8.5.3, Clinician Xanthoma Scale; Section 8.5.4, Pediatric Quality of Life Inventory (PedsQL); Section 8.5.5, Patient Impression of Change; Section 8.5.6, Caregiver Impression of Change; Section 8.5.7, Caregiver Global Therapeutic Benefit	Edited text to indicate all assessments will be performed as outlined in the Schedule of Procedures in Section 16.1.
Section 8.6.1, Contraception Requirements	Sexually active female subjects of childbearing potential must continue to use **acceptable** contraception with their partners, or refrain from sexual activity, from the time of screening ~~until the end of the study~~, **throughout** the study **period and for 30 days following the last dose of the study drug.** **If hormonal contraceptives are used they should be administered according to the package insert.** **Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of the IP.** **Acceptable methods of contraception are:** Acceptable methods of contraception are ~~condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized.~~ **a. Hormonal contraceptives (eg, oral contraceptive pill, depot, patch, intramuscular implant or injection, or vaginal ring), stabilized for at least 30 days if first use, plus condoms; and/or** **b. Barrier method, eg, (i) condom (male or female) or (ii) diaphragm, with spermicide; or** **c. Intrauterine device (IUD).** **d. or a sexual partner who is surgically sterilized.**

Section	Description of Change
	Male Contraception: **Contraception is required for all sexually-active male subjects and their partners. All male subjects agree not to donate sperm, and to use 1 of the following approved methods of contraception until 30 days following study discharge:** **a. Male condom with spermicide** **b. Intrauterine device with spermicide (use by female sexual partner)** **c. Female condom with spermicide (use by female sexual partner)** **d. Contraceptive sponge with spermicide (use by female sexual partner)** **e. Intravaginal system (eg, vaginal ring with spermicide, a diaphragm with spermicide, or a cervical cap with spermicide) (use by female sexual partner)** **f. Oral, implantable, transdermal, or injectable hormonal contraceptive (use by female sexual partner).**
Section 8.6.2, Fasting Requirements	On these visit days study drug should be administered as usual (1 mL, **5 mL**, or 0.~~5 mL~~ **25** qAM, ac), in the morning 30 minutes before breakfast.
Section 9.1.1, LUM001	Added new composition of LUM001 1.0 mL, 0.5 mL, and 0.25 mL Oral Solution tables.
Section 9.1.2, Placebo	Added new composition of placebo 1.0 mL, 0.5 mL, and 0.25 mL Oral Solution tables.
Section 10.1, Study Drug Administration	**The dose may also be down-titrated, at the investigator's discretion and in consultation with the sponsor medical monitor, for subjects experiencing intolerance (eg, gastrointestinal symptoms such as diarrhea, abdominal pain, cramping) to a given dose. If the subject is on twice daily dosing regimen, dose reduction should first be attempted with the afternoon dose. Subjects who were previously down-titrated may be rechallenged during the long-term exposure period.** **…** ~~Study drug will be dispensed to subjects/caregivers at the study site.~~ ~~…~~ ~~Each subject dose for subjects who weigh 10 kg or more~~ **Subjects** will ~~be administered orally as a~~ **receive a grape-flavored** solution containing ~~study drug~~ (LUM001 ~~or placebo~~) using the syringes provided. . Each subject dose ~~for subjects who weigh less than 10 kg~~ will be administered orally as **once** a ~~0.5 mL solution containing study drug (LUM001day~~ **(QD)** ~~or placebo~~ **twice a day (BID)** using the ~~syringe~~s **syringe** provided. The ~~daily volume administered will not change during the course of the study~~. Study drug **first dose** should be taken at least 30 minutes prior to the first meal of the day ~~(qAM, ac) and should~~ **and the second dose, where applicable, should be taken at least 30 minutes prior to dinner (evening meal). The doses will not** be administered **q12h in order to better cover the luminal bile acid release associated with dinner and to minimize the risk of disturbing sleep due to the potential for abdominal pain and diarrhea at night. It is recommended that the doses should be taken** approximately at the same time each day for the duration of the

Section	Description of Change
	treatment period.
Section 10.2, Treatment Compliance	Subjects and/or caregivers will be asked to complete a paper diary indicating when they took their study medication and when they ate breakfast **and, for subjects who receive a BID regimen, when they ate dinner (evening meal).**
Section 10.5.1, General Monitoring Rules	If an individual subject exhibits a CTCAE Grade 3 treatment emergent ~~toxicity~~ **laboratory abnormality,** with the exception of the specific rules outlined below (Sections 10.5.2), dosing ~~will~~ **can** be suspended. ~~Continued dosing with study drug may be considered~~ **or continued as per the investigator's judgement and** following discussion with the sponsor medical monitor. **If suspended** the… **The Data Monitoring Committee (DMC) will be notified of any SAE as specified in the DMC charter.**
Section 10.5.2, Safety Monitoring Rules	**Of note: the INR re-test should be conducted by the central laboratory, but may also be conducted at a local laboratory on an as needed basis….** In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to study investigators **and medical monitors** immediately… **The investigator should also assess the need to capture an AE, its severity according to the CTEAE directives and potential causality. These assessments should also include an evaluation of whether criteria for an SAE are fulfilled (see Section 11.2.3), in particular whether the event should be considered as an important medical event, ie. an event that would have met one of the other seriousness criteria in the absence of appropriate medical interventions.**
Section 10.6, Adjustment of Dose	If an individual subject exhibits a treatment emergent CTCAE Grade 2 or greater drug-related GI toxicity, study drug dose may be lowered to a previously well tolerated dose; **later attempts to escalate the dose are permitted. If the subject is on twice daily dosing regimen, dose lowering should first be attempted with the afternoon dose.**
Section 11.3, Monitoring and Recording of Adverse Events	**In addition, AEs that occur while the subject is not enrolled in the study during a gap period will be collected as medical history unless the AE started within 30 days of last dose.**
Section 11.3.1, Serious Adverse Events	The collection of SAEs will begin after the subject signs the informed consent/assent form and stop ~~at the end of the subject's follow-up period which is defined as Week 52 for subjects who do not roll over into the optional treatment follow-up period, Week 100 for subjects who do roll over into the optional treatment follow-up period, or 28 days after the last dose of study drug for those subjects that terminate prior to the Week 96 visit~~ **30 days after the last dose of study drug.**
Section 11.3.2, Non-serious Adverse Events	The recording of non-serious AEs will begin after the subject signs the informed consent/assent form and will stop ~~at the end of the subject's follow-up period, which is defined as Week 52 for subjects who do not roll over into the optional treatment follow-up period, Week 100 for subjects who do roll over into the optional treatment follow-up period, or 30 days after the last dose of study drug for those subjects that terminate prior to the Week 96 visit~~ **30 days after the last dose of study drug**.
Section, 11.3.3.2 Severity	**Please also refer to Section 10.5.2 regarding specific safety**

Section	Description of Change
	monitoring for liver chemistry tests given that subjects with ALGS may have abnormal liver enzyme levels at baseline.
Section 12.2.2, Efficacy Populations	The main population for efficacy will be the modified intention-to-treat population (MITT), defined as all subjects who were enrolled, received study medication through Week 18, had a reduction from baseline in serum bile acids of ≥50% at the Week 12 **or Week 18** measurement.
Section 12.2.5.1, Efficacy Variables	**A sensitivity analysis will also be conducted using subjects who experienced a reduction from baseline in serum bile acids of ≥50% at the Week 48 measurement.** **… in subjects who previously responded to LUM001 treatment, as defined by a reduction in ItchRO scale >1 point from baseline to Week 12 or Week 18.** **In addition, an analysis for a daily score defined as an average of morning and evening scores will be conducted.**
Section 12.2.6.1, Safety Assessments	• **Serum alpha-fetoprotein (AFP)**
Section 12.2.8.2, Laboratory Tests	Changes within a treatment group for selected safety measures will be assessed at Weeks 3, 6, 12, 18, 22, 28, 38, 48, 60, 72, 84, 96, **and at additional time points during the 52-week and long-term optional treatment periods…**
Section 12.2.8.6, Serum Alpha-fetoprotein	(new section) **Assessments of serum AFP will be listed for individual subjects and summarized using descriptive statistics by study visit.**
Section 16.1.2, Schedule of Procedures E-F	Added Overall Scheme and Corresponding Schedule of Procedures Added Schedule of Procedures E-F: Rollover under Protocol Amendment 4: Schedule of Procedures E – Extension of Long-term Optional Follow-up Treatment Period, for subjects ineligible for ADE, applicable as follows: • Subject did not yet complete the optional follow up treatment period as outlined under Protocol Amendment 3 and is able to consent to Protocol Amendment 4 activities without an interruption in LUM001 dosing, OR • Subject completed long-term optional follow up treatment period as outlined under PA3 and dosing interruption was <7 days. • Subject deemed ineligible for ADE. Schedule of Procedures F – Extension of Long-term Optional Follow-up Treatment Period, for subjects eligible for ADE, applicable as follows: • Subject did not yet complete the long-term optional follow up treatment period as outlined under Protocol Amendment 3. and is able to consent to Protocol Amendment 4 activities without an interruption in LUM001 dosing, OR • Subject completed the optional follow up treatment period as outlined under PA3 and dosing interruption was <7 days. • Subject deemed eligible for ADE.
Section 16.1.3, Schedule of Procedures G-I	Added Schedule of Procedures G-I: Rollover under Protocol Amendment 4:

Section	Description of Change
	Schedule of Procedures G – Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, applicable as follows: • Subject previously completed (or early terminated from) the optional follow up treatment period as defined under Protocol Amendment 3 and has subsequently experienced an interruption in LUM001 dosing ≥7days • Subject is considered eligible for study re-entry under Protocol Amendment 4 • Subject eligibility will be assessed for afternoon dose escalation at Protocol Amendment 4 DE Week 8 shown in the table below. o If subject is found to be ineligible for ADE, subject will move from Schedule G to Schedule H. o If subject is found to be eligible for ADE, subject will move from Schedule G to Schedule I. Schedule of Procedures H – Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject ineligible for ADE Schedule of Procedures I – Long-term Optional Follow-up Treatment Period: Re-entry under Protocol Amendment 4, subject eligible for ADE Added Schedule of Procedures J - Study Termination and End of Treatment Procedures
Section 16.2, List of Laboratory Analytes	Added alpha-fetoprotein (AFP) under Marker of hepatocellular carcinoma
Section 16.7, Pediatric Quality of Life Inventory (PedsQL™)	**Subjects will continue to fill out the same questionnaire used at baseline for continuity of data collection, regardless of subsequent birthdays after the baseline visit.**

16.13.3 Protocol Amendment 3 Summary of Changes

Protocol Number: LUM001-304

Protocol Title: LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BL**I**ND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN API**C**AL S**O**DIUM-DEPE**N**DENT B**I**LE A**C**ID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Amendment: **3**

Date: 13 Nov 2015

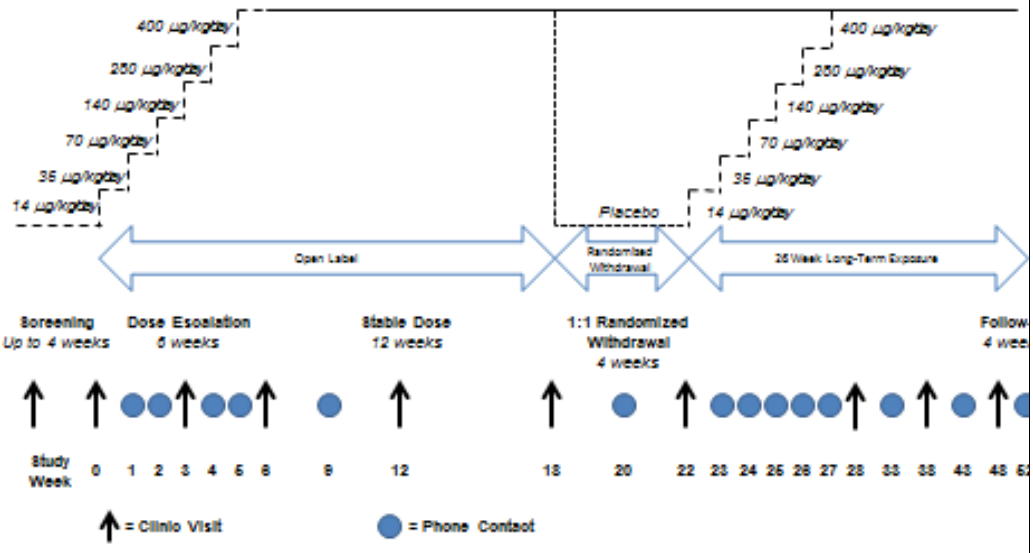
The changes below were made to Protocol Amendment 2.

The following table provides a summary list of changes that were included in Protocol Amendment 3 (*new text indicated in bold; deleted text indicated in strikethrough)*:

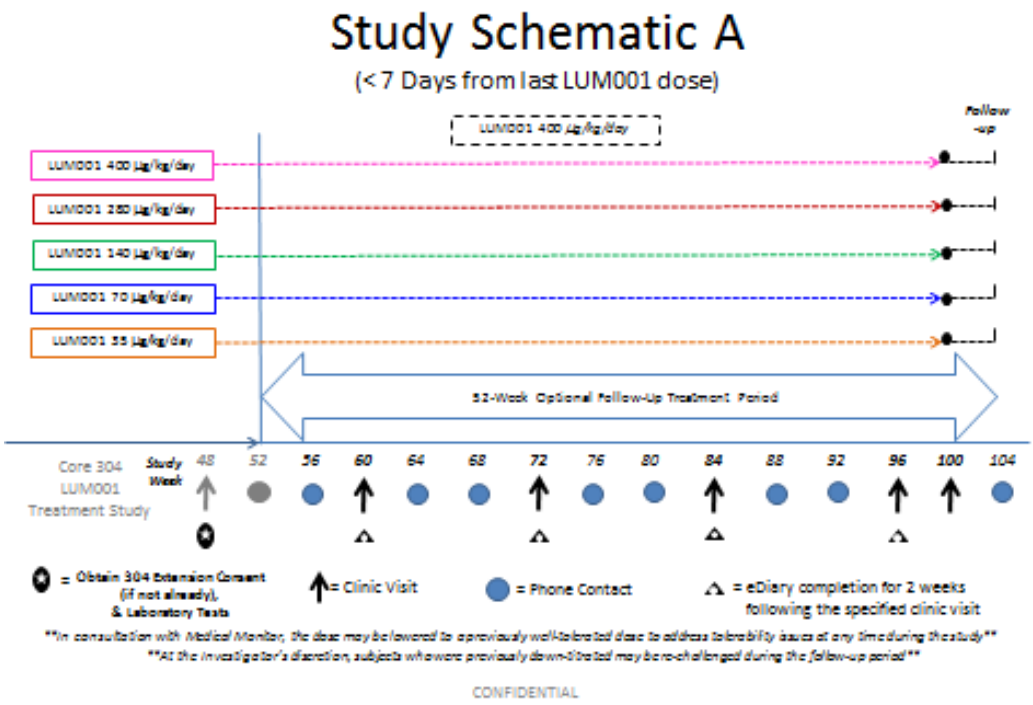
Section	Description of Change
Title Page, Sponsor Medical Monitor	**Added:** **Sponsor Medical Monitor:** **Susanne Schmidt, MD, PhD** **Premier Research** **Office: +1 215 282 5406** **Cell: +1 267 838 2380** **Email: medmonitorLUM304@premier-research.com**
Title Page, Medical Lead	**Changed from:** Ciara Kennedy, PhD Lumena Pharmaceuticals, Inc. Phone: 00-1-858-337-7922 Email: cikennedy@shire.com **To:** **Beatriz Caballero, MD** **Shire, Inc.** **Zahlerweg 10** **6300 Zug** **Switzerland** **Phone: +41(0) 41 288 42 30** **Email: bcaballero@shire.com**
Study Synopsis, Objectives; Section 3, Study Objectives	• To evaluate the effect of LUM001 on serum bile acid levels in children with ALGS. • To evaluate the effect of LUM001 on biochemical markers of cholestasis and liver disease in children with ALGS. • To evaluate the effect of LUM001 on pruritus in children with ALGS. • To evaluate the long-term ~~durability of~~ effect of LUM001 in children with ALGS 48-weeks of treatment. • To evaluate the long-term safety and tolerability of LUM001 in children with ALGS. **Objectives of Optional Follow-up Treatment Period (After Week 48):** • **To offer eligible subjects treated in the LUM001-304 study continued study treatment after Week 48 until the first of the following occur: (i) up to 52 weeks of additional treatment (Week 100), or (ii) in the event that a new study opens to enrollment.** • **To obtain safety and efficacy data in patients treated long term on LUM001 including genotyping characteristics.**
Synopsis (Section 1), Study Design and Overall Study Duration and Follow-up (Sections 5.1 and 5.4), Schedule of Procedures (Appendix 16.1)	**This is a long-term, open-label study with a double-blind, placebo-controlled, randomized drug withdrawal period in children with ALGS designed to evaluate the safety and efficacy of LUM001. The study is divided into 5 parts: a 6-week open-label, dose escalation period at doses up to 400 µg/kg/day, a 12-week stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, a 26-week long-term stable dosing period at doses up to 400 µg/kg/day, and an optional 52-week follow-up treatment period for eligible subjects who choose to stay on treatment with LUM001. Subjects' participation in the optional follow-up treatment period will continue until the first of the following occur: (i) completion of 52 weeks of additional treatment (Week 100), or (ii) in the event that a new study of LUM001 opens to enrollment.** ~~This is a long-term, open-label study with a double-blind, placebo-controlled, randomized drug withdrawal period in children with ALGS designed to evaluate the safety and efficacy~~

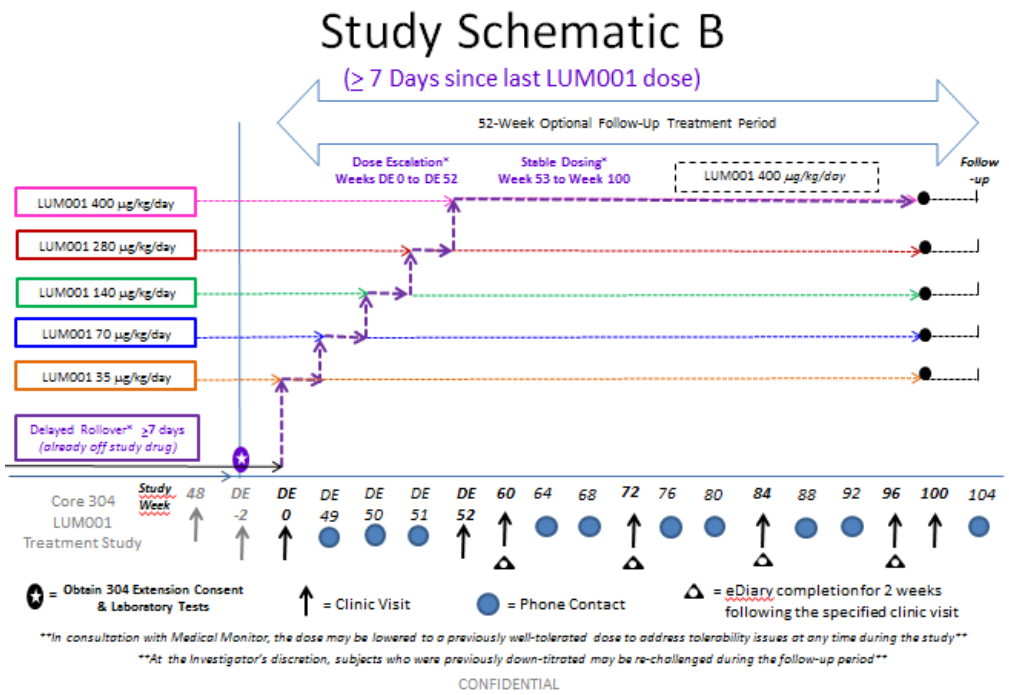
Section	Description of Change
	~~of LUM001. The study is divided into 4 parts: a 6-week open-label, dose escalation period at doses up to 400 µg/kg/day, a 12-week stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, and a 26-week long-term stable dosing period at doses up to 400 µg/kg/day~~.
Synopsis (Section 1), Study population (Section 7)	Exclusion Criteria Subjects will be excluded from the study if they meet any of the following criteria: 1. Chronic diarrhea requiring ongoing intravenous fluid or nutritional intervention. 2. Surgical interruption of the enterohepatic circulation. 3. Previous liver transplant. 4. Decompensated cirrhosis [ALT >15 x ULN, INR >1.5 (unresponsive to vitamin K therapy), albumin <3.0 g/dL, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy]. 5. History or presence of other concomitant liver disease. 6. 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 (eg, inflammatory bowel disease). 7. History or presence of gallstones or kidney stones. 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. Recent medical history or current status that suggests that the subject may be unable to complete the study. 11. Any female who is pregnant or lactating or who is planning to become pregnant during the study period. 12. Known history of alcohol or substance abuse. 13. Administration of bile acid or lipid binding resins within 28 days prior to screening and throughout the trial. 14. Known hypersensitivity to LUM001or any of its components. 15. Receipt of investigational drug, biologic, or medical device within 28 days prior to Screening, or 5 half-lives of the study agent, whichever is longer. 16. History of non-adherence to medical regimens, unreliability, mental instability or incompetence that could compromise the validity of informed consent or lead to non-adherence with the study protocol based upon investigator judgment. 17. Any other conditions or abnormalities which, in the opinion of the investigator or **sponsor** medical monitor, may compromise the safety of the subject, or interfere with the subject participating in or completing the study. 18. Subjects weighing over 50 kg at screening. **Eligible subjects for the 52-week follow-up period:** **Subjects will be considered eligible for the optional 52-week follow-up treatment period if they have:** • **Completed the protocol through the Week 48 visit with no safety concerns. Subjects who were discontinued due to safety reasons can be rechallenged if blood tests are back to relatively normal values for this patient population and subject does not meet any of the protocol's stopping rules. The decision will be made by the investigator in**

Section	Description of Change
	consultation with the sponsor medical monitor. • **Subjects who have undergone a surgical disruption of the enterohepatic circulation will not be eligible to enter into the follow up treatment period.** • **Subjects who were discontinued for other reasons will be considered for the optional 52-week follow-up treatment period on an individual basis. The decision will be made by the investigator in consultation with the sponsor medical monitor.**
Synopsis (Section 1)	All subjects will receive LUM001, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day. After completion of the 12-week stable dosing period, subjects will be randomized 1:1 to either a 4-week study drug withdrawal period during the study or will remain on study drug. Subjects will then enter a 26-week long-term stable dosing period and all subjects will receive LUM001, up to 400 µg/kg/day or a maximum daily dose of 20 mg/day. **Subjects will then be considered for an optional 52-week follow-up treatment, if eligible, to continue on their highest tolerated dose.**
Synopsis (Section 1), Study Design (Section 5.1)	**Optional Follow-up Treatment Period** **At Week 48, all subjects will be assessed by the investigator to determine their willingness and eligibility to roll-over into the 52-week, follow-up treatment period. The 3 following possible scenarios may occur:** • **Subjects who are eligible to roll over into the optional follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level.** • **Subjects who are eligible to roll over into the optional follow-up treatment period with a LUM001 dosing interruption of ≥7 days, will be dose escalated up to 400 µg/kg/day or highest tolerated dose following a 5-week dose escalation beginning at 35 µg/kg/day.** • **Subjects who do not wish to enter the follow-up treatment period will be contacted via telephone by the study site approximately 28 days after the last dose of study drug.** During the study, the study drug may be adjusted if there is a change of ≥10% in weight since the screening visit or if there is a change of ≥10% in weight since the last weight-based medication adjustment to maintain the target dose (µg/kg/day). ~~The anticipated adverse reaction or intolerance is gastrointestinal in nature (e.g., diarrhea, abdominal pain, cramping, etc.). During the respective escalation periods, in the absence of intolerance, escalation to the next dose level for an individual subject will occur following a scheduled phone call or visit (see Schedule of Procedures, Section 16.1).~~ If a subject experiences intolerance due to gastrointestinal **symptoms (eg, diarrhea, abdominal pain, cramping) at any time during the study,** the physician investigator in consultation with the sponsor medical monitor may lower the dose to a previously tolerated dose. ~~At the investigator's discretion, subjects who had their dose reduced due to intolerability may have a one-time dose re-challenge during the long-term exposure period with a higher dose.~~
Synopsis (Section 1), Overall Study Duration and Follow-up (Section 5.4)	Added to synopsis: **For subjects in the 52-week optional follow-up treatment period with ≥7 days since the last dose of LUM001, dosing will start at 35 µg/kg/day, and will then be increased over the first 5 weeks up to 400 µg/kg/day or to the maximum tolerated dose. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical studies of LUM001 and allows for subjects to reach 400 µg/kg/day or a maximum tolerated dose within a 5-week period. The dose may be down-titrated, at the investigator's discretion and in consultation with the sponsor medical monitor, for**

Section	Description of Change
	subjects experiencing intolerance to a given dose. Change in Section 5.5: **Subjects who complete 48 weeks of treatment may be eligible to receive treatment for up to 52 weeks during the optional follow-up treatment period (see Figure 3 and Figure 4). Study activities will be conducted as described in the Schedule of Procedures (Section 16.1).** **Figure 1: Study Design for LUM001-304 (Up to and Including Week 52)** 

Section	Description of Change
	Figure 2: Follow-up Treatment Scheme (No Interruption in LUM001 Dosing or Interruption <7 days)



Section	Description of Change
	Figure 3: Follow-up Treatment Scheme (Interruption in LUM001 Dosing ≥7 Days) 
Synopsis (Section 1), Study Schedule (Section 8.1)	Week 48/~~Study Termination~~: **Subjects will be evaluated by the investigator to determine whether they are eligible to roll over into the optional 52-week follow-up treatment period. Eligible subjects must have documented consents in order to continue in the optional follow-up treatment period.** A physical exam (including collection of vital signs, height and weight measurements) will be performed. Blood and urine samples will be taken for clinical laboratory testing, including a fasting lipid panel and determination of fat-soluble vitamins, bile acids, other cholestasis biochemical markers, and possibly LUM001 drug level analysis. Female subjects who are of childbearing potential will have a urine pregnancy test. The clinician scratch scale, xanthoma scale, and PedsQL questionnaires will be completed. The Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments will be completed. Concomitant medications and adverse events will be recorded. ItchRO and study drug compliance will be assessed and all remaining study drug and study supplies will be collected. **eDiaries will be returned to the site and** study drug will be discontinued at this visit ~~and eDiaries will be returned to the site~~ **if the subject chooses not to participate in the optional follow-up treatment period.** Subjects who withdraw from the study prior to completion of all treatment period clinic visits should undergo the procedures specified for the Week 48/Study Termination visit (Section 16.1). Follow-up **Phone Call** ~~Period~~: **For subjects who do not roll over into the optional follow-up treatment period,** a safety follow-up phone call will be made 4 weeks after the last dose of study drug. This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded. **Follow-up Treatment Period (post-Week 48 to Week 100): Subjects who are eligible to roll over onto the follow-up treatment period will continue to receive study drug at the dose they were receiving at Week 48 for up to 52 weeks of additional treatment or in the**

Section	Description of Change
	event that a new study opens to enrollment, whatever occurs first. **Subjects who are eligible to roll over into the follow-up treatment period with no LUM001 dosing interruption or an interruption of <7 days will be maintained at the same dose level.** ~~Telephone contacts to occur at Week 52 and Week 56.~~ **During the follow-up treatment period, subjects will return to the clinic at Weeks 60, 72, 84, 96, and 100; and telephone contacts to occur at Weeks 64, 68, 76, 80, 88, and 92.** **Subjects with ≥7 days since last dose of LUM001 will be dose escalated up to 400 µg/kg/day or to the highest tolerated dose with 35 µg/kg/day. This escalation regimen is supported by the safety profile observed in completed and ongoing clinical trials of LUM001 and allows for subjects to reach 400 µg/kg/day or highest tolerated dose within a 5-week period. The dose escalation (DE) period will proceed as follows:** • **Week DE-2 Clinic Visit: obtain consent, weight, and draw blood for laboratory analyses.** • **Week DE 0 Clinic Visit: PI evaluates laboratory results, study drug is dispensed, and subject begins at 35 µg/kg/day dose level (if no safety concerns).** • **Week DE 49 Telephone Contact: subject escalates to 70 µg/kg/day dose level.** • **Week DE 50 Telephone Contact: subject escalates to 140 µg/kg/day dose level if prior dose level was tolerated.** • **Week DE 51 Telephone Contact: subject escalates to 280 µg/kg/day dose level if prior dose level was tolerated.** • **Week DE 52 Clinic Visit: laboratory tests and dose escalates to 400 µg/kg/day dose (maximum daily dose of 20 mg), if prior dose level was tolerated.** **If any subject experiences intolerance , the investigator, in consultation with the sponsor medical monitor, may lower the dose to a previously tolerated dose at any time during the entire follow-up treatment period. At the investigator's discretion, and in consultation with the sponsor medical monitor subjects who were previously down titrated may be rechallenged during the follow-up treatment period.** **Safety and clinical laboratory evaluations and a physical exam (including collection of vital signs, height and weight measurements) will be completed at each clinic visit. In addition, the clinician scratch scale, clinician xanthoma scale, and PedsQL will be administered and study drug compliance will be assessed (PedsQL will not be performed at DE-2 or DE52). The Patient and Caregiver Impression of Change (PIC & CIC), and the Caregiver Global Therapeutic Benefit assessments will be completed at Weeks 84, 96, and 100. Subjects/caregivers will receive follow-up phone calls at Weeks 64, 68, 76, 80, 88, and 92. Concomitant medications and any AEs will be evaluated and recorded at all clinic visits and at scheduled telephone contacts.** **Twice daily completion of the electronic diary will be required by caregivers and age appropriate subjects during the 2 weeks following the Week 60, 72, 84, and 96 clinic visits. Electronic diaries will be provided to subjects and caregivers at these visits and re-training on the use of the diary will occur, as appropriate.** **At the physician investigator's discretion, withdrawal of concomitant medications used for the treatment of pruritus may occur during the long-term exposure period.** **With the exception of the Week 96 and Week 100 visit (Study Termination), additional study drug will be supplied at each clinic visit during the follow-up treatment period. Used and unused study drug will be collected at every visit.**

Section	Description of Change
	Subjects will be encouraged to complete all study activities and visits. Any subject who withdraws from the study prior to completion of all treatment period clinic visits should undergo safety and clinical laboratory evaluations, including determination of serum bile acids, other cholestasis biochemical markers, fat soluble vitamins, and plasma drug level. In addition the following assessments should be completed: the ItchRO (Pt and Obs), the clinician scratch scale, clinician xanthoma scale, the PedsQL, the Patient Impression of Change, the Caregiver Impression of Change, and the Caregiver Global Therapeutic Benefit assessments, as defined for ET (see Schedule of Procedures, Section 16.1) Efforts must be made to follow subjects for at least 4 weeks following their last dose of study drug. **<u>At completion of the Follow-up Treatment Period:</u> a safety follow-up phone call will be made 4 weeks after the last dose of study drug (Week 100). This call will be made for all subjects who complete the study, as well as any subject who terminates from the study early. Concomitant medications and adverse events noted during this phone call will be recorded.**
Synopsis (Section 1), Pruritus and Quality of Life Assessments (Section 8.5), Efficacy Variables (Section 12.2.5.1)	From the synopsis: Evaluations ~~for the durability of the therapeutic effect~~ will be the mean change from Baseline (Day 0) to Week 18, prior to randomization, and the change from Week 18 to Week 48 in: • Biochemical markers of cholestasis and liver disease [alanine aminotransferase (ALT), alkaline phosphate (ALP), gamma-glutamyltransferase (GGT) and bilirubin (total and direct)]. • Pruritus as measured by the electronic diary ItchRO instruments (ItchRO(Obs), caregiver instrument/ItchRO(Pt) patient instrument). The change from Baseline (Day 0) to Week 48 in xanthomas, as measured by clinician xanthoma scale will also be evaluated. **Additional assessments of efficacy variables will occur during the 52-week optional treatment period. For subjects entering the 52-week optional treatment period with ≥7 days since last dose of LUM001, any of the above evaluations may also occur at clinic visits during the DE period.** Additional exploration of evaluations of safety ~~and the durability of the therapeutic effect~~ will be specified in the statistical analysis plan. Section 8.5: 8.5 Pruritus and Quality of Life Assessments 8.5.1 Itch Reported Outcome (ItchRO™) 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 48 clinic visit (or sooner if the subject has withdrawn from the study before the Week 48 visit). **For subjects who enter the optional follow-up treatment period, daily completion of the diary will also occur during the 2 weeks following the Week 60, 72, 84, and 96 clinic visits.** 8.5.2 Clinician Scratch Scale A clinician's assessment of pruritus made by the principal investigator or appropriate designee using the clinician scratch scale (Section 16.5) will be recorded at screening, Day 0 (baseline), Weeks 3, 6, 12, 18, 22, 28, 38, and 48. **For subjects who enter the optional follow-up treatment period the clinician scratch scale will be recorded at Weeks 60, 72, 84, 96, and 100. For subjects with interruptions in LUM001 dosing of ≥7 days, assessments will also**

Section	Description of Change
	be conducted during the DE period at DE -2, DE Day 0, and DE 52. 8.5.3 Clinician Xanthoma Scale A clinician's assessment of xanthomatosis will be made by the principal investigator or appropriate designee using the clinician xanthoma Scale (Section 16.6). This assessment will be completed at Baseline (Day 0) and at Weeks 18, and 48. **For subjects who enter the optional follow-up treatment period the clinician xanthoma scale will be recorded at 60, 72, 84, 96, and 100. For subjects with interruptions in LUM001 dosing of ≥7 days, assessments will also be conducted during the DE period at DE Day 0, and DE 52.** 8.5.4 Pediatric Quality of Life Inventory (PedsQL) The PedsQL™ is a questionnaire that will be administered to subjects and/or caregivers at the Week 0 (baseline), 18, 22, and 48. **For subjects who enter the optional follow-up treatment period, the PedsQL will be administered at Weeks 60, 72, 84, 96, and 100** using the age-appropriate PedsQL module (see Section 16.7). **For subjects with interruptions in LUM001 dosing of ≥7 days, the PedsQL will also be administered at DE Day 0.** The PedsQL is a validated, modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescents (Varni, Seid, & Kurtin, 2001). **In addition to the core generic PedsQL module, the multidimensional fatigue and family impact questionnaire will also be administered at the Week 0 (baseline), 18, 22, and Week 48 using the age-appropriate module (see Section 16.7). Age at baseline will be used as the age for the determination of the appropriate module to be used for the study and this same module will be used for the duration of the study (regardless of subsequent birthdays after the baseline visit).** 8.5.5 Patient Impression of Change The Patient Impression of Change (PIC) is designed to assess the subject's perception of his/her itching after various points of study drug treatment compared to his/her itching prior to the start of treatment with study drug. The PIC will be completed, by subjects who were 9 years of age or older at the Week 18, 22, and 48 visits. **For subjects who enter the optional follow-up treatment period, the PIC will be completed by subjects who were 9 years of age or older at the Week 60, 72, 84, 96, and 100 visits (see Section 16.8).** 8.5.6 Caregiver Impression of Change The Caregiver Impression of Change (CIC) is designed to assess the caregiver's perception of the subject's itch related symptoms and xanthoma severity after various points 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 18, 22, and 48 visits. **For subjects who enter the optional follow-up treatment period the CIC will be completed at Week 84, 96, and 100 visits (see Section 16.9).** 8.5.7 Caregiver Global Therapeutic Benefit The Caregiver Global Therapeutic Benefit (CGTB) questionnaire is designed to assess the caregiver's perception of the treatment benefits on the subject's itching compared to the side effects experienced with study drug. The CGTB will be completed by all caregivers at the Week 18, 22, and 48 visits. **For subjects who enter the optional follow-up treatment period the CGTB will be completed at Week 84, 96, and 100 visits (see Section 16.10).** Section 12.2.5.1: The following additional efficacy evaluations will be assessed: Change from baseline to Weeks 18, 22, 48, **60, 72, 84, 96, and 100** in: o Fasting serum bile acid levels.

Section	Description of Change
	o Liver enzymes (ALT, ALP) and bilirubin (total and direct). o Pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO). o Other biochemical markers of cholestasis [total cholesterol, low-density lipoprotein cholesterol (LDL-C)]. o Bile acid synthesis [serum 7α-hydroxy-4-cholesten-3-one (7αC4)]. Responder analysis at Weeks 18, 48, **60, 72, 84, 96, and 100** in: o Pruritus response rates as measured by ItchRO (Observer ItchRO/patient ItchRO) o Clinician scratch scale Change from baseline for PedsQL at Week 18, 22, 48, **60, 72, 84, 96, and 100** and change from Week 18 to Week 22. o Patient Impression of Change (PIC) at Week 18, 22, 48**, 84, 96, and 100** and change from Week 18 to Week 22. o Caregiver Impression of Change (CIC) at Week 18, 22, 48, **84, 96, and 100** and change from Week 18 to Week 22. o Caregiver Global Therapeutic Benefit (CGTB) assessment at Weeks 18, 22, 48, **84, 96, and 100** and change from Week 18 to Week 22. Evaluations ~~for the durability of the therapeutic effect~~ will be the mean change from Baseline (Day 0) to Week 18, prior to randomization, and the change from Week 18 to Week 48 **and Week 18 to Week 100** in: • Biochemical markers of cholestasis and liver disease [alanine aminotransferase (ALT), alkaline phosphate (ALP), gamma-glutamyltransferase (GGT) and bilirubin (total and direct)]. • Pruritus as measured by the electronic diary ItchRO instruments (ItchRO(Obs), caregiver instrument/ItchRO(Pt) patient instrument). The change from Baseline (Day 0) to Week 48 **and to Week 100** in xanthomas, as measured by clinician xanthoma scale will also be evaluated. **For subjects entering the 52-week optional treatment period with ≥7 days since last dose of LUM001, any of the above evaluations may also occur at clinic visits during the DE period.** Additional exploration of evaluations ~~of durability of therapeutic effect~~ will be specified in the statistical analysis plan.
Dose Escalation Period (Section 5.5.2.1)	~~The anticipated adverse reaction or intolerance is gastrointestinal in nature (e.g., diarrhea, abdominal pain, cramping, etc.). In the absence of intolerance as determined by the physician investigator, escalation to the next dose level for an individual subject will occur following a scheduled phone call or visit (see Schedule of Procedures, Section 16.1).~~ If a subject experiences intolerance due to gastrointestinal symptoms **(eg, diarrhea, abdominal pain, cramping) at any time during the study**, the physician investigator in consultation with the sponsor medical monitor may lower the dose to a previously tolerated dose. In these circumstances an unscheduled visit will occur and the appropriate replacement study medication will be issued to the subject as quickly as possible.
Genetic Testing (Section 8.2) and List of Laboratory Analytes	JAGGED1 **and NOTCH2** mutations can be predictive of ALGS. For ALGS subjects who meet clinical diagnostic criteria for ALGS (see Section 16.3) but do not have documentation of a JAGGED1 **or NOTCH2** mutation, the clinical diagnosis of ALGS may be confirmed by genotyping. Genetic counseling, as appropriate, will be provided to subjects and their legal caregivers. **Subjects for whom prior genotyping was performed may need to have an optional repeat analysis performed if the original information collected at screening was**

<table>
<tr><th>Section</th><th>Description of Change</th></tr>
<tr><td>(Appendix 16.2)</td><td>insufficient for complete documentation of the diagnosis of ALGS including the type of mutation recorded. For those participants for which the type of the mutation cannot be documented, genetic testing may be conducted and the results recorded.</td></tr>
<tr><td>Study Drug Description (Section 9.1)</td><td>Table 1: Composition of LUM001 1.0 mL Oral Solution
<table>
<tr><th>Component</th><th>Quantity per 1.0 mL</th></tr>
<tr><td>LUM001</td><td>0.02 <s>0.05</s> to 20 mg</td></tr>
<tr><td>Propylene Glycol</td><td>250 mg</td></tr>
<tr><td>Sucralose</td><td>7.5 mg</td></tr>
<tr><td>Grape Flavoring Agent</td><td>5 mg</td></tr>
<tr><td>Water</td><td>q.s. to 1.0 mL</td></tr>
</table>
Table 2: Composition of LUM001 0.5 mL Oral Solution
<table>
<tr><th>Component</th><th>Quantity per 0.5 mL</th></tr>
<tr><td>LUM001</td><td>0.02 <s>0.05</s> to 20 mg</td></tr>
<tr><td>Propylene Glycol</td><td>125 mg</td></tr>
<tr><td>Sucralose</td><td>3.75 mg</td></tr>
<tr><td>Grape Flavoring Agent</td><td>2.5 mg</td></tr>
<tr><td>Water</td><td>q.s. to 0.5 mL</td></tr>
</table></td></tr>
<tr><td>Monitoring and Recording Adverse Events (Section 11.3)</td><td>Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. The investigator should always group signs and symptoms into a single term that constitutes a single unifying diagnosis if possible.

11.3.1 Serious Adverse Events

In the interest of subject safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to study drug) should be reported to the sponsor or designee within 24 hours of the study center’s first knowledge of the event. The collection of SAEs will begin after the subject signs the informed consent/assent form and stop at the end of the subject’s follow-up period which is defined as Week 52 for subject who do not roll over into the optional treatment follow-up period, Week <s>52</s> 100 for subjects who do roll over into the optional treatment follow-up period, or 28 days after the last dose of study drug for those subjects that terminate the prior to the Week <s>48</s> 100 visit.

11.3.2 Non-serious Adverse Events

The recording of non-serious AEs will begin after the subject signs the informed consent/assent form and will stop at the end of the subject’s follow-up period, which is defined as Week 52 for subjects who do not roll over into the optional treatment follow-up period, Week 100 for subjects who do roll over into the optional treatment follow-up period, or 30 days after the last dose of study drug for those subjects that terminate prior to the Week 100 visit. The investigator will monitor each subject closely and record all observed or volunteered</td></tr>
</table>

Section	Description of Change
	AEs on the Adverse Event Case Report Form.
Subject Disposition (Section 12.2.4.1)	Subject disposition will be summarized descriptively. The number and percentage of subjects enrolled, completed, and withdrawing, along with reasons for withdrawal, will be tabulated overall, and by study phase and treatment group. For purposes of analysis there will be 3 study phases: Dose escalation/stable dose (Weeks 0-18), Randomized Withdrawal (Weeks 19-22) and Long-Term Exposure (Weeks 23-48 **and 23-100**).
Laboratory Tests (Section 12.2.8.2)	A separate listing will present laboratory values of all subjects who change from normal to abnormal or from abnormal to normal during the course of the study, where normal ranges for this population are outlined in the SAP. Changes within a treatment group for selected safety measures will be assessed at Weeks 3, 6, 12, 18, 22, 28, 38, **48, 60, 72, 84, 96,** and final study evaluation visit using methods to be specified in the SAP prior to unblinding the data.
Schedule of Procedures (Section 16.1)	Added to Screening – Week 22 (footnote): **Optional genotype sample will be performed to provide a full characterization and the associated documentation of the mutation in support of the diagnosis of ALGS.** Schedule of Procedures (cont'd) – Long-term Exposure: Week 23–Week 48: "Study Termination" removed. Schedule of Procedures – Follow-up Treatment Period (FTP) for Those Subjects <7 Days from the Last Dose of LUM001 and Schedule of Procedures – Follow-up Treatment Period for Those Subjects ≥ 7 Days from the Last Dose of LUM001added.
List of Laboratory Analytes (Section 16.2)	NOTCH2 added.
Overall change	Throughout the protocol, reference evaluating durability of effect of LUM001 was removed. Durability of effect may not be assessed in this study, as a treatment effect has not yet been established, and the randomized withdrawal design is not statistically powered.

16.13.4 Protocol Amendment 2 Summary of Changes

Protocol Number: LUM001-304

Protocol Title: LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BL**I**ND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN API**C**AL S**O**DIUM-DEPE**N**DENT B**I**LE A**C**ID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Amendment: **2**

Date: 08 May 2015

The changes below have been made to Protocol Amendment 1.

The following table provides a summary list of changes to Protocol Amendment 2:

Section	Description of Change
Study Synopsis and Section 7	Exclusion criteria added: 18. Subjects weighing over 50 kg at screening.
Study Synopsis	"…26-week open label period…" changed to "…enter a 26-week long-term stable dosing period…"
Study Synopsis, Section 4.5	"equivalent to approximately 30 mg daily dose in a 70 kg adult" changed to "equivalent to approximately 20 mg daily dose in a 50 kg subject"
Study Synopsis; Sections 5.5.2.1, 5.5.2.4, and 8.1.5	Maximum daily dose changed from 30 mg/day to 20 mg/day.
Study Synopsis, Section 8.1.3, Table 6 and Table 7	Time of usage of placebo corrected to the following: "Study drug (or placebo) will be supplied at Weeks 12 and study drug (or placebo) supplied at Week 18." changed to: "Study drug will be supplied at Week 12 and study drug (or placebo) supplied at Week 18."
Study Synopsis and Sections 6.2, 12.2.2, and 12.2.5.1	Responder definition corrected from Week 18 to Week 12: …serum bile acid levels from baseline to Week 12 … serum bile acids ≥50% at the Week 12 measurement
Study Synopsis; Section 8.1.3; Section 16.1: Schedule of Procedures – Screening – Week 22, Footnote d; Section 16.1: Schedule of Procedures – Long-Term Exposure: Week 23 – Week 48 / Study Termination, Footnote c	"2 to 4 hours post-dosing" changed to "approximately 4 hours post-dosing"
Study Synopsis, Section 12.2.3	Language added to address the randomization and statistical management of data generated from siblings

Section	Description of Change
	enrolled in the study: **Siblings** The enrollment of siblings is allowed. During the placebo-controlled, randomized drug withdrawal period, siblings will be assigned in a blinded manner to the same treatment arm. The data from all enrolled participants (including siblings) will be used for the safety analysis. For the efficacy analysis, data from only one of the siblings will be used. The choice of which subject's data to use in the efficacy analysis will be done in a random fashion before the LUM001-304 study is unblinded. Details of the analysis methods will be outlined in the SAP.
Section 5.5.3, Section 8.1.8	Language added to describe a planned extension study: Subjects who complete the study may be eligible for participation in an extension study of LUM001.
Section 6.2	Language added to address the randomization of siblings enrolled in the study: During the placebo-controlled, randomized drug withdrawal period, siblings will be assigned in a blinded manner to the same treatment arm.
Section 6.4, Section 12.2.4.1	Randomized withdrawal period corrected from "Weeks 18-22" to "Weeks 19-22"
Section 8.5.4	"Age at screening…" changed to "Age at baseline…" "…birthdays after the screening visit" changed to "…birthdays after the baseline visit"
Section 10.1	"…at least 8 weeks" changed to"…at least 12 months"
Sections 10.5.2.4, Section 16.2	"tocopherol [(α)], total lipids" changed to "tocopherol [α]" Total lipids removed from 16.2 table.
Section 16.1, Schedule of Procedures – Long-Term Exposure: Week 25 – Week 48 / Study Termination	Header changed to: … Long-Term Exposure: Week 23 – Week 48
Section 16.1, Schedule of Procedures – Long-Term Exposure: Week 23 – Week 48 / Study Termination	Study days corrected to: 161, 168, 175, 182, 189, 196, 231, 266, 301

16.13.5 Protocol Amendment 1 Summary of Changes

Protocol Number: LUM001-304

Protocol Title: LONG-TERM, OPEN-LABEL STUDY WITH A DOUBLE-BL**I**ND, PLACEBO-CONTROLLED, RANDOMIZED DRUG WITHDRAWAL PERIOD OF LUM001, AN API**C**AL S**O**DIUM-DEPE**N**DENT B**I**LE A**C**ID TRANSPORTER INHIBITOR (ASBTi), IN PATIENTS WITH ALAGILLE SYNDROME

Amendment: **1**

Date: 06 Mar 2015

The changes below were made to the original protocol.

The following table provides a summary list of changes that were included in Protocol Amendment 1:

Section	Description of Change
Exclusion Criteria (Section 1, Synopsis and Section 7, Subject Eligibility)	Additional exclusion criteria were added: • History or presence of gallstones or kidney stones. • Known hypersensitivity to LUM001 or any of its components.