

Protocol Title:

A Multicenter, 24-Month, Randomized, Open-Label, Active Control, Parallel Arm, Phase 2 Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal Children with Idiopathic Growth Hormone Deficiency (GHD)

NCT #: 04614337

Date: 28 April 2022

1.0 TITLE PAGE

CLINICAL STUDY PROTOCOL

OraGrowth²¹⁰

TRIAL

STUDY NUMBER:	LUM-201-01
PROTOCOL TITLE:	A Multicenter, 24-Month, Randomized, Open-Label, Active Control, Parallel Arm, Phase 2 Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal Children with Idiopathic Growth Hormone Deficiency (GHD)
NCT NUMBER	04614337
EUDRACT NUMBER	2020-000874-92
SPONSOR:	Lumos Pharma, Inc. 4200 Marathon Blvd. Suite 200 Austin, Texas 78756 Telephone: [REDACTED]
SPONSOR CONTACT:	Name: [REDACTED] Title: Senior Director Clinical Operations
MEDICAL MONITOR:	Name: [REDACTED] Medical Monitor WuXi Clinical Development, Inc. Telephone: [REDACTED] [REDACTED] Medical Monitor & Chief Medical Officer Lumos Pharma, Inc. Telephone: [REDACTED]
PROTOCOL VERSION:	7.0
DATE:	28 April 2022

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Multicenter, 24-Month, Randomized, Open-Label, Active Control, Parallel Arm, Phase 2 Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal Children with Idiopathic Growth Hormone Deficiency (GHD)

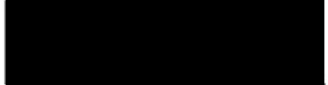
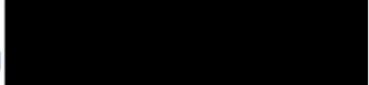
Protocol Version: 7.0

Protocol Date: 28 April 2022

This study protocol was subject to critical review and has been approved by the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and principles of Good Clinical Practice (GCP) as described in the International Council for Harmonisation (ICH) guideline E6, in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312, and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Signature	Date
 Lumos Pharma, Inc.	<p>DocuSigned by:</p>  <p>Signing Reason: I approve this document Signing Time: 4/28/2022 14:24 CDT 77A652CA01374FDB9BDDE1C3DE79E760</p>	4/28/2022 14:24 CDT
 Operations Lumos Pharma, Inc.	<p>DocuSigned by:</p>  <p>Signing Reason: I approve this document Signing Time: 4/28/2022 14:35 CDT BE8ABC851AB94973A8E183A39D31AF7C</p>	4/28/2022 14:35 CDT

INVESTIGATOR'S AGREEMENT

**A Multicenter, 24-Month, Randomized, Open-Label, Active Control,
Parallel Arm, Phase 2 Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal
Children with Idiopathic Growth Hormone
Deficiency (GHD)**

**Protocol Version: 7.0
Protocol Date: 28 April 2022**

The information contained in this protocol and all other information relevant to this study are the confidential and proprietary information of Lumos Pharma, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Lumos Pharma, Inc.

I have read the protocol for Study LUM-201-01, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, as well as access to all information provided by Lumos Pharma, Inc. I will discuss the material with them to ensure that they are fully informed about the study.

Printed Name of Investigator

Signature of Investigator

Date

2.0 SYNOPSIS

Name of Sponsor/Company: Lumos Pharma, Inc.	
Name of Investigational Product: LUM-201	
Name of Active Ingredient: Ibutamoren mesylate	
Title of Study: A Multicenter, 24-Month, Randomized, Open-Label, Active Control, Parallel Arm, Phase 2 Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal Children with Idiopathic Growth Hormone Deficiency (GHD)	
Study Centers and Principal Investigators: Multicenter study, with approximately 50 sites planned in the United States (US), Australia, Israel, New Zealand, Poland, Russia, and Ukraine	
1. Study Period (Years): Date first subject enrolled: December 2020 Estimated date last subject completed: April 2025	Phase of development: 2
Objectives: Primary Objective <ul style="list-style-type: none"> Preliminary clinical validation of predictive enrichment marker (PEM) strategy intended to select subjects likely to respond to therapy with LUM-201 based upon the percentage of subjects defined as PEM test positive (GH $\geq$ 5 ng/mL within 60 minutes of a single dose of LUM-201 and baseline insulin-like growth factor 1 [IGF-1] $>$ 30 ng/mL [$>$ 3.92 nmol/L]) who have a positive growth response defined as $\geq$ 6.85 cm/yr annualized height velocity (AHV) from Baseline (Day 1 visit) to Month 6 visit. Primary Clinical Objective <ul style="list-style-type: none"> To select a pediatric dose of LUM-201 for use in future studies including Phase 3 trial(s) based on comparison of 6-month AHVs achieved by daily recombinant human growth hormone (rhGH) and the dose levels of LUM-201 treatment in subjects with pediatric growth hormone deficiency (PGHD) selected by predictive enrichment markers (PEMs) Key Secondary Objective <ul style="list-style-type: none"> To assess the reproducibility of the PEM positive classification of subjects Other Secondary Objectives <ul style="list-style-type: none"> To assess additional clinical parameters of efficacy including: <ul style="list-style-type: none"> Change in height standard deviation score (HT-SDS) Change in height velocity standard deviation score (HV-SDS) Change in weight and weight SDS Change in body mass index (BMI) and BMI SDS Change in predicted adult height Change in Bone Age (BA) compared to Chronological Age (CA) (eg, BA/CA) ratio To assess the safety and tolerability of oral LUM-201 To further explore pharmacokinetics (PK) of LUM-201 based upon plasma LUM-201 concentrations To determine short- and long-term pharmacodynamic (PD) (GH, IGF-1, IGFBP-3) responses to daily LUM-201 	

- To characterize variance in AHVs of subjects treated with rhGH and LUM-201 to enable sample size estimates for future trials

Study Design and Methodology:

Study Design

This is a multicenter, up to 24 months, randomized, open-label, active control, parallel arm, Phase 2 study in naïve-to-treatment prepubertal children with idiopathic GHD.

Screening Portion of Study

Subjects must have an established diagnosis of idiopathic PGHD to be eligible. Additionally, subjects must be prepubertal and naïve-to-treatment for PGHD. The diagnostic evaluation must include two standard of care GH stimulation tests, or a combined clonidine/arginine stimulation test. One glucagon stimulation test with simultaneous assessment of adrenocortical function is preferred, while insulin, arginine, clonidine, levodopa (L-DOPA), exercise, and overnight sampling tests are also acceptable as the other GH stimulation test, provided the testing was completed within 12 months prior to enrollment in the Screening portion of the protocol. Investigator review of additional entry criteria will be performed during the Screening period for determination of eligibility. Consistent with the diagnosis of PGHD, subjects should have a height SDS < -2.0 or a HT-SDS ≥ 2 SD below MPH HT-SDS. If the other data (slow HV, low IGF-1, peak GH < 10 , and 6-month BA delay) are all consistent with idiopathic GHD, the subject may be enrolled with a height SDS > -2.0 after consultation with the MMs. In either case, baseline AHV must be ≤ 5.5 cm/year.

Approximately 140 subjects will be enrolled to the Screening portion of the protocol. The Screening portion will include performance of a baseline PEM test. The PEM test criteria are IGF-1 concentration > 30 ng/mL (> 3.92 nmol/L) and the peak serum GH concentration of ≥ 5 ng/mL observed during the 60-minute period following the single oral administration of LUM-201 (0.8 mg/kg). Subjects who meet all Inclusion Criteria and both PEM criteria will be declared “PEM positive” and be eligible for the Treatment portion of the study. Subjects who fail to meet one or both of these criteria will be classified as “PEM negative” and be ineligible for the Treatment portion.

Treatment Portion of Study

Following completion of the Screening portion of the protocol, subjects successfully screened will be entered into the Treatment portion of the protocol. A total of 80 subjects (20 per group) will be randomized into the Treatment portion of the protocol 1:1:1:1 to receive one of three LUM-201 daily dosing administrations (0.8 mg/kg/day, 1.6 mg/kg/day, 3.2 mg/kg/day) or daily rhGH (34 μ g/kg/day). The randomization to the treatment arms will be stratified by age (< 7.5 yrs, ≥ 7.5 yrs) and Baseline height standard deviation score (HT-SDS, < -2.5 , ≥ -2.5).

Eligible subjects will return for follow-up clinic visits at the Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit, and, if on LUM-201 treatment and meeting the minimum AHV growth criterion, Month 15 visit, Month 18 visit, Month 21 visit, and Month 24 visit. Subjects who are randomized to the rhGH treatment will have the opportunity to transition to another longer-term study, after the Month 12 visit, where they will receive treatment with LUM-201.

The interval history of subjects not completing the study will be collected by telephone 30 days after their final visit. Reasons for early study discontinuation will be recorded.

Study Procedures – Screening Period

The Screening period will commence after written informed consent and, where applicable, assent to participate in this study has been provided. The Screening visit will be conducted in the morning after an overnight fast (after 10 p.m.) to allow for standardized conditions for laboratory tests and the PEM samples. The PEM test consists of baseline IGF-1 concentrations and the serum GH response at pre-dose (time 0), 30 and 60 minutes after a single oral 0.8 mg/kg dose of LUM-201. At the Screening visit a complete history and physical including height (in triplicate by stadiometer), arm span (in duplicate), body weight and vital signs will be recorded. Procedures performed at this Screening visit include IGF-1, safety labs, the LUM-201 test, and standard X-rays for BA determination. A BA taken during the prior 9 months can be used to assess eligibility with the BA corrected by one month for each month from the date of the previous BA screen. Eligibility will be based on the central BA from Intrinsic. Medical and medication histories will be taken at the Screening visit. Baseline electrocardiograms (ECGs) for all subjects will be performed in triplicate at the Screening visit prior to and one hour after LUM-201 (PEM stimulation test) administration.

All eligibility and screening data will be reviewed by the PI and MM(s) before the subject is confirmed eligible for the Treatment Period. Only subjects with positive Screening visit PEM testing will return for Day 1 visit.

Study Procedures – Treatment Period

Subjects will be randomized into one of four stratified treatment arms. A central randomization service will be used, and the Investigator will be notified of treatment assignment by email. Subjects will return on Day 1 visit to have a second PEM test and commence the treatment period study procedures. LUM-201 subjects will start their randomized LUM-201 dose the day following Day 1 visit.

Height (in triplicate by stadiometer), body weight and vital signs will be recorded on Day 1 visit, and at the Months 1, 3, 6, 9, 12, 15, 18, 21, and 24 visits. Laboratory samples for safety, PK for LUM-201 and PD (GH and/or IGF-1 and IGFBP-3) data will be collected at Treatment period visits, as indicated in the Schedule of Assessments (Table 1). In the case of adverse safety or laboratory events, the Principal Investigator (PI) or Medical Monitor (MM) may request additional testing. A second PEM test will be performed on Day 1. Standard X-rays for BA determination will be performed at Month 6 visit and Month 18 visit. Interval histories, adverse events (AEs), and concomitant medications will be collected at all Treatment period visits. Triplicate ECGs will be performed on all subjects at the Day 1 visit, prior to PEM test dose administration and 1 hour $\pm$ 10 minutes after the PEM test dose administration. LUM-201 subjects will have triplicate ECGs performed prior to and one hour after study drug administration at Month 3 visit, Month 6 visit and Month 12 visit. Single ECGs recording will be performed for subjects on the LUM-201 arms at Month 18 and Month 24 visits. Subjects randomized to rhGH will have triplicate ECGs performed prior to laboratory draws at Day 1 visit, Month 3 visit, Month 6 visit, and Month 12 visit. Bone ages and ECGs will be interpreted by a central reader. The heights of parents will be measured by stadiometer at one visit during the study, if possible, or otherwise by self-report.

The schedule of assessments is provided in Table 1.

Safety Surveillance

Appropriate surveillance, monitoring, and intervention will be performed to ensure subject safety, as necessary. Ongoing safety review of AEs and Serious Adverse Events (SAEs) will be performed by the PI and MM. All AEs assessed by the Investigator as severe in intensity and possibly related to study drug will be discussed with the Sponsor and the Investigator and may result in the subject discontinuing study drug. Additionally, a Data Safety Monitoring Board (DSMB), consisting of specialists in pediatric endocrinology, will review the study at periodic intervals, as specified in the DSMB Charter.

Inclusion Criteria

The subject must meet the inclusion criteria listed below to be eligible for participation in the study.

1. Have an established diagnosis of idiopathic PGHD made prior to screening for entry into this study. This diagnosis is to be made in standard of care fashion incorporating biochemical, radiographic and auxological data. Specific inclusion criteria listed in this section for inclusion into this study protocol which are also used to diagnose PGHD in general are not intended to replace, supplant, or be an all-

- inclusive substitute for a standard of care diagnosis. Eligible subjects must be naïve-to-treatment and be prepubertal.
2. The diagnostic workup must include a maximal GH response < 10 ng/mL from two prior GH stimulation tests within the past 12 months (eligible tests include: glucagon, insulin, arginine, clonidine, and L-DOPA, exercise, and overnight sampling), or a single combined GH stimulation test using clonidine and arginine.
 3. At the Screening visit or in the prior 12 months have a morning or random cortisol ≥ 7 μ g/dL (193 nmol/L). Subjects with morning or random cortisol response < 7 μ g/dL require a stimulated cortisol test (ACTH, insulin, glucagon) to be eligible for the study. Stimulated cortisol response should be ≥ 14 μ g/dL (386 nmol/L).
 4. Be willing to provide written informed consent (and assent where applicable) to participate in this trial.
 5. At the Screening visit, be age ≥ 3.0 years and age ≤ 11.0 years for girls and ≤ 12.0 years for boys.
 6. Have HT-SDS ≤ -2.0 or a HT-SDS ≥ 2 SD below MPH HT-SDS. If the other data (slow HV, low IGF-1, peak GH < 10 , and 6-month BA delay) are all consistent with idiopathic GHD, the subject may be enrolled with a height SDS > -2.0 after consultation with the MMs. The use of National Growth Charts to compute HT-SDS is permitted for ex-US sites.
 7. Have a baseline height velocity ≤ 5.5 cm/year based on at least 6-months of growth.
 8. Have a BA examination at Screening or within the 9 months prior to Screening that is delayed by ≥ 6 months with respect to chronological age. BA should be based on the apparent BA of the proximal and distal phalanges, as opposed to the metacarpals, carpals and distal forearm. A central BA reader will make the final determination on BA eligibility.
 9. Have prepubertal status as evidenced by Tanner Stage I breast development in girls and testicular volume < 4.0 mL in boys.
 10. Have an arm span to height ratio $> 96.5\%$.
 11. In girls, have genetic testing results to rule out Turner syndrome. If SHOX genetic testing results are available, they need to be negative.
 12. Have normal thyroid function. Subjects diagnosed with hypothyroidism must have documented successful treatment for at least 30 days prior to Day 1.
 13. Baseline IGF-1 concentration > 30 ng/mL (> 3.92 nmol/L) and a peak GH response of ≥ 5 ng/mL from the Screening LUM-201 stimulation PEM test.
 14. Subjects who are sexually active must use an acceptable form of contraception.

Exclusion Criteria

Potential study subjects meeting any of the exclusion criteria listed below will not be eligible for participation in the study.

1. Any medical or genetic condition which, in the opinion of the Investigator or MM, can be an independent cause of short stature and/or limit the response to exogenous growth factor treatment. (Examples: diabetes, idiopathic short stature (ISS), SHOX-deficiency, any chondrodysplasia, constitutional growth delay, SGA, other named syndromes).
2. A medical or genetic condition that, in the opinion of the Investigator and/or MM, adds unwarranted risk to use of LUM-201 or rhGH.
3. Use of any medication that, in the opinion of the Investigator and/or MM, can independently cause short stature or limit the response to exogenous growth factors (Example: glucocorticoids).
4. The presence of any circumstance likely to prevent successful completion of this trial.
5. Evidence or history of an intracranial mass (e.g., pituitary tumor, craniopharyngioma).
6. Prior treatment with growth factors including, but not limited to, GH, IGF-1, and GH secretagogues. (These may be used for limited times as a diagnostic test).
7. Suspicion of absent pituitary function as evidenced by a maximal stimulated GH ≤ 3 ng/mL on two prior standard of care GH stimulation tests, or pituitary deficiencies beyond GH and thyroid function, or a diagnosis of organic PGHD. Note: if a maximal stimulated GH response is > 3 ng/mL on one of the prior standard of care GH stimulation tests, subject is potentially eligible for participation in the study.

8. Malnutrition as evidenced by medical history or a BMI < 5th percentile.
9. BMI > 95th percentile.
10. Gestational age-adjusted birth weight < 3rd percentile (small for gestational age).
11. Participation in any therapeutic trial of investigational drug(s) within the prior 6 months.
12. Known or suspected allergy to LUM-201, rhGH or one of their excipients.
13. Unwilling to accept randomization assignment.
14. Treatment with medications known to be moderate or strong inhibitors or strong inducers of CYP3A/4.
15. Treatment with medications known to be predominantly metabolized (< 5% contribution by other isoforms) by either CYP3A/4, CYP2C8, CYP2C9 or CYP2C19.
16. Treatment with medications known to act as strong inhibitors of P-glycoprotein (P-gp) or potent substrates of P-gp or Multidrug and toxin extrusion protein 1 (MATE1).
17. History of spinal, cranial, or total body irradiation.
18. Recent commencement (within three months of the Screening visit) of non-stimulant therapy to treat attention deficit hyperactivity disorder (ADHD). MM should be contacted prior to screening of any potential subjects diagnosed with ADHD.

Number of Subjects (Planned): Approximately 140 subjects will be enrolled in the Screening portion which should be adequate to fill the Treatment portion of study, randomizing 20 subjects to each of the three LUM-201 treatment arms and 20 to the daily rhGH treatment arm (total of 80 randomized subjects).

Investigational Product, Dosage and Mode of Administration:

All subjects will receive a single 0.8 mg/kg dose of LUM-201 to conduct the PEM tests at the Screening visit and Day 1 visit. Subjects randomized to LUM-201 will receive oral LUM-201 at doses of approximately 0.8 mg/kg/day, 1.6 mg/kg/day or 3.2 mg/kg/day. Subjects will take one dose of LUM-201 every morning without regard to meals for up to 24 months, except on the mornings of their clinic visits. At all study visits, the LUM-201 dose will be administered in clinic.

Duration of Treatment:

The total duration of treatment for each randomized subject is up to 24 months.

The on-study time for each subject randomized to LUM-201 treatment will be up to approximately 27 months, including Screening (up to 56 days) and treatment with LUM-201 (up to 24 months) and follow up (30 days).

The on-study time for each subject randomized to rhGH treatment will be approximately 15 months, including Screening (up to 56 days) and treatment with rhGH (12 months), and follow up (30 days).

End of study is defined as the last study visit for the last subject enrolled in the trial.

Reference Therapy, Dosage and Mode of Administration:

After the Day 1 visit, subjects randomized to rhGH will receive a daily evening dose of rhGH (Norditropin®) 34 µg/kg administered by subcutaneous (SC) injection for 12 months. Subjects will be administered rhGH by the parent or caregiver under supervision of the study staff at clinic visit or at home (which may include self-injection in some older subjects), as described in the prescribing information.

Criteria for Evaluation:

Clinical Outcome Measurements:

- Height collected in triplicate at all clinic visits
- Weight collected at all clinic visits
- Bone Age collected at baseline, Month 6 and at Month 18 visits

PK and/or PD:

- Plasma LUM-201 concentrations (in LUM-201-treated subjects)
- Serum GH (LUM-201 subjects only), IGF-1, IGF-1 SDS and IGFBP-3

Safety:

Safety assessments will include collection of AEs and SAEs, routine laboratory tests (hematology, chemistry panel including liver enzymes, and urinalysis), hemoglobin A1c (HbA1c), serum glucose, free thyroxine (T4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), lipids, physical examinations, interval history, vital signs, and ECGs.

Statistical Methods:

Statistical Hypotheses

The primary endpoint of the study is confirmation of the ability for the PEM test to select for LUM-201 treatment response. Treatment response to determine the primary endpoint will be based upon 6-month annualized AHVs from the combined cohort of all subjects treated with LUM-201. It is assumed that the PEM test will improve the response rate to approximately 70%, against a null hypothesis of 50%. Positive response is defined as annualized height velocity ≥ 6.85 cm per year. This sample size will provide $> 85\%$ power for a one-sided test of this hypothesis with alpha of 0.025.

Key secondary endpoint of the study includes assessment of reproducibility of the PEM positive classification of subjects who are undergoing the PEM tests (LUM-201 stimulation test and baseline IGF-1) at Screening visit and Day 1 visit.

Clinical Efficacy Analyses

The primary clinical objective is to select a pediatric dose of LUM-201 for use in future studies including a potential phase 3 trial based upon comparison of 6-month AHV achieved by daily rhGH and the dose levels of daily LUM-201 treatment in subjects with PGHD selected by PEMs. The AHV will be presented for the combined cohort of 60 subjects to determine the proportion of responders. To support the dose finding objective of the study, each treatment group will also have the AHV presented using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), and the optimal dose will be the dose that is associated with the highest AHV that shows acceptable safety and tolerability.

The relationship of AHV and Baseline (Screening visit and/or Day 1 visit, depending on the variable) characteristics will be explored by analysis of covariance (ANCOVA) model with terms for treatment group, subject age, gender, HT-SDS, IGF-1 SDS, peak GH to stimulation test and PEM LUM-201 test results. Additional exploratory analyses may be described in the statistical analysis plan (SAP).

PEM Reproducibility Analyses

Subjects with a positive PEM test at screening will have a second PEM test performed on Day 1 to permit analysis of reproducibility of a positive PEM test. With a sample size of 80 randomized subjects the goal will be to show that the lower boundary of the 95th confidence interval for positive agreement rate is ≥ 0.8 . (Positive agreement rate = number of positive agreements/number of subjects with two tests).

Interim Analyses

An interim analysis of all available data will be conducted after 40 subjects have completed the Month 6 visit. The purpose of this interim analysis is to evaluate the safety and 6-month AHV as well as continued growth response in the 6 to 12-month period.

A primary analysis of all available data will be conducted after 80 subjects have completed the Month 6 visit. The purpose of this analysis is to evaluate the safety and continued growth response in the baseline to 6-month period.

Safety Analyses

AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables of treatment-emergent AEs (TEAEs) will be provided. Laboratory, vital sign, and ECG parameters will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation, also including the change from Baseline. Shift tables for laboratory parameters will be produced showing the frequency of shifts from Baseline to the worst -on study value in and out of the normal range.

Table 1 Schedule of Assessments

Visit	Screening	Day 1	Month 1	Month 2 (remote)	Month 3	Month 4 (remote)	Month 5 (remote)	Month 6	Month 9	Month 12 ^a	Month 15 ^b	Month 18 ^b	Month 21 ^b	Month 24 ^b	Follow-up Remote Contact
Informed consent/assent	X														
Inclusion/exclusion criteria review	X														
Medical history ^c	X														
Physical examination ^d	X	X	X		X			X	X	X	X	X	X	X	
Interval history ^e		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
Prior medications	X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs and weight ^f	X	X	X		X			X	X	X	X	X	X	X	
Stadiometer height ^g	X	X	X		X			X	X	X	X	X	X	X	
Arm span	X														
Fundoscopy	X														
GH Stimulation Test Confirmation ^h	X														
Confirmation of normal adrenal function	X														
Bone Age ⁱ	X							X				X			
ECG ^j	X	X			X			X		X		X		X	
Laboratory assessments															
Hematology, CBC	X	X	X		X			X		X		X		X	
Serum chemistry panel	X	X	X		X			X		X		X		X	
HbA1c	X				X			X		X		X		X	
Fasting serum glucose, insulin concentrations ^k	X				X			X		X					

Visit	Screening	Day 1	Month 1	Month 2 (remote)	Month 3	Month 4 (remote)	Month 5 (remote)	Month 6	Month 9	Month 12 ^a	Month 15 ^b	Month 18 ^b	Month 21 ^b	Month 24 ^b	Follow-up Remote Contact
Fasting cortisol	X							X							
Thyroid panel (TSH, Free T ₄ , T ₃)	X		X					X		X		X		X	
Lipids ^l	X							X		X		X		X	
Urinalysis	X	X	X		X			X		X					
PK: Plasma LUM-201 (LUM-201 subjects only, except at screening) ^m	X		X		X			X		X					
PD: GH (LUM-201 subjects only) ⁿ								X		X					
PD: IGF-1 (all subjects)	X	X	X		X			X	X	X	X	X	X	X	
IGFBP-3 (all subjects) ^o		X	X		X			X	X	X	X	X	X	X	
PEM test ^p	X	X													
Karyotype test ^q	X														
Randomization confirmation		X													
Study drug accountability			X		X			X	X	X	X	X	X	X	
Study drug dispensed		X	X		X			X	X	X	X	X	X		
Commence daily treatment with LUM-201 or rhGH ^r		X													
Weight-based dose adjustment ^s			X		X			X	X	X	X	X	X		X

Abbreviations: CBC = complete blood count; ECG = electrocardiogram; ET = early termination; GH = growth hormone; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth binding protein 3; LDL = low density lipoprotein; MRI = magnetic resonance imaging; PD = pharmacodynamic; PEM = Predictive Enrichment Marker; PK = pharmacokinetic; rhGH = recombinant human growth hormone; SC = subcutaneous; T3 = triiodothyronine; T4 = free thyroxine; TSH = thyroid stimulating hormone

- Subjects on the rhGH arm will end treatment in the LUM-201-01 protocol after the completion of the Month 12 visit.
- For LUM-201 subjects only who achieve a 12-month AHV of ≥ 6.7 cm/year may proceed into the 2nd year of the study. Subjects who achieve a 12-month AHV of < 6.7 cm/year will be withdrawn from the trial and may be switched to SOC at the discretion of their physician.
- Medical history to include, when available: prior height assessment(s), which ideally will consist of two height measurements at least 6 months apart as documented in the medical records, either obtained by a specialist or the referring physician (e.g., pediatrician, family doctor), parental heights (by stadiometer or by report at any visit), age of maternal menarche, heights and ages of full siblings. Medical history also to include prior genetic testing and a copy of prior cranial MRI study report, where applicable.
- Complete physical examination to include Tanner staging at Screening visit. Physical examination focused on changes from prior visit is acceptable for all other clinic visits. Tanner staging should be included in Month 6 visit and Month 12 visit examinations. In addition, for subjects continuing study participation after Month 12, Tanner staging

- should be done at Month 18 visit and Month 24 visit. Fundoscopy is required at the Screening visit and for subjects reporting headache or visual changes at a subsequent visit if there is a suspicion of increased intracranial pressure. Injection sites to be inspected for rhGH subjects.
- e. Interval history includes evaluation of general health status since the last visit and query for headache, visual disturbance, joint pain, scoliosis, and change in eating behavior. If present, these events should be recorded.
- f. Vital signs include temperature, respiratory rate, pulse rate, and blood pressure. Body weight, in kg, taken in light clothing without shoes or socks.
- g. Standing height, without shoes or socks, in triplicate, by calibrated stadiometer. Height value replicates should be ≤ 0.2 cm. At Screening visit arm span with arms parallel to the floor (in duplicate, value replicates should be ≤ 0.2 cm) should be measured and recorded.
- h. Screened subjects shall have had two standard GH stimulation tests within 12 months of Screening visit, or a single combined test using clonidine and arginine Ref added). Those historical results will be used for eligibility. The acceptable standard GH stimulation tests are glucagon, insulin, arginine, clonidine, L-DOPA, exercise, and overnight sampling tests.
- i. Digitized radiograph of left hand and wrist to be interpreted by a central reader. Bone age (BA) using Greulich-Pyle atlas to be used to satisfy inclusion criteria, based on the BA of the proximal and distal phalanges, recognizing that in normal children the BA of the metacarpals, carpal and distal forearm may be delayed vs the BA of the phalanges. A BA result within 9 months of the Screening visit may be used to satisfy eligibility. In these cases, the BA/chronological age (CA) will be compared to the BA/CA at the 6-month study Visit. One month will be added to the BA result for every month elapsed between the BA date and Screening visit date.
- j. Triplicate ECGs will be performed for all subjects at Screening visit, Day 1 visit, Month 3 visit, Month 6 visit, and Month 12 visits. Single ECG recording will be performed for subjects on the LUM-201 arms at Month 18 visit and Month 24 visit. ECGs will be interpreted by a central reader using age-related normative data.
- k. Fasting glucose and insulin may be repeated if indicated by a suspicion of evolving glucose intolerance.
- l. Fasting LDL, HDL, total cholesterol, and triglycerides for the first 12 months. Non-fasted in the second 12 months (Months 13-24).
- m. PK plasma LUM-201 samples will be obtained for all subjects at Screening visit and for subjects randomized to LUM-201 at other in-clinic treatment period visits as indicated below:
- Screening visit: 30 and 60 minutes post-dose
 - Month 1 visit: single sample 30 minutes post-dose
 - Month 3 visit and Month 12 visit: only a pre-dose (trough) collection
 - Month 6 visit: pre-dose and at 30 and 60 minutes post-dose collection
 - ± 10 minute window is allowed for all post-dose PK sample collections
- n. Serum GH samples will be collected at Month 6 visit and Month 12 visit pre-dose and 30 and 60 minutes post-dose for subjects randomized to LUM-201. ± 10 -minute window is allowed for post-dose PD sample collections.
- o. Serum IGF-1 and IGFBP-3 samples will be collected pre-dose at Day 1 visit, Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit, Month 15 visit, Month 18 visit, Month 21 visit, and Month 24 visit.
- p. The PEM test will be done at the Screening visit and Day 1 visit in the fasting state. All subjects will receive a dose of LUM-201 0.8 mg/kg at time 0. Blood samples for IGF-1 and GH will be drawn pre-dose. LUM-201 (PK) and GH (PD) samples will be drawn at 30 and 60 minutes post LUM-201 dose at Screening visit. At Day 1 visit blood samples for IGF-1 and GH will be drawn pre-dose. GH (PD) samples will be drawn at 30 and 60 minutes post LUM-201 dose. Symptoms occurring during the test will be reported as Adverse Events.
- q. Karyotype for female subjects may be obtained at screening if not already available.
- r. LUM-201 doses will be assigned by the central randomization service. LUM-201 subjects will start their randomized LUM-201 dose the day following Day 1 visit. The dose of daily rhGH will be 34 μ g/kg/day SC.
- s. Study drug dispensed as needed. Dose adjustment is based on subject's weight.

SUMMARY OF CHANGES

Amendment Rationale

The primary purpose of this amendment is to: clarify the study population as having idiopathic PGHD, to specify the primary clinical endpoint is AHV, and extend the treatment portion of the study to 24 total months.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough for deletions and underlines for insertions. Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment. Changes affecting the meaning of the content of the protocol are summarized in the table below; “Section (Page[s]) Affected” refers to the location in Protocol 201-01 Version 7.0 with tracked changes. Where helpful, “Summary” includes the tracked changes updates to text, or a description of the changes.

Section (Page[s]) Affected	Change	Summary
1.0 Title Page (1 – 4)	Revision of study length and clarification of study population (idiopathic). These revisions are reflected throughout the protocol.	A Multicenter, 12 <u>24</u> -Month, Randomized, Open-Label, Active Control, Parallel Arm, Phase 2 Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal Children with Idiopathic Growth Hormone Deficiency (GHD)
2.0 Synopsis (5 – 15)	Revision of objective classification and Study Design and Methodology. These revisions are reflected throughout the protocol.	Revision to all sections within the synopsis detailing: <ul style="list-style-type: none">- Addition of Primary Clinical Objective and revision of Key Secondary Objective- Modified Study Design and Methodology; changes reflected herein and throughout the protocol as appropriate, including but not limited to:<ul style="list-style-type: none">o Procedures for assessing agreed upon AHV in subjectso Revisions throughout to align with updated eligibility criteriao Modified schedule of assessments to include revised and additional study visits, and procedures to occur therein
4.0 Introduction and Background (28-30)		<ul style="list-style-type: none">- Additional disease background information and justification for treatment population.- Inclusion of recently approved SOC treatment options.

Section (Page[s]) Affected	Change	Summary
5.0 Study Objectives (31)	Revision of Primary Clinical and Key Secondary objectives	Categorical revision of the Secondary Objectives to Primary Clinical and Key Secondary Objectives
6.0 Investigational Plan (32 – 39)	Revision of Schema of Study Design (Figure 1)	
	Expanded upon Rationale for Study	The following text was added: As shown in Table 3, where an analysis was performed assessing the subjects with PEM-positive idiopathic PGHD, the dose-dependent increase in HV in response to treatment with LUM-201 was enhanced, and the HV response to the 0.8 mg/kg/day dose was not significantly lower than the response to rhGH at 42 µg/kg/day over 6 months.
7.0 Selection and Withdrawal of Subjects (39 – 43)	Addition of contraception language and	Addition of contraception requirement text: - Subjects who are sexually active must use an acceptable form of contraception. Revision of inclusion and exclusion language, as first described in the Synopsis.
9.0 Study Treatments (44-47)	Revision to treatment adherence	The following text was revised: - A subject who misses more than 20% of the intended doses over any 30-day interval, or more than 10 20% of the intended doses over the entire Treatment period without good reason such as meeting a stopping rule or the treatment of an intercurrent illness will be considered non-compliant.
11.0 Study Assessments and Procedures (47 – 62)	Revision and addition of study procedures to align with revised Schedule of Assessments	Applicable revisions are described in the Schedule of Assessments and reflected in detail in this section.
13.0 Statistics (66-73)	Revision of text to align with Synopsis.	Addition of text to align with the revised Synopsis, specifically in relation to the revised endpoints. Change of growth chart reference: CDC to WHO
	Clarification of data analysis plan for treatment beyond 12 months	The following clarifying text was added: - For the summary and analysis of data after 12 months, subjects who do not continue beyond month 12 will simply be excluded, and not be considered missing. Data collected from subjects who are treated after month 12 will then be carried forward if there are missing visits from month 12 to 24.

Section (Page[s]) Affected	Change	Summary
	Addition of protocol adherence text to align with Section 9.0	Text was revised to reflect the treatment adherence for the 6 and 12 month Per Protocol Population in Section 9.0. In addition, the following text was added: - The 24 month Per Protocol Population includes all randomized subjects who complete Month 24 and have not missed more than 20% of scheduled doses over the 24-month Treatment portion and who do not have any significant protocol deviations. The Per Protocol Population will be used for the primary evaluation of treatment response.
19.4 Appendix 1: Birth weights (grams) for the 3rd percentile by gestational age (82)	Table revised to reflect WHO reference.	Revision from CDC referenced to WHO referenced table.
19.4 Appendix 4: Specialty Laboratory Testing (85-86)	Revision of special laboratory specimens collection based on revised study visit procedures per the Schedule of Assessments.	
19.6 Appendix 6: Growth Charts (88-102)	All Growth charts revised to reflect WHO reference.	
19.7 Appendix 7: Blood Volume Collection (103)	Revision of blood volume collection based on revised study visit procedures per the Schedule of Assessments.	An additional table was added to reflect differences in blood volumes in rhGH and LUM-201 arms.
19.8 Appendix 8: Running Summary of Changes (104-119)		Inclusion of summary of changes from Protocol Version 4.1 to Version 5.1.

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3.0 ABBREVIATIONS AND DEFINITIONS

ADHD	attention deficit hyperactivity disorder
ADL	activities of daily living
AE	adverse event
AHV	annualized height velocity
ALT	alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT])
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
CDC	Centers for Disease Control
CI	confidence interval
CFR	Code of Federal Regulations
C _{max}	maximum concentration
CRF/eCRF	case report form/electronic case report form
CRO	contract research organization
CRT	controlled room temperature
CTCAE	Common Terminology Criteria for Adverse Events
CTS	Clinical Trial Supplies
L-DOPA	levodopa
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone releasing hormone
GHRP-6	GH-releasing hexapeptide
GHSR1a	GH secretagogue receptor
HbA1c	hemoglobin A1c

HDL	high-density lipoprotein
HT-SDS	height standard deviation score
HV	height velocity
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IGFBP-3	insulin-like growth factor binding protein 3
IGF-1	insulin-like growth factor 1
IMP	investigational medicinal product
IND	investigational new drug
IEC	Independent Ethics Committee
IH	intracranial hypertension
IRB	Institutional Review Board
ISS	Idiopathic Short Stature
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor
MPH	mid-parental height
MRI	magnetic resonance imaging
PD	pharmacodynamic(s)
PEM	Predictive Enrichment Marker
PGHD	pediatric growth hormone deficiency
PI	Principal Investigator
PK	pharmacokinetic(s)
rhGH	recombinant human growth hormone
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
SHOX	short stature homeobox
SST	somatostatin

SUSAR	serious unexpected suspected adverse reaction
T3	triiodothyronine
T4	free thyroxine
TEAE	treatment-emergent adverse events
TSH	thyroid-stimulating hormone
tsp	teaspoon
US	United States
yr	year
WBC	white blood cell

4.0 INTRODUCTION AND BACKGROUND

Initially, children with growth hormone (GH) deficiency were treated with replacement human GH extracted from pituitary glands of deceased organ donors. Beginning in 1985, recombinant human growth hormone (rhGH) received approval from national health authorities for long-term treatment of growth failure or short stature in children with GH deficiency. Subsequently, rhGH has been approved for short stature in several additional pediatric indications. rhGH is administered as a daily subcutaneous (SC) injection. Patients with untreated growth hormone deficiency (GHD) frequently attain adult heights less than 5 feet and have abnormal body composition (1). Treatment with rhGH initiates a period of accelerated or “catch-up” growth (2). Normal adult heights and body compositions have been attained when rhGH was begun at an early age and continued throughout the growing years (3,4,5,6,7). However, adherence with daily injections represents a treatment burden difficult to overcome in a substantial number of patients. Lack of adherence can lead to substantial losses of treatment effect (8,9,10). Long-acting formulations of rhGH, taken weekly, have completed Phase 3 trials and have been approved for use and may offer one alternative to decrease the treatment burden of daily injections (11,12,13). An additional alternative would be administration of an orally active compound to restore secretion of adequate levels of endogenous GH.

LUM-201 (ibutamoren mesylate, L-163,191; formerly MK 0677) is a potent, orally active, non-peptidyl GH secretagogue and a mimetic of GH-releasing hexapeptide (GHRP-6), an effective GH secretagogue in man (14,15). LUM-201 and other GH secretagogues, along with the endogenous peptide hormone ghrelin, act on the GH secretagogue receptor (GHSR1a) in the anterior pituitary and hypothalamus to stimulate the release of GH. This pathway represents an additional regulation of GH release from pituitary somatotrophs to that mediated by growth hormone releasing hormone (GHRH; stimulating) and somatostatin (SST; inhibitory), the latter acting through SST receptor subtypes 2 and 5 to block GHRH-mediated effects. Both stimulatory pathways as well as the inhibition of SST lead to the enhanced pulsatile release of GH.

4.1 Background of the Disease

GHD in childhood is an uncommon disorder, occurring in about 1 in 4000 children (16,17). Children with untreated GHD will have significant short stature and abnormal body composition; in most cases, adult height is less than 5 feet (1.52 m) (18). GHD is the consequence of low or absent secretion of GH from the pituitary gland. GHD has numerous causes that produce a range of phenotypes from very severe in cases of absence of the pituitary gland to more moderate in cases of diminished baseline secretion of GH from an otherwise intact and functional but reduced pituitary gland. In children, GHD results in inadequate circulating insulin-like growth factor 1 (IGF-1) levels. Low circulating IGF-1 concentrations are also used as a diagnostic criterion (16).

Along with significant growth failure, children with untreated GHD will have abnormal body composition with decreased bone mineralization, decreased lean body mass, and increased fat mass. Adults with GHD have decreased lean body mass, increased fat mass, weakness, reductions

in exercise capacity, muscle mass/strength, cardiac performance, bone density, and neuropsychological disturbances.

PGHD has traditionally been subdivided into “organic” PGHD and “idiopathic PGHD”. Organic PGHD includes all causes of severe GHD where the cause is known, including congenital absence of the anterior pituitary, a neoplasm involving the anterior pituitary, or surgical or radiation therapy of the brain that damages the anterior pituitary somatotrophs, resulting very low GH levels, very low IGF-1 levels, and lifelong GHD with the need for treatment with rhGH even after peak height is attained post-puberty. Approximately 40% of the PGHD population has some form of organic PGHD.

In contrast, idiopathic PGHD, as the name implies, has no obvious cause for the GH deficiency. Patients with idiopathic GHD typically show somewhat less severe features of GHD in comparison to patients with organic GHD, including somewhat higher height SDS values, somewhat higher IGF-1 values, and somewhat smaller BA delays, resulting in somewhat smaller responses to rhGH. The cause in most cases is thought to reflect an impairment in the hypothalamic regulation of GH release during childhood, as many subjects with a diagnosis of idiopathic PGHD when tested after attainment of peak adult height (epiphyseal closure) no longer test positive for GHD, and so do not require continued treatment with rhGH as adults. Idiopathic PGHD comprises approximately 60% of the PGHD population. To date, although endocrinologists do characterize their patients with PGHD as either organic or idiopathic, the treatment has been restricted to parenteral rhGH.

4.2 Background of Treatment Options

Current treatment of children with GHD is limited to daily or once-weekly SC injections of rhGH. Treatment is required for an average of approximately seven years, but in the cases of organic GHD may persist throughout life.

Several patient pre-treatment characteristics have been found to correlate with higher first year on-treatment height velocities (HVs). First year HVs are increased in younger patients, in those with greater initial height deficits and in those with more severe GHD (low stimulated GH response and/or low IGF-1 standard deviation scores [SDS]) (19,20,21,22), and greater BA delays. In a randomized trial adjusting rhGH dose to observed IGF-1 responses, the rhGH dose, and IGF-1 response observed were independent correlates of growth response during the first 2 years of growth (23). Baseline IGF-1 and GH response to standard of care GH stimulation tests have also been found to be independent predictors of 12-month growth response to rhGH (24). While current standard of care is limited to daily injections of rhGH, several long-acting rhGH forms are currently in clinical development, and one (SKYTROFA) has been recently approved in the US, while another (NGENLA) has been recently approved ex-US.

LUM-201 is a secretagogue intended to stimulate release of GH from subjects with a functional but reduced pituitary axis. Therefore, it is most likely to benefit subjects with idiopathic PGHD, i.e., those subjects who do not have the lowest stimulated GH responses and / or the lowest baseline IGF-1 values, and likely retain adequate anterior pituitary somatotrophs. Subjects diagnosed with

the most severe PGHD have the highest first year on-treatment HVs when treated with rhGH. Subjects with idiopathic PGHD are likely to be those who respond to LUM-201 and may have lower overall first year on-treatment HVs when compared to subjects from a study of rhGH that includes more severe subjects (24). However, when subjects likely to respond to LUM-201 as defined by our PEM strategy are treated with LUM-201 and compared to a group of subjects with idiopathic PGHD as selected by the same PEM criteria treated with rhGH, it is the premise of this clinical investigation that their annualized first year on-treatment HVs will be similar.

4.3 Summary of Nonclinical and Clinical Data for LUM-201

Comprehensive safety pharmacology and toxicology studies for LUM-201 have been completed (including chronic and juvenile toxicology, genotoxicity, 2-year carcinogenicity, and developmental and reproductive toxicology) and support chronic (> 12 months) use of LUM-201 in the pediatric population.

To date, LUM-201 has been studied in more than 1200 people (~230 children and ~1000 adult and elderly subjects). LUM-201 has been generally well-tolerated in healthy volunteer, pediatric, young adult, and elderly subjects enrolled in clinical studies. In the current LUM-201-01 and LUM-201-03 Phase 2 studies, doses of LUM-201 across the dose range of 0.8- to 3.2 mg/kg/day have shown good safety and tolerability for up to 12 months of dosing.

4.4 Potential Risks and Benefits to Human Subjects

The most commonly reported adverse event associated with LUM-201 administration in PGHD studies was increased appetite.

No drug-related serious clinical or laboratory adverse events were reported in the three prior pediatric trials conducted with LUM-201.

Detailed information on these and other risks of LUM-201 in humans is provided in the Investigator's Brochure (IB) for LUM-201.

The potential benefit of LUM-201 is acceleration of linear growth.

For risks and benefits of rhGH (Norditropin®) refer to the latest Prescribing Information of Norditropin® for injection® (25).

4.5 Mitigation Procedures for Public Health Emergency

During a Public Health emergency as declared by Local or Regional authorities (e.g., pandemic, epidemic or natural disaster), mitigation procedures to ensure the participant's safety and trial integrity are listed in the relevant sections of the protocol. Notification of the Public Health emergency should be communicated and discussed with the sponsor and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5.0 STUDY OBJECTIVES

5.1 Primary Objective

- Preliminary clinical validation of predictive enrichment marker (PEM) strategy intended to select subjects likely to respond to therapy with LUM-201 based upon the percentage of subjects defined as PEM test positive ($\text{GH} \geq 5 \text{ ng/mL}$ and $\text{IGF-1} > 30 \text{ ng/mL}$ [$> 3.92 \text{ nmol/L}$]) who have a positive growth response (“responders”) defined as $\geq 6.85 \text{ cm/yr}$ AHV from Baseline (Day 1) to Month 6.

5.2 Primary Clinical Objective

- To select a pediatric dose of LUM-201 for use in future studies including Phase 3 trial(s) based on comparison of 6-month AHVs achieved by daily rhGH and the dose levels of LUM-201 treatment in subjects with pediatric growth hormone deficiency (PGHD) selected by predictive enrichment markers (PEMs)

5.3 Key Secondary Objective

- To assess the reproducibility of the PEM positive classification of subjects

5.4 Other Secondary Objectives

- To assess additional clinical parameters of efficacy (at Month 6 and Month 12) including:
 - Change in height standard deviation score (HT-SDS)
 - Change in height velocity standard deviation score (HV-SDS)
 - Change in weight and weight SDS
 - Change in body mass index (BMI) and BMI SDS
 - Change in predicted adult height
 - Change in BA
- To assess the safety and tolerability of oral LUM-201
- To further explore pharmacokinetics (PK) of LUM-201 based upon plasma LUM-201 concentrations
- To determine short and long-term pharmacodynamic (PD) (GH, IGF-1, IGFBP-3) responses to daily LUM-201
- To characterize variance in AHVs of rhGH and LUM-201 to enable sample size estimates for future trials

6.0 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a multicenter, up to 24-month, randomized, open-label, active control, parallel arm, Phase 2 study of daily oral LUM-201 in naïve-to-treatment, prepubertal children with PEM+ idiopathic GHD. Figure 1 presents the study schema.

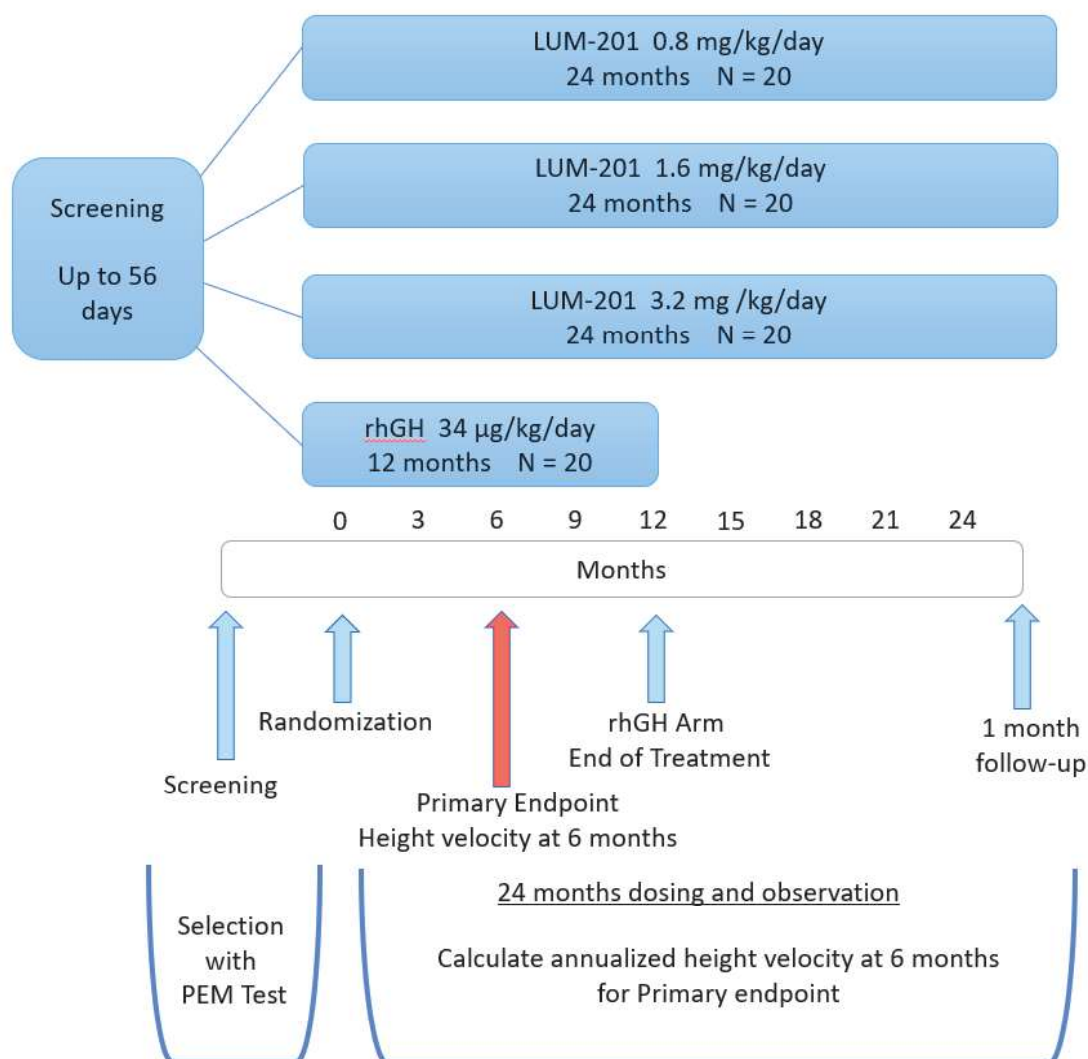


Figure 1 Schema of Study Design

Abbreviations: PEM = predictive enrichment marker; rhGH = recombinant human growth hormone

6.2 Rationale for the Study

Children with GHD have inadequate growth. Growth can be restored with daily or weekly injections of rhGH. The rationale for this study is that in a properly selected cohort of patients with idiopathic PGHD, LUM-201 administered at previously tested or higher doses may achieve similar catch-up growth as compared to rhGH and provide a safe and effective oral treatment alternative to injections for similar patients. LUM-201 is an orally administered GH secretagogue that can augment secretion of endogenous GH while maintaining natural physiologic patterns of pulsatility. A dose-finding study of LUM-201 was conducted in naïve-to-treatment, prepubertal children with GHD, including organic PGHD subjects, randomized to receive either placebo, 0.4 mg/kg/day or 0.8 mg/kg/day LUM-201 once daily by mouth (Merck Study 020). After 6 months, the placebo group received rhGH, 42 µg/kg/day as SC injections. The mean HVs for these groups are shown in [Table 2](#), and demonstrate a trend towards a dose-related increase in HV in response to treatment with LUM-201 when all patients evaluated in Merck Study 020 are considered. As shown in [Table 3](#), where an analysis was performed assessing the subjects with PEM-positive idiopathic PGHD, the dose-dependent increase in HV in response to treatment with LUM-201 was enhanced, and the HV response to the 0.8 mg/kg/day dose was not significantly lower than the response to rhGH at 42 µg/kg/day over 6 months. This indicates a need to both extend dose finding for LUM-201 and properly select candidates for treatment with a secretagogue, as described below.

Table 2 Height Velocity at 6 Months in Merck Study 020 (cm/yr)

	Placebo n = 22	LUM-201 0.4 mg/kg/d n = 22	LUM-201 0.8 mg/kg/d n = 24	rhGH 42 µg/kg/d n = 20
Mean (SD) height velocity at 6 months (cm/yr)	4.5 (1.4)	6.0 (1.9)	6.9 (1.9)	11.1 (4.0)
P-value versus Placebo	N/A	0.0046	< 0.0001	< 0.0001

Abbreviations: rhGH = recombinant human growth hormone; SD = standard deviation

6.3 Rationale for Selection of the Treatment Population

GH stimulates the release of IGF-1. GH and IGF-1 are the primary hormonal mediators of growth during childhood. In a preliminary study of LUM-201 in childhood ([Merck Study 019](#)), LUM-201 stimulated the release of IGF-1 but only in those with higher baseline IGF-1 levels ([27](#)). This was the first evidence in children that LUM-201 might only benefit a subset of patients with PGHD. This subset can be viewed as those children with less severe, idiopathic PGHD as evidenced by the higher baseline IGF-1 level. Subsequently, in Merck Study 020 pediatric subjects had a peak GH response to single dose LUM-201 and baseline IGF-1 measured prior to being randomized to treatments with LUM-201 or placebo. The baseline IGF-1 concentration in conjunction with the peak GH to a single pre-treatment LUM-201 dose (0.8 mg/kg) were found to be an effective PEM strategy for AHVs ([Table 3](#)) when using PEM cut-off values identified by receiver operating characteristic and iterative filtering techniques. The PEM cut-off values identified in Study 020 are:

- Baseline IGF-1 concentration > 30 ng/mL (> 3.92 nmol/L)
- Peak GH $\geq$ 5 ng/mL to single 0.8 mg/kg LUM-201 dose

Subjects meeting both criteria are classified as PEM positive, all others are considered PEM negative. The results in Table 3 indicate that a positive PEM status enriches the LUM-201 treatment population; *PEM positive* subjects had greater AHVs than PEM negative subjects. Conversely, with rhGH treatment, *PEM negative* subjects had greater AHVs than PEM positive subjects. This is to be expected with rhGH therapy as PEM negative subjects are expected to have more severe organic PGHD and therefore have greater first year on-treatment AHVs as they experience catch-up growth. PEM status may become an effective treatment allocation test for LUM-201 and rhGH.

Table 3 Effect of Predictive Enrichment Markers on Annualized Height Velocities

Dose (daily)	PEM Negative Mean Height Velocity $\pm$ SD (cm/yr)	PEM Positive Mean Height Velocity $\pm$ SD (cm/yr)	p-value PEM-negative vs. PEM-positive
0.4 mg/kg LUM-201	5.75 $\pm$ 2.1 (n = 10)	6.18 $\pm$ 1.8 (n = 12)	0.6041
0.8 mg/kg LUM-201	5.41 $\pm$ 2.0 (n = 9)	7.71 $\pm$ 1.3 (n = 15)	0.0025
42 μ g/kg rhGH	14.0 $\pm$ 4.1 (n = 9)	8.8 $\pm$ 1.8 (n = 11)	0.0013

Abbreviations: PEM = Predictive Enrichment Marker; rhGH = recombinant human growth hormone; SD = standard deviation

6.4 Rationale for Selection of LUM-201 Dose Range in Children

The rationale for selection of the LUM-201 dose range in children is based on prior demonstration of growth using LUM-201 0.8 mg/kg, the PD (GH) and growth response relationships relative to anticipated maximal biological effect, and PK considerations. The selected doses are supported by the clinical and non-clinical safety profiles.

The rationale for the range of selected doses is based on

1. LUM-201 doses up to 0.8 mg/kg have had an acceptable safety profile in prepubertal children. Additionally, LUM-201 has been evaluated extensively in adults and has demonstrated an acceptable safety profile.
2. The safety margins defined by the toxicology studies in juvenile animals support exploration of the highest LUM-201 dose proposed for PGHD.
3. 0.8 mg/kg/day is the anchor dose and has been shown in the Merck Study 020 to improve 6-month AHVs.

4. While the 0.8 mg/kg/day dose improved 6-month AHVs over placebo treatment in Merck Study 020, similar patients with less severe degrees of GHD as defined by the PEM strategy outlined in this protocol treated with daily rhGH have demonstrated greater HVs (19, 26). AHV on this dose in these patients was statistically different from AHV observed with 0.4 mg/kg/day, indicating a dose-response. Accordingly, the optimal dose of -LUM-201 for growth promotion in children may be higher than 0.8 mg/kg, the highest dose previously tested in children.
5. Examination of the LUM-201 dose and PD (GH release) relationship in healthy adults indicates that the 0.8 mg/kg dose is only about 30% up the dose-response curve, and that a plateau in GH response is anticipated to occur at a dose ~3.2 mg/kg in children. Accordingly, a dose of 3.2 mg/kg may be necessary to stimulate maximal GH response and therefore growth, whereas a higher dose would not be expected to provide additional benefit.
6. Since the variation of LUM-201 PK parameters is predicted to be high, it is anticipated that a dose range based on dose doubling would be needed to detect any LUM-201 dose level driven differences in PK, PD, and growth effects.

Accordingly, the selected LUM-201 doses for the current study are 0.8 mg/kg/day, 1.6 mg/kg/day and 3.2 mg/kg/day.

6.5 Rationale for Study Design

The study employs multiple pediatric endocrine sites to facilitate recruitment of the specified population size. The study is actively controlled (LUM-201 versus daily rhGH) so that children with established GHD do not spend an inordinate time in an untreated state. Norditropin® was selected as the comparator drug because it is available in all study locations. The primary objective is based upon favorable growth response and therefore HV which is dependent on age and severity of the growth disorder, so these two factors will be controlled by stratification, which, in turn, necessitates a parallel arm dosing study.

6.6 Study Duration and Dates

Subjects completing the study will participate for approximately 15-27 months (up to 56 days in Screening, 12-24 months on treatment, and 1-month follow-up).

6.7 Safety Reviews and Stopping Rules

The Medical Monitor (MM) will monitor safety and clinical laboratory safety events on an ongoing basis. An independent Data Safety Monitoring Board (DSMB) will review safety data commencing with treatment start (see Section 6.11). As balanced randomization requires parallel study design, first planned DSMB review will take place after two subjects each in 1.6 mg/kg and 3.2 mg/kg dose arms have been on treatment for 1 month, unless a safety concern is identified earlier, in which case DSMB will meet immediately. Subsequent DSMB meetings will take place approximately every 3 months, and additionally on an *ad hoc* basis as dictated by

safety events of interest. All available clinical data will be provided to the DSMB members by the contract research organization (CRO). DSMB members will review data for any potential risks to subjects and to determine if criteria for any Stopping Rules have been met.

6.8 Stopping Rules

6.8.1 Individual Subjects

Any subject who meets any of the following criteria should immediately have further study related therapy withheld until the subject can be thoroughly evaluated and the data discussed by the treating physician, medical monitor, Sponsor, and as needed the DSMB.

1. The MM and/or the Principal Investigator (PI) concludes it is unsafe for the subject to continue
2. A new diagnosis emerges that could influence the response to treatment
3. Occurrence of serious adverse events related to study drug
4. A new medication is commenced that could influence the response to treatment
5. Occurrence of new intracranial tumor
6. Development of new malignancy
7. Glucose at any time > 200 mg/dL
8. QTcB interval increase of ≥ 60 msec from baseline or QTcB value ≥ 500 msec (mean value of three tracings)
9. Clinically relevant laboratory abnormalities, including serum ALT and/or AST > 3x upper limit of normal (ULN).

Subjects meeting an individual stopping criterion may be withdrawn from the trial.

Subjects meeting an individual stopping criterion may, after thorough evaluation, return to study treatment if there is agreement between the PI, medical monitor and the Sponsor provided that it can be clearly determined factors that resulted in a stopping criterion met were not related to study therapy or have been appropriately managed, and resumption of study therapy is not believed to provide increased or unwarranted risk to the subject.

Subjects treated with LUM-201 who do not meet the 6.7 cm/yr AHV criterion at Month 12 will be withdrawn from the trial and may be switched to SOC at the discretion of their physician.

If an IGF-1 increase above 2 SDS is noted, this result is not considered a stopping rule, but the PI should contact the MM to discuss whether it should be repeated and the appropriateness of

potentially reducing the dose of either LUM-201 or rhGH if an IGF-1 SDS $> +2.0$ is confirmed/persistent.

6.8.2 LUM-201 Treatment Arms

An LUM-201 arm may be discontinued if the determination is made that it is unsafe to continue because of an unexpected frequency, severity or type of adverse event (AE).

6.9 Discussion of Study Design

This study is designed to confirm the ability of the PEM test to select for subjects who will respond to LUM-201 treatment, the reproducibility of the positive PEM test result, and the HV response of LUM-201 compared to rhGH. The response to LUM-201 will be based on the annualized height velocity at Month 6. Up to 18 additional months of study treatment will be used to further characterize overall safety and growth response to LUM-201.

The individual assessments employed are standard pediatric practice for the evaluation of growth and growth-promoting treatments in children. The frequency of blood tests, electrocardiograms (ECGs), PK/PD markers, and BAs are appropriate to the evaluation of a new investigational product (LUM-201) and its comparison to a standard of treatment (daily rhGH).

6.10 Study Endpoints

6.10.1.1 Clinical Outcome Measurements:

- Height collected in triplicate at all clinic visits
- Weight collected at all clinic visits
- Bone Age collected at baseline (Screening visit), Month 6 visit, and Month 18 visit

6.10.2 PK/PD Endpoints

- Plasma LUM-201 concentrations (in LUM-201-treated subjects)
- Serum GH (LUM-201 subjects only), IGF-1, IGF-1 SDS and IGFBP-3

6.10.3 Safety Endpoints

AEs and SAEs, routine laboratory tests (hematology, chemistry panel including liver enzymes and urinalysis), HbA1c, serum glucose, free thyroxine (T4), total triiodothyronine (T3), thyroid-stimulating hormone (TSH), lipids, physical examinations, interval history, vital signs, and ECGs.

6.11 Data and Safety Monitoring Board (DSMB)

The DSMB will consist of pediatric endocrinologists experienced with growth studies.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

The Study population will consist of naïve-to-treatment, prepubertal subjects (at Screening) with an established diagnosis of idiopathic PGHD by standard criteria including standard GH

stimulation testing. Subjects must also meet the defined Inclusion and Exclusion criteria. Subjects who are sexually active must use an acceptable form of contraception. Once eligible for screening, subjects will undergo screening procedures including the PEM test (GH response to a single 0.8 mg/kg dose of LUM-201 and IGF-1 baseline blood draw) necessary to be classified by our PEM strategy. The treatment population will be the subset of these PGHD subjects classified as PEM positive believed to have the potential to respond to oral LUM-201.

Approximately 140 subjects will be enrolled in the Screening Portion of study which should be adequate to fill the Treatment Portion of study, randomizing 20 subjects to each of the three LUM-201 treatment arms and 20 to the daily rhGH treatment arm (total of 80 randomized subjects). This is based upon data available from prior studies with LUM-201 that predict approximately 50%-60% of subjects being classified as PEM positive.

7.1 Inclusion Criteria

To be eligible to participate in the study, subjects must fulfill all of the following inclusion criteria.

1. Have an established diagnosis of idiopathic PGHD made prior to screening for entry into this study. This diagnosis is to be made in standard of care fashion incorporating biochemical, radiographic and auxological data. Specific inclusion criteria listed in this section for inclusion into this study protocol which are also used to diagnose PGHD in general are not intended to replace, supplant, or be an all-inclusive substitute for a standard of care diagnosis. Eligible subjects must be naïve-to-treatment and be prepubertal.
2. The diagnostic work up must include a maximal GH response < 10 ng/mL from two prior GH stimulation tests or one combined clonidine/arginine GH stimulation test within the past 12 months (eligible tests include: glucagon, insulin, arginine, clonidine, and L-DOPA, exercise, and overnight sampling). If the preponderance of data including growth curves strongly supports a diagnosis of idiopathic GHD, including two GH stimulation tests showing peaks > 3 but < 10 ng/mL > 12 months previously, a current stimulation test does not necessarily need to be repeated.
3. At Screening visit or in the prior 12 months have a morning or random cortisol ≥ 7 $\mu\text{g/dL}$ (193 nmol/L). Subjects with morning or random cortisol response < 7 $\mu\text{g/dL}$ require a stimulated cortisol test (ACTH, insulin, glucagon) to be eligible for the study. Stimulated cortisol response should be ≥ 14 $\mu\text{g/dL}$ (386 nmol/L).
4. Be willing to provide written informed consent (and assent where applicable) to participate in this trial.
5. At Screening visit, be age ≥ 3.0 years and age ≤ 11.0 years for girls and ≤ 12.0 years for boys.

6. Have HT-SDS ≤ -2.0 or a HT-SDS ≥ 2 SD below MPH HT-SDS. Both must be accompanied by a low baseline HV (e.g., ≤ 5.5 cm/year). If the other data (slow HV, low IGF-1, peak GH < 10 , and 6-month BA delay) are all consistent with idiopathic GHD, the subject may be enrolled with a height SDS > -2.0 after consultation with the MMs. The use of National Growth Charts to compute HT-SDS is permitted for ex-US sites.
7. Have a baseline height velocity ≤ 5.5 cm/year based on 6-12 months of growth.
8. Have a BA examination at Screening or within the 9 months prior to Screening that is delayed by ≥ 6 months with respect to chronological age. BA should be based on the apparent BA of the proximal and distal phalanges, as opposed to the metacarpals, carpals and distal forearm. A central BA reader will make the final determination on BA eligibility.
9. Have an arm span to height ratio $> 96.5\%$.
10. Have prepubertal status as evidenced by Tanner Stage I breast development in girls and testicular volume < 4.0 mL in boys.
11. In girls, have genetic testing results to rule out Turner syndrome. If SHOX genetic testing results are available, they need to be negative.
12. Have normal thyroid function. Subjects diagnosed with hypothyroidism must have documented successful treatment for at least 30 days prior to Day 1.
13. Baseline IGF-1 concentration > 30 ng/mL (> 3.92 nmol/L) and a peak GH response of ≥ 5 ng/mL from the first Screening PEM test.
14. Subjects who are sexually active must use an acceptable form of contraception.

7.2 Exclusion Criteria

Potential study subjects meeting any of the exclusion criteria listed below will not be eligible for participation in the study.

1. Any medical or genetic condition which, in the opinion of the Investigator or MM, can be an independent cause of short stature and/or limit the response to exogenous growth factor treatment. (Examples: diabetes, idiopathic short stature (ISS), Turner Syndrome, constitutional growth delay, SGA and chondrodysplasias, or other named syndromes).
2. A medical or genetic condition that, in the opinion of the Investigator and/or MM, adds unwarranted risk to use of LUM-201 or rhGH.

3. Use of any medication that, in the opinion of the Investigator and/or MM, can independently cause short stature or limit the response to exogenous growth factors (Example: glucocorticoids).
4. The presence of any circumstance likely to prevent successful completion of this trial.
5. Evidence or history of an intracranial mass (e.g., pituitary tumor, craniopharyngioma).
6. Prior treatment with growth factors including, but not limited to, GH, IGF-1, and GH secretagogues. (These may be used for limited times as a diagnostic test.)
7. Suspicion of absent pituitary function as evidenced by a maximal stimulated GH ≤ 3 ng/mL on two prior standard of care GH stimulation tests, or pituitary deficiencies beyond GH and thyroid function, or a diagnosis of organic PGHD. Note: If a maximal stimulated GH response is > 3 ng/mL on one of the prior standard of care GH stimulation tests, subject is potentially eligible for participation in the study.
8. Malnutrition as evidenced by medical history or a BMI $< 5^{\text{th}}$ percentile.
9. BMI $> 95^{\text{th}}$ percentile.
10. Gestational age-adjusted birth weight $< 3^{\text{rd}}$ percentile (small for gestational age), as noted in [Appendix 1](#).
11. Participation in any therapeutic trial of investigational drug(s) within the prior 6 months.
12. Known or suspected allergy to LUM-201, rhGH, or one of their excipients.
13. Unwilling to accept randomization assignment.
14. Treatment with medications known to be moderate or strong inhibitors or strong inducers of CYP3A/4 as noted in [Appendix 2](#).
15. Treatment with medications known to be predominantly metabolized ($< 5\%$ contribution by other isoforms) by either CYP3A/4, CYP2C8, CYP2C9 or CYP2C19 as noted in [Appendix 2](#).
16. Treatment with medications known to act as strong inhibitors of P-gp or potent substrates of P-gp or MATE1 as noted in [Appendix 2](#).
17. History of spinal, cranial, or total body irradiation.
18. Recent commencement (within three months of the Screening Visit) of non-stimulant therapy to treat ADHD. MM should be contacted prior to screening of any potential subjects diagnosed with ADHD.

7.3 Subject Withdrawals and Replacements

Consent may be withdrawn at any time for any reason by the subject or subject caregiver without prejudice to further treatment. The MM, PI or DSMB may withdraw a subject (Section 6.11). If possible, subjects who withdraw prior to Month 12 visit should complete the activities of the Month 12 visit and return at the scheduled Month 12 visit for a final evaluation of the endpoints.

To meet study requirements, the Sponsor may continue to enroll additional subjects to offset effects of withdrawn subjects.

8.0 ENROLLMENT, RANDOMIZATION, AND BLINDING PROCEDURES

8.1 Randomization

Eligibility will first be determined by standard diagnostic criteria for non-organic PGHD. Subjects will then be offered the opportunity to provide informed consent and enroll in the Screening portion of the study. During the Screening portion of the study, subjects will undergo a baseline IGF-1 blood draw and a LUM-201 stim test (PEM test). Subjects classified as PEM positive by the PEM strategy will be enrolled into the Treatment portion of the protocol. All eligibility and Screening data will be reviewed by the PI and MM(s) and the subject confirmed eligible prior to randomization. Subjects will be randomized into one of four treatment arms at a 1:1:1:1 ratio. The randomization will be centralized across all sites and will be stratified by age (< 7.5 yrs, ≥ 7.5 yrs) and HT SDS (< -2.5 , ≥ -2.5). The randomization will be assigned by an electronic system after approval by the MM(s). Subjects will return on Day 1 visit to repeat the PEM test; subjects randomized to rhGH will commence treatment immediately following randomization, and LUM-201 subjects will start their randomized LUM-201 dose the day following Day 1 visit.

8.2 Methods of Subject Assignment

Each screened subject will receive a Subject Number generated when the study Screening visit form is completed in the study website. The MM(s) will review all data from Screening (Visit 1) (and additional data requested of the PI, if required). The MM will approve randomization for all subjects satisfactorily completing all inclusion/exclusion criteria. Subject Numbers will not be reassigned.

8.3 Blinding

This study is an open-label study; no blinding is required. However, every effort will be made to keep the MMs blinded to treatment allocation.

9.0 STUDY TREATMENTS

9.1 Description of Treatments

All subjects will receive a single oral 0.8 mg/kg dose of LUM-201 at Screening visit. Subjects who test PEM positive will receive a second PEM test at Day 1 visit. Subjects who test PEM negative will not be included in the Treatment portion of the study.

All randomized subjects will commence their assigned dose on Day 1 visit for those randomized to rhGH and the day following Day 1 for those randomized to LUM-201 and continue treatment until Month 12 visit. At Month 12 visit, subjects randomized to rhGH will be offered the option to transition to another longer-term study in which they will receive LUM-201. Subjects randomized to LUM-201 who have $AHV \geq 6.7$ cm/yr at Month 12 may continue LUM-201 treatment for an additional 12 months. Subjects not meeting the 6.7 cm/yr AHV criterion at Month 12 will be withdrawn from the trial and may be switched to SOC at the discretion of the PI and subject.

9.1.1 LUM-201

Subjects randomized to LUM-201 will receive approximately 0.8 mg/kg/day, 1.6 mg/kg/day or 3.2 mg/kg/day as an oral dose taken in the morning without regard to meals.

9.1.2 rhGH

All subjects randomized to the rhGH treatment arm will receive daily SC injections of commercially available rhGH (Norditropin® multi-use pen) at 34 µg/kg, the highest rhGH dose available for pediatric GHD in geographical regions of interest.

9.2 Administration of Treatment

All subjects and their caregivers will receive instruction on the storage, handling, and administration of their randomized study drug on Day 1 visit. At all subsequent study visits, LUM-201 will be administered at the Health Care Facility by trained study staff. On non-visit days medications will be administered at home. LUM-201 subjects will start their randomized LUM-201 dose the day following Day 1 visit. The rhGH is to be administered via SC injection at clinic on Day 1 and afterwards at home once daily in the evening per manufacturer instructions. Visiting health care professionals may assist in the administration of rhGH injections at home.

As per section 4.5, should a Public Health emergency be declared that limits or prevents on-site study visits, delivery to and administration of study drug at the subject's home may be permitted, providing this is permitted by Local or Regional Health Authorities and Ethics committees as appropriate. Dispatch of the study drug to the subject's home remains under the accountability of the Investigator. In this case, regular telephone/video calls will occur between the site and subject and/or their caregiver for the purposes of safety monitoring of treatment until on-site visits can resume. Home healthcare provider visits to aid in safety monitoring of the investigational product investigations may also be implemented, as appropriate.

The quantity of study drug administered will be adjusted based on body weight at Month 1 visit, Month 3 visit, Month 6 visit, Month 9 visit, Month 12 visit, Month 15 visit, Month 18 visit, and Month 21 visit time points at the instruction of the study staff to the subject's caregiver.

LUM-201 tablets are not to be divided, chewed or crushed. The number of tablets prescribed at each visit will be weight specific. Subject's weight should be rounded to the nearest kg.

During Screening visit and Day 1 visit, subjects will be administered a single ~0.8 mg/kg LUM-201 dose. These supplies will be provided separately as 9 mg tablets in single count bottles.

9.2.1 Treatment Interruption

Study drug may be stopped temporarily due to a subject meeting any of the Stopping Rules or for new medical events at the discretion of the PI and/or MM. The underlying cause of any such interruption will be thoroughly evaluated and treated as appropriate by the PI and other treating physicians. Results of the evaluation will be reviewed by the PI, MM, the Sponsor, and as necessary the DSMB. The decision to then restart therapy or to remove subjects from the study or from a treatment arm will be made by the same panel on a case-by-case basis in consideration of the interests and well-being of each individual subject.

Any subject who experiences a continuous interruption in therapy of greater than 14 days may be removed from the study at the discretion of the MM and their physician.

9.3 Concomitant Medications

Restrictions on concomitant medications are noted in the Inclusion and Exclusion Criteria (Sections 7.1 and 7.2), Norditropin® prescribing information (when applicable) and in Appendix 3. Commencement of new medications that can influence subject's safety or response to study drug are prohibited. Medications required for treatment of intercurrent illness will be reviewed by the MM. Generally, use of medications for treatment of intercurrent illness will be allowed for up to 2 weeks, with study drug administration paused, as needed. If illness persists past 2 weeks, the MM should be consulted, and the subject may need to terminate study drug treatment unless alternate management options are available. Hypothyroidism discovered during the Screening portion of the study requires treatment for a minimum of 30 days prior to randomization. Short-term stress doses of glucocorticoids may be used as per standard medical practice of the PI.

9.4 Restrictions

All subjects must complete an overnight (after 10 p.m.) fast prior to the PEM test at the Screening visit and Day 1 visit, and before Month 3 visit, Month 6 visit, and Month 12 visit. There are no other restrictions regarding diet or exercise, except for prohibited consumption of grapefruit or grapefruit juice. Subjects planning foreign travel should consult with their Study Coordinator.

9.5 Treatment Adherence

Administration of all LUM-201 or rhGH doses will be performed by health care professionals or the caregiver. A subject who misses more than 20% of the intended doses over the entire Treatment period without good reason such as meeting a stopping rule or the treatment of an intercurrent illness will be considered non-compliant.

Efforts should be made to complete all protocol-specified activities within the allotted time frame. Failure to adhere to the schedule for PK/PD and safety data sample collection may be cause for withdrawal.

9.6 Packaging and Labeling

LUM-201 will be supplied in high-density polyethylene (HDPE) bottles with an induction seal and a polypropylene child-resistant closure. Each bottle is packaged with a 1-gram desiccant and may include a polyester coil. Supplies for PEM testing as part of the PEM strategy will be single-count bottles each containing one 9 mg tablet. Clinical supplies will be provided as 100-count bottles of either 9, 18, or 36 mg tablet strength.

The rhGH (Norditropin[®], somatropin) will be supplied in a ready to use, multi-dose pen injection device. Single use needles will be provided.

9.7 Storage, Transport, and Accountability

LUM-201 shall be stored, transported, and used at controlled room temperature (CRT), defined as 15°C to 25°C (59°F to 77°F).

The rhGH shall be stored, transported and used in accordance with manufacturer instructions. The product should be stored at refrigerated temperatures of 2°C to 8°C (36°F to 46°F) and prevented from freezing and prolonged exposure to sunlight. After first injection, Norditropin[®] pens can either be stored outside of the refrigerator (up to 77°F) for use within 3 weeks, or in the refrigerator (between 36°F and 46°F) for use within 4 weeks.

All unused study drug shall be returned by the subject to the Study Site. The number of remaining tablets will be recorded.

9.8 Investigational Product Retention at Study Site

Unused materials (LUM-201 and rhGH) no longer needed for the trial will be held by the Study Site at the storage conditions in Section 9.7. Product returned by subjects will be held by the Study Site at ambient temperature. Such supplies should be segregated from other Product and clearly marked as not to be used on the Study.

9.8.1 Prohibited Medications

If a subject needs to start medications capable of altering the safety or efficacy of study drug (e.g., guanfacine hydrochloride or a potent CYP3A4 inducer or inhibitor) while on trial, they may be excluded from continued trial participation. See Appendix 2 for complete details regarding prohibited medications.

9.9 Overdose Instructions

For cases of suspected overdose, the PI should contact the MM.

10.0 RISKS/PRECAUTIONS

Increases in intracranial hypertension (IH), retinal damage due to increased intracranial pressure, and glucose abnormalities have been noted in patients treated with rhGH (1,3). It is not known if similar adverse events will be associated with LUM-201 treatment. The PI should contact the MM should signs or symptoms of IH, primarily headache or visual changes occur.

11.0 STUDY ASSESSMENTS AND PROCEDURES

As per Section 4.5, should a Public Health emergency be declared that limits or prevents on-site study visits, alternative methods of care may be implemented by the investigator if allowable by the local health authority, ethics committee and permitted the site policies. Most study assessments could take place by a health care professional at subject's home, if appropriate per Public Health Emergency guidelines.

11.1 Clinical Assessments including Efficacy

11.1.1 Height and Weight and Arm Span

Height will be measured without shoes or socks, in triplicate, by a calibrated stadiometer. Height value replicates should be ≤ 0.2 cm. Weight will be measured in light clothing only.

Arm span will be measured in duplicate in the standing position, back and buttocks against the wall, with no rounding of the back. Arms and hands should be held parallel to floor and vertical pencil marks made on wall at the ends of the middle phalanges. Two measures between pencil marks with a tape measure should be repeatable to within 0.2 cm.

The heights of both parents should be measured, if possible. Reported heights should be recorded for parents unavailable for measurement.

11.1.2 Predictive Enrichment Markers (PEMs)

The PEM test consists of baseline IGF-1 concentrations and the serum GH response at pre-dose (time 0), 30 and 60 minutes after a single oral 0.8 mg/kg dose of LUM-201.

Screening Visit

Subjects will undergo the PEM test during Screening visit after an overnight (10 p.m.) fast. Blood samples for LUM-201 PK analysis will also be taken at these time points at Screening visit only. Subjects who test PEM positive at Screening visit are eligible for the Treatment Period of the study and will undergo a second PEM test performed on Day 1 visit. Subjects who test PEM negative at Screening visit will not be included in the Treatment Period of the study.

Day 1 Visit

Subjects who test PEM positive at Screening visit will have a second PEM test performed on Day 1 visit. Subjects will undergo the PEM test during Day 1 visit after an overnight (10 p.m.) fast.

11.1.3 Bone Age

Digitized radiographs of the left hand and wrist will be recorded at Screening visit, Month 6 visit, and Month 18 visit and will be interpreted by the central reader to determine BA. A BA result within 9 months of Screening visit may be used to satisfy eligibility. In these cases, 1 month will be added to the BA result for every month elapsed between the BA date and Screening date to calculate the baseline BA.

11.2 Assessments of Pharmacokinetic (PK) and Pharmacodynamic (PD)

Plasma LUM-201 concentration(s) in LUM-201 treated subjects will be measured at Screening visit and Treatment portion clinic visits, as indicated in the Schedule of Assessments ([Table 1](#)). Serum IGF-1 and IGFBP-3 are the PD markers that will be evaluated in all subjects (LUM-201 and rhGH treatment groups). GH concentrations will be measured in LUM-201 treated subjects only. PK/PD markers concentration measurements will be performed by central laboratories. Taking into consideration the requirements of the “Ethical considerations for clinical trials on medicinal products conducted with the pediatric population, 2008” document and also the needs of this specific protocol, the Sponsor implemented the volumes as defined in [Appendix 7](#).

Every effort was made to minimize the harm, also by the means of utilizing modern analytical techniques at the selected central laboratory. Collection of blood samples to measure PK and PD markers has been designed to minimize number and volume of blood collections while allowing for adequate evaluation of PK characteristics and PD response to the investigational product administration. In addition to serving as a PD marker, IGF-1 concentration data are also used for evaluation of the safety profile of the investigational product. If the blood limit per weight or age of the participants is to be exceeded, only samples up to that blood volume limit should be collected, in the following order of priority: GH samples, IGF-1 sample, chemistry/lipids, TSH/T3/Free T4, Insulin, Hematology, PK samples. Therefore, and depending on the visit, PK sample(s), for example, may be omitted for participants from whom collection of such samples would surpass the blood collection limits per local regulations.

11.3 Assessments of Safety

Safety assessments will be based on reports of AEs (see Section 12.0 for full details), physical examination results, vital signs, ECG measurements, and clinical laboratory parameters.

11.3.1 Physical Examination

A complete physical examination, including Tanner staging, will be performed at the Screening visit. Physical examination focused on changes from prior visit is acceptable for all other clinic visits. Tanner staging should be included in Month 6 visit and Month 12 visit examinations. In addition, for subjects continuing study participation after Month 12, Tanner staging should be done at Month 18 visit and Month 24 visit. Tanner staging to include breast development, pubic hair and, in males, testicular volumes. Injection sites to be examined for all daily rhGH subjects. Fundoscopy will be performed at the Screening visit and at visits where headache or visual changes is recorded as an AE. Signs of increased intracranial pressure should be confirmed by an ophthalmologist and lead to appropriate medical evaluation.

11.3.2 Vital Signs

Vital signs should be recorded in the sitting position after five minutes of rest. Vital signs include pulse, blood pressure, respiratory rate, and temperature.

11.3.3 Electrocardiograms (ECG)

A 12-lead ECG (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, QT/QTc, morphology, and overall interpretation) will be recorded in triplicate for all subjects at Screening visit, Day 1 visit, Month 3 visit, Month 6 visit, and Month 12 visit, as described in Table 1, and as described in the Medpace Core Laboratories Site Acquisition Manual. Single ECG recording will be performed for subjects on the LUM-201 arms at Month 18 visit and Month 24 visit. Results will be interpreted by a central reader. ECGs collected prior to study drug administration at the Screening visit will be used as baseline.

11.3.4 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the following time points. For more information, refer to the LUM-201-01 (OraGrowth 210) Laboratory Manual, and (Appendix 5) in this protocol.

Serum chemistry panel (including alanine aminotransferase [AST], aspartate aminotransferase [ALT], gamma glutamyl transferase [GGT], alkaline phosphatase, bilirubin, and glucose) will be performed at:

- i. Screening visit*
- ii. Day 1 visit*
- iii. Month 1 visit*
- iv. Month 3 visit*
- v. Month 6 visit*

- vi. Month 12 visit*
- vii. Month 18 visit
- viii. Month 24 visit

* fasting

Complete blood count (CBC, including hemoglobin, hematocrit, red blood cell indices, white blood cell count [WBC], and platelet count) will be performed at:

- ix. Screening visit
- x. Day 1 visit
- xi. Month 1 visit
- xii. Month 3 visit
- xiii. Month 6 visit
- xiv. Month 12 visit
- xv. Month 18 visit
- xvi. Month 24 visit

Lipid studies (low- and high-density lipoproteins [LDL and HDL, respectively] cholesterol, and triglycerides) will be collected at:

- xvii. Screening visit*
- xviii. Month 6 visit*
- xix. Month 12 visit*
- xx. Month 18 visit
- xxi. Month 24 visit

*fasting

Urinalysis (Multi-stix readings) will be performed at the site at all clinic visits through Month 12, except Month 9 visit. Urine samples from morning void can be brought to clinic if there is uncertainty that a subject will be able to provide a urine sample during the clinic visit.

Thyroid function (T3, T4, and TSH) will be performed at:

- xxii. Screening visit
- xxiii. Day 1 visit
- xxiv. Month 1 visit
- xxv. Month 3 visit
- xxvi. Month 6 visit
- xxvii. Month 12 visit

Hemoglobin A1c will be performed at the following visits:

- xxviii. Screening visit*

- xxix. Month 3 visit*
- xxx. Month 6 visit*
- xxxi. Month 12* visit
- xxxii. Month 18 visit
- xxxiii. Month 24 visit

*fasting

Fasting glucose, and insulin concentrations will be performed at the following visits, and may be repeated for a suspicion of carbohydrate intolerance:

- xxxiv. Screening visit
- xxxv. Month 3 visit
- xxxvi. Month 6 visit
- xxxvii. Month 12 visit

Clinical laboratory tests were implemented to allow adequate surveillance of subject safety throughout the study duration. All blood samples will be shipped to a central laboratory as described in the Laboratory Manual. Urine samples will be analyzed locally. Repeat laboratories, if needed, may be analyzed locally per site's standard procedures.

11.4 Study Procedures

11.4.1 Informed Consent

Informed consent must be provided for each subject by the legally authorized representative prior to any study activity. Where applicable, subjects will also complete an Assent Form.

Should a Public Health emergency be declared that may challenge the ability to obtain a standard written information consent including limits to on-site visits, the investigator may conduct the informed consent discussion by telephone/video call if allowable by the health authority, ethics committee and permitted by site policies.

11.4.2 Medical History and Genetic Testing

A complete medical history will be obtained at the Screening visit.

It is anticipated that genetic studies to rule out Turner syndrome (in females) and SHOX mutations will be available at the Screening visit as part of medical history. Where needed, karyotyping for Turner syndrome may be performed as part of the activities of the Screening portion. The subject can participate in the screening procedures including PEM testing but may not be declared eligible to continue to the Treatment portion of the study until the genetic studies are available and Turner syndrome has been ruled out. Arm span/height ratio measurement will be performed as a screening procedure to rule out mesomelia consistent with chondrodysplasias.

11.4.3 Other Study Procedures

Medical assessments and treatments required by intercurrent illness or trauma may be employed at the discretion of the PI.

11.4.4 Sample Collection, Storage and Shipping

Biological samples collection, processing, storage, and shipping instructions, whether collected at the study site, or at an alternate location such as subject's home, in case of the Public Health Emergency, will be provided in a study-specific laboratory manual.

11.4.5 Dispensing Study Drug

Site staff will dispense study drug per Pharmacy Manual instructions.

11.5 Study Activities

11.5.1 Screening Period

11.5.1.1 Screening Visit

The Screening visit will be conducted after an overnight fast (beginning at 10 p.m.). The following procedures will be conducted.

- Obtain informed consent (and assent where applicable)
- Verify inclusion and exclusion criteria
- Record medical history, especially baseline AHV based on at least 6 months (either in your office, or data provided by the referring physician, ideally by stadiometer, or in the absence of either of these sources from the caregivers.)
- Measure height of mother and father at this or one of the subsequent visits (record reported height for parents unavailable for measurement)
- Record age of maternal menarche and heights and ages of full siblings, if available
- Record prior and current medications
- Conduct complete physical examination including Tanner pubertal staging
- Conduct fundoscopy
- Record vital signs (prior to PEM test and approximately 1 hour after the PEM test)
- Record ECGs in triplicate (prior to PEM test dose administration and 1 hour $\pm$ 10 minutes after the PEM test dose administration)
- Record height and weight and collect prior AHV(s)
- Record arm span
- Assess BA

- Collect samples for:
 - CBC
 - clinical chemistry
 - lipids
 - thyroid functions
 - urinalysis
 - HbA1c, fasting glucose, and insulin concentrations
 - Fasting cortisol
 - genetic testing for Turner syndrome (females only)
- Review of available pre-screening data by PI
- Confirm subject has been appropriately screened for adrenal insufficiency
- Record which standard of care GH stimulation tests were used within the past 12 months and whether subjects were primed
- PEM test: collect serum samples at 0 (pre-dose), 30 and 60 minutes ($\pm$ 10 minutes for both) after a single LUM-201 0.8 mg/kg dose
- IGF-1 baseline blood draw in conjunction with pre-dose PEM test blood draw
- Collect plasma samples for LUM-201 PK (samples taken at 30 and 60 minutes $\pm$ 10 minutes for both after LUM-201 0.8 mg/kg PEM stimulation test dose administration)
- Record AEs (post PEM stimulation test)
- Schedule Day 1 visit within 56 days

Following receipt of all Screening data, the MM will determine if Screening criteria have been met and randomization for successfully screened subjects will be requested.

11.5.2 Treatment Period

11.5.2.1 Day 1 Visit

Day 1 visit will be conducted after an overnight fast (beginning at 10 p.m.) and within 56 days after the Screening visit. The following procedures will be conducted.

- Review of Screening results by PI
- Randomization confirmation
- Record interval history
- Record AEs
- Record concomitant medications

- Record height and weight
- PEM stimulation test: collect serum samples at 0 (pre-dose), 30, and 60 minutes (± 10 minutes for both) after a single, oral LUM-201 0.8 mg/kg dose
- IGF-1 baseline and insulin-like growth factor binding protein 3 (IGFBP-3) blood draws in conjunction with pre-dose PEM stimulation test blood draw
- Record vital signs (before and approximately 30 and 60 minutes [± 10 minutes for both] after LUM-201)
- Conduct physical exam focused on changes from prior visit
- Collect urine sample
- Collect pre-dose blood samples for safety laboratories
- Record ECGs in triplicate (prior to PEM stimulation test article administration and 1 hour ± 10 minutes after the PEM test)
- Administer study drug (rhGH subjects only)
- Instruct caregivers on storage and administration of study drug (LUM-201 subjects will start their randomized LUM-201 dose the day following Day 1 visit)
- Dispense study drug adequate to permit dosing through Month 1 visit
- Remind caregiver to begin at-home administration of study drug on the following day
- Schedule Month 1 visit for 30 ± 3 days

11.5.2.2 Month 1 Visit

The following procedures will be conducted.

- Conduct physical examination focused on changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications
- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect urine sample
- Collect pre-dose samples for safety laboratories
- Collect pre-dose IGF-1 and IGFBP-3 samples for LUM-201 subjects (collect IGF-1 and IGFBP-3 samples for rhGH-treated subjects along with other blood collections)

- Collect plasma PK samples for LUM-201 subjects only (approximately 60 minutes [$\pm$ 10 minutes] post-dose)
- Adjust dose to current body weight (Administer LUM-201 for LUM-201 subjects only)
- Dispense study drug
- Schedule Month 3 visit for 60 ± 5 days

11.5.2.3 Month 2 ($\pm$ 5 days) Remote Visit

This is a telephonic (remote) visit. The following procedures will be conducted.

- Record interval history
- Record AEs
- Record concomitant medications
- Inquire about study drug administration compliance and remind participants about importance of compliance

11.5.2.4 Month 3 Visit

Month 3 visit will be conducted after an overnight fast (beginning at 10 p.m.). The following procedures will be conducted.

- Conduct physical examination focused on changes from prior visit
- Record interval history
- Record AEs
- Record ECGs in triplicate 1 hour $\pm$ 10 minutes after LUM-201 administration for LUM-201 subjects, and prior to blood draws for rhGH subjects
- Record concomitant medications
- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect urine sample
- Collect pre-dose serum IGF-1 and IGFBP-3 samples for LUM-201 subjects (collect IGF-1 and IGFBP-3 samples for rhGH-treated subjects along with other blood collections)
- Collect pre-dose plasma PK samples for LUM-201 subjects only
- Collect samples for safety laboratories (pre-dose)
- Adjust drug dose to current body weight (Administer LUM-201 for LUM-201 subjects only)

- Dispense study drug
- Schedule next clinic visit for 90 ± 3 days

11.5.2.5 Month 4 (± 5 days) Remote Visit

This is a telephonic (remote) visit. The following procedures will be conducted.

- Record interval history
- Record AEs
- Record concomitant medications
- Inquire about study drug administration compliance and remind participants about importance of compliance

11.5.2.6 Month 5 (± 5 days) Remote Visit

This is a telephonic (remote) visit. The following procedures will be conducted.

- Record interval history
- Record AEs
- Record concomitant medications
- Inquire about study drug administration compliance and remind participants about importance of compliance

11.5.2.7 Month 6 Visit (Performed after an overnight [10 p.m.] fast)

The following procedures will be conducted.

- Conduct physical examination focusing on Tanner pubertal staging and changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications
- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect urine sample
- Collect pre-dose serum IGF-1 and IGFBP-3 samples for LUM-201 subjects (collect these samples for rhGH-treated subjects along with other blood collections)

- Collect serum GH samples pre-dose, 30, and 60 minutes (± 10 minutes for both) post-dose for LUM-201 subjects
- Collect plasma samples from LUM-201 randomized subjects for LUM-201 PK (blood samples taken at 0 [pre-dose], 30, and 60 [± 10 minutes for both] after LUM-201 administration)
- Collect samples for safety laboratories (pre-dose)
- Conduct X-ray to determine BA
- Record ECGs in triplicate 1 hour ± 10 minutes after LUM-201 administration for LUM-201 subjects, and prior to blood draws for rhGH subjects
- Adjust drug dose to current body weight (Administer LUM-201 for LUM-201 subjects only)
- Dispense study drug
- Schedule next clinic visit for 90 ± 3 days

11.5.2.8 Month 9 Visit

The following procedures will be conducted.

- Conduct physical examination focused on changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications
- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect pre-dose serum IGF-1 and IGFBP-3 samples for LUM-201 subjects (collect these samples for rhGH-treated subjects along with other blood collections)
- Adjust drug dose to current body weight (Administer LUM-201 for LUM-201 subjects only)
- Dispense study drug
- Schedule next clinic visit for 90 ± 3 days

11.5.2.9 Month 12 Visit (Performed after an overnight [10 p.m.] fast)

The following procedures will be conducted.

- Conduct physical examination focusing on Tanner pubertal staging and changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications

- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect urine sample
- Collect samples for safety laboratories (pre-dose)
- Collect pre-dose serum IGF-1 and IGFBP-3 samples for LUM-201 subjects (collect these samples for rhGH-treated subjects along with other blood collections)
- Collect pre-dose plasma PK samples for LUM-201 subjects only
- Collect serum GH samples pre-dose, 30, and 60 minutes (± 10 minutes for both) post-dose for LUM-201 subjects
- Record ECGs in triplicate 1 hour ± 10 minutes after LUM-201 administration for LUM-201 subjects, and prior to blood draws for rhGH subjects
- Determine 12-month AHV and if the criterion of 6.7 cm/yr is met continue treatment with LUM-201. If the AHV criterion is not met subject will be withdrawn from the study
- For subjects continuing treatment with LUM-201:
 - Adjust drug dose to current body weight and administer LUM-201
 - Dispense study drug
 - Schedule next clinic visit for 90 ± 3 days

11.5.2.10 Post-treatment Contact for Subjects Completing Study at Month 12 Visit (30 ± 5 days after Month 12 Visit, by telephone)

The following procedures will be conducted.

- Record interval history
- Record concomitant medications
- Record AEs
- Complete EOS Form

11.5.2.11 Month 15 Visit

The following procedures will be conducted.

- Conduct physical examination focused on changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications

- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect pre-dose serum IGF-1 and IGFBP-3 samples
- Adjust drug dose to current body weight and administer LUM-201
- Dispense study drug
- Schedule next clinic visit for 90 ± 3 days

11.5.2.12 Month 18 Visit

The following procedures will be conducted.

- Conduct physical examination focusing on Tanner pubertal staging and changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications
- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect samples for safety laboratories (pre-dose)
- Collect pre-dose serum IGF-1 and IGFBP-3 samples
- Record single ECG 1 hour $\pm$ 10 minutes after LUM-201 administration
- Conduct X-ray to determine BA
- Adjust drug dose to current body weight and administer LUM-201
- Dispense study drug
- Schedule next clinic visit for 90 ± 3 days

11.5.2.13 Month 21 Visit

The following procedures will be conducted.

- Conduct physical examination focused on changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications

- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect pre-dose serum IGF-1 and IGFBP-3 samples
- Adjust drug dose to current body weight and administer LUM-201
- Dispense study drug
- Schedule next clinic visit for 90 ± 3 days

11.5.2.14 Month 24 Visit

The following procedures will be conducted.

- Conduct physical examination focusing on Tanner pubertal staging and changes from prior visit
- Record interval history
- Record AEs
- Record concomitant medications
- Complete drug accountability/compliance check
- Record vital signs
- Record height and weight
- Collect samples for safety laboratories (pre-dose)
- Collect pre-dose serum IGF-1 and IGFBP-3 samples
- Administer LUM-201 (last dose of LUM-201)
- Record singular ECGs 1 hour $\pm$ 10 minutes after LUM-201 administration

11.5.2.15 Post-treatment Contact for Subjects Completing Month 24 Visit or Early Termination Subjects (30 ± 5 days after the last study visit, by telephone)

The following procedures will be conducted.

- Record interval history
- Record concomitant medications
- Record AEs
- Complete EOS Form

12.0 ADVERSE EVENT ASSESSMENT AND REPORTING

12.1 Definitions

12.1.1 Adverse Event (AE)

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal finding in laboratory tests or other diagnostic procedures), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug and from any route of administration, formulation, or dose, including an overdose.

Disease progression is not considered to be an AE or serious adverse event (SAE). If there are specific AEs that are always part of disease progression, these do not need to be reported as AEs or SAEs. Pre-existing medical conditions (other than natural progression of the disease being studied) judged by the Investigator or subject to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period will be reported as AEs or SAEs as appropriate.

An AE or SAE can also be a complication that occurs as a result of protocol mandated procedures.

12.1.2 Serious Adverse Events (SAEs)

An AE is considered serious, if in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE.

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

- Inpatient hospitalization or prolongation of an existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.

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

12.2 Adverse Event Reporting and Descriptions

Record new AEs from the start of study treatment until 30 days after the last dose of study treatment in the LUM-201-01 trial, or until the subject starts new GHD treatment, including new investigational treatment, whichever occurs earlier. Also record Screening procedure-related AEs that occur before the start of study treatment.

Record all AEs either observed by the Investigator or one of his or her medical collaborators, or reported by the subject spontaneously, or in response to the direct question below, in the AEs section of the subject's CRF/eCRF, in the source document, and if applicable, record on the SAE form. Whenever possible, the Investigator should group signs and symptoms (including laboratory tests or other results of diagnostic procedures) into a single diagnosis under a single term. For example, cough, rhinitis, and sneezing might be reported as "upper respiratory infection" or a pulmonary infiltrate, positive sputum culture, and fever might be reported as "pneumonia."

To optimize consistency of AE reporting across centers, ask the subject a standard, general, non-leading question to elicit any AEs (such as "Have you had any new symptoms, injuries, illnesses or started any new medications since your last visit?").

Death is an outcome of an SAE and usually not itself an SAE, unless it is death with no identifiable cause or event. In all other cases, record the cause of death as the SAE. Investigators will assess the status of previously reported, and occurrence of new AEs and SAEs at all subject evaluation time points during the study.

If an SAE occurs, based on the Investigator's judgment, then the appropriate therapy will be administered. Patients will be monitored closely as appropriate. Any SAE will be followed until the event resolves (i.e., when the event no longer meets any of the seriousness criteria), the condition stabilizes, or until the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the patient is lost to follow-up or withdraws consent). The MMs should be contacted within 24 hours of site knowledge of an SAE, including at minimum the subject number, the SAE term, the start date, and the preliminary attribution (related or not related).

12.2.1 Severity

Use the definitions found in the Common Terminology Criteria for Adverse Events (CTCAE) v5 (November 2017) for grading the severity (intensity) of AEs. The CTCAE v5 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE and provides additional guidance. Should a subject experience any AE not listed in the CTCAE v5, use the following grading system to assess severity:

- Grade 1 – Mild; asymptomatic or mild symptoms not impacting activities of daily living (ADLs); clinical or diagnostic observations only; intervention not indicated.

- Grade 2 – Moderate; minimal impact on ADLs, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL, such as attending school, activities, etc.
- Grade 3 – Severe or medically significant but not immediately life-threatening; substantial impact on ADLs, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death related to AE.

12.2.2 Relationship to Study Treatment (Suspected Adverse Reactions)

Assess all AEs/SAEs for relationship to study treatment or if applicable, to study procedure.

If an AE/SAE occurs before the first dose of study drug, report it only if it is considered related to a study-specific procedure (e.g., bleeding or injection site reaction). Those events will be recorded in the study database but will not be part of the treatment emergent AE analysis.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the general guideline shown below. Multi-drug regimens should have a causality assessment of each component to aid in analysis.

Related (Suspected Adverse Reaction)

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE such as a plausible temporal relationship between the onset of the AE and administration of the drug; and/or the AE follows a known pattern of response to the drug; and/or the AE abates or resolves upon discontinuation of the drug or dose reduction and, if applicable, reappears upon re-challenge. Further examples of the type of evidence that would suggest a causal relationship between the drug and the AE:

A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.

One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., acute myocardial infarction in a child).

An aggregate analysis of specific events observed in a clinical study (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study

population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Not Related
(Not Suspected)

AEs that do not meet the definition above.

12.2.3 Expected Adverse Events

Expected AEs include injection site reactions with rhGH, increased appetite, and joint pain. All expected AEs (if untoward reactions) should be reported as AEs.

Deviations from expected results for subject age that are deemed as clinically significant by the PI should be recorded as AEs.

12.2.4 Pregnancy and Abortion

Although it is unlikely, in the event of pregnancy, subjects will be discontinued from treatment but followed through to completion/termination of the pregnancy.

12.3 Reporting Requirements for Serious Adverse Events

All SAEs regardless of causality will be reported by the Investigator to the MM within 24 hours, and through the 30-day period after the last dose of study treatment. Deaths and SAEs occurring after the 30-day safety follow-up period AND considered related to study treatment or study procedures must also be reported.

Report all SAEs (initial and follow-up information) on an SAE form and send the form to the Sponsor or designee, including both MMs, within 24 hours of the discovery of the event or information (see below). The Sponsor or designee may request follow-up and other additional information from the Investigator (e.g., hospital admission or discharge notes, laboratory results). SAEs will be followed up through completion or treatment termination.

Drug Safety Contact Information	
Telephone Number	
[REDACTED]	
Fax Number	
[REDACTED]	
Email	
Drug Safety Inbox	[REDACTED]

Report all deaths with the primary cause of death as the SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, report the primary cause of death on the autopsy report as the SAE term. Forward autopsy and postmortem reports to the Sponsor or designee, as outlined above.

If study treatment is discontinued, temporarily suspended or dose reduced because of an SAE, include this information in the SAE report.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (i.e., not defined as expected in the current IB, clinical study protocol, or approved labeling for marketed drugs). In this case, the Sponsor or designee will report to the relevant regulatory authorities and forward a formal notification describing the SUSAR to Investigators, according to regulatory requirements. Each Investigator must then notify his or her IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with IRB/IEC policy.

12.4 Follow-up for Adverse Events

Follow all AEs and SAEs that are encountered during the protocol-specified AE reporting period (1) to resolution, (2) until the Investigator assesses the subject as stable and the event is following a clinically expected outcome, or (3) until the subject is lost to follow-up or withdraws consent.

13.0 STATISTICS

13.1 Statistical Hypotheses

The primary endpoint of the study is confirmation of the ability for the PEM test to select for LUM-201 treatment response. Positive growth response (“response”) is defined as ≥ 6.85 cm/yr AHV from Baseline (Day 1 visit) to Month 6 visit. Treatment response to determine the primary endpoint will be based upon annualized AHVs from the combined cohort of all subjects treated with LUM-201. It is assumed that the PEM test will improve the response rate from approximately 50% to 70%.

Although AHV will also be reported after 6 months, the primary clinical endpoint of the study is the comparison of the AHV at 6 months on all three LUM-201 doses to that of rhGH at 34 $\mu\text{g}/\text{day}$, and to select a pediatric dose of LUM-201 for use in future studies.

Key secondary endpoints of the study include:

- Assessment of reproducibility of the PEM positive classification in subjects who are undergoing a PEM test at Screening visit and Day 1 visit.

13.2 Sample Size Calculation

In the Merck 020 study of children with GHD (Table 2, Table 3) data from the 24 subjects in the 0.8 mg/kg/day dose group was used to define a cut-point for the PEM test (Appendix 3). Based on the results of the Merck 020 study, approximately 70% of subjects defined as PEM positive (GH ≥ 5 ng/mL and IGF-1 > 30 ng/mL [> 3.92 nmol/L]) had a positive growth response (“responders” defined as ≥ 6.85 cm/yr), while approximately 50% of subjects who were PEM negative had a positive growth response.

Confirmation of the ability for the PEM test to select for LUM-201 treatment response (“responders”) will be based on a total of 60 LUM-201 subjects, 20 in each of three dose levels. The null hypothesis is a responder proportion of 50%, with the alternative hypothesis of 70%. This will be based on the proportion of responders across all three dose levels. This sample size will provide $>85\%$ power for a one-sided test of this hypothesis with alpha of 0.025.

In addition, 20 subjects will be randomized to daily rhGH treatment. The resulting mean and variance in the height velocities from each LUM-201 dose level and daily rhGH will be used to guide the design for a Phase 3 study.

To assess reproducibility of the PEM positive classification, subjects who have tested PEM positive at Screening visit will have the PEM test repeated at Day 1 visit. The lower limit of the 95th confidence interval of positive agreement rate is expected to be greater than 80%.

Reproducibility of 80% is believed to be appropriate due to the intended purpose of the PEM classification. A compound with a similar mechanism of action, macimorelin, has been approved as a single dose diagnostic for growth hormone deficiency in adults. It has demonstrated an approximate 90% reproducibility. That drug is intended to diagnose adults, with a single test, growth hormone deficiency in a large population and such a level of reproducibility is important. The intended use of the PEM classification is different. It is intended to determine the potential utility of a particular therapeutic approach within a population that has already been diagnosed with PGHD. In this much more limited population, essentially all individuals will be treated and no individuals without the appropriate diagnosis will be exposed to treatment. Any increased imprecision introduced with a reproducibility level of 80% as opposed to 90% is clinically acceptable as any clinical consequences will be minimal. If individuals are incorrectly classified as PEM negative, they will still be eligible for established standard of care treatment. Any individuals incorrectly classified as PEM positive can be readily identified by clinical observation if they fail to respond to therapy with LUM-201 and switched to standard of care therapy without clinical detriment as the window to start growth hormone therapy and achieve catch-up growth is wide in prepubertal children.

13.3 Statistical Methods

PEM Classification - Treatment Response Rate

Treatment response is defined as $HV \geq 6.85$ cm/yr. Counts, percentages and confidence intervals will be presented for all LUM-201 treated subjects and by each treatment group to provide an estimate of the treatment response rate for these PEM positive subjects. The overall PEM response rate will be tested against the null of 0.5 with a Chi-square statistic.

PEM Reproducibility

Subjects having a positive first PEM test will have a second PEM test. The positive agreement rate for the two test results will be calculated along with the 95th confidence interval.

Dose Finding Objective – Height Velocity

Descriptive statistics will be compiled, by dose group, for 6-month AHV, change in HT-SDS, change in HV-SDS, change in weight, weight SDS, BMI, and BMI SDS. An analysis of covariance (ANCOVA) will be performed on the three LUM-201 dosing arms with 6-month AHV as the dependent variable and age and treatment arm as independent variables. In addition, peak GH response to LUM-201 PEM stimulation test, Baseline (Screening visit) HT-SDS, Baseline IGF-1 SDS (computed as the average of the pre-dose samples collected at Screening visit and Day 1 visit) will be included as covariates. The least square means from this ANCOVA will be used to estimate the annual HV for each treatment group. The same analyses will be done using the 12-month AHV.

13.4 General Considerations

Summaries and descriptive statistics will be provided by treatment group. Summaries of all AEs, SAEs, and SUSARs will be compiled for individual subjects as well as by treatment groups. AEs will be classified as to severity and relationship to drug.

Although an otherwise open-label study, the MMs will be blinded to treatment allocation data as it accrues. This blinding is to insure unbiased decisions regarding safety data interpretation and retention of subjects by the MMs.

The gender, age, height, weight, treatment group, and BA of subjects entering puberty by Month 12 visit will be described. Entrance into puberty is defined as Tanner Stage 2 breast development in girls and testicular volumes ≥ 4.0 mL in boys.

The AHV at the time point t_2 is defined as follows:

$$\left(\frac{h_2 - h_1}{t_2 - t_1} \right) 365.25,$$

where h_2 and h_1 are the heights (cm) measured at t_2 and t_1 (in days), respectively. Of note, h_1 is the height measured on Day 1 visit, prior to commencement of the randomized study drug treatment.

Standard Deviation Scores for height, weight, and BMI will be computed using the Percentile Data Files from the WHO Child Growth Standards available from the World Health Organization (WHO) website (28, 29).

Birth Weight percentile for gestational age will be computed using the percentile tables from WHO Int. (32).

Standard Deviation Scores for IGF-1 will be computed using reference standards for healthy United States (US) children available from the central reference laboratory.

Mean values and change from Screening visit values will be compiled, by treatment group, for all clinical laboratory tests. Shift tables may be employed to document treatment related changes.

The PI will interpret the Screening portion BA to determine eligibility for randomization, based on the BA of the proximal and distal phalanges, as opposed to the metacarpals, carpals and distal forearm. A central BA reader will make the final determination on BA eligibility. Where the BA was performed prior to the Screening visit, one month will be added to the BA for every month elapsed between date of the BA and the Screening visit (maximum of 9 months). For analytical purposes, all BA results will be determined by a central reader using the Greulich and Pyle method (30). Baseline (prior to commencement of randomized treatment) BA and change from Screening visit to Month 6 visit will be compiled for each treatment group. The ratios of BA to chronological age (BA/CA) at Screening visit and Month 6 visit, and the change in the ratio between Screening visit and Month 18 visit will be described.

Target HT-SDS will be computed from the observed maternal and paternal heights, their height SDS as determined from the WHO Child Growth Standards (29), and the calculation method of Hermanussen and Cole (31).

Missing and Spurious Data

For laboratory assays, values below the lower limit of quantification will be treated as 0 for statistical summaries.

For height related endpoints up to 12 months, missing results will be imputed by carrying the last non-missing height value forward and using this value to derive HV and HT-SDS at the analysis time points. This is a conservative estimate of HV and change in HT-SDS, as it assumes no further change in HT-SDS after the last measurement. For the summary and analysis of data after 12 months, subjects who do not continue beyond month 12 will simply be excluded, and not be considered missing. Data collected from subjects who are treated after month 12 will then be carried forward if there are missing visits from month 12 to 24.

In addition, multiple imputation using SAS PROC MI will be used. The imputation will be by treatment group. The imputation model will include the randomization stratification factors and the terms used in the ANCOVA model. A total of 100 imputed datasets will be created, and the ANCOVA model specified for the primary analysis will be used to calculate the least squares

means and 95% confidence interval (CI). The results will then be combined using SAS PROC MIANALYZE.

13.5 Analysis Populations

13.5.1 Intent-to-treat (Full Analysis Set)

The Full Analysis Set includes all subjects enrolled in the Treatment portion of the study who underwent randomization and have received at least one dose of study treatment.

13.5.2 Per Protocol

The 6 month Per Protocol Population includes all randomized subjects who complete Month 6 and have not missed more than 20% of scheduled doses over the 6-month Treatment portion and who do not have any significant protocol deviations. The Per Protocol Population will be used for the primary evaluation of treatment response.

The 12 month Per Protocol Population includes all randomized subjects who complete Month 12 and have not missed more than 20% of scheduled doses over the 12-month Treatment portion and who do not have any significant protocol deviations. The Per Protocol Population will be used for the primary evaluation of treatment response.

The 24 month Per Protocol Population includes all randomized subjects who complete Month 24 and have not missed more than 20% of scheduled doses over the 24-month Treatment portion and who do not have any significant protocol deviations. The Per Protocol Population will be used for the primary evaluation of treatment response.

13.5.3 Safety Population

The Safety Population is defined as all subjects enrolled to either the Screening or Treatment portions of the study and having at least one dose of study drug.

13.5.4 PK/PD Population

The PK/PD population is defined as all subjects who omitted no scheduled study drug dose in the three days prior to the PK/PD blood sample collections.

13.6 Demographics and Baseline Characteristics

Demographic and Baseline Characteristics include:

- Age
- Gender
- Race/Ethnicity
- Birth weight and gestational age

- Birth weight percentile for gestational age
- Prior endocrine test results (adrenal and/or thyroid function)
- Historical (standard of care) GH stimulation test results
- Screening BA result (by PI and by central reader)
- Maternal and paternal heights
- Target HT-SDS (computed from maternal and paternal heights)
- PEM test results
- Height and HT-SDS
- Weight and weight SDS
- BMI and BMI SDS
- Tanner Stage
- Baseline IGF-1, IGF-1 SDS, and IGFBP-3 (computed as the average of the pre-dose samples collected at Screening visit and Day 1 visit)

13.7 Additional Analyses

The data from Month 6 visit, Month 9 visit, and Month 12 visit will be summarized to allow for assessments of growth response to 12 months of treatment.

13.7.1 Safety and Tolerability

The safety and tolerability endpoints include:

- AEs
- SAEs
- SUSARs
- Clinical Laboratory Safety Events
- ECGs

13.7.2 PK/PD

- PK: plasma LUM-201 concentrations
- PD: serum GH, IGF-1, IGF-1 SDS, and IGFBP-3

13.7.3 Sample Size Estimation for Phase 3

AHV and CV for the rhGH treatment arm and LUM-201 treatment arms selected for Phase 3 will be used to determine the sample size for a Phase 3 study.

13.7.4 Other Analyses

Exploratory, post hoc analyses will be performed to determine if IGF-1 and IGFBP-3 concentrations and SDS changes from Baseline are correlated to dose-specific 6-month HV and 12-month AHV.

IGF-1, IGF-1 SDS and IGFBP3 responses to LUM-201 and rhGH will be compared.

13.8 Retention of Data

The Investigator must ensure that clinical study records are retained according to national regulations, as documented in the clinical trial agreement entered into with the Sponsor in connection with this study. The Investigator will maintain all records and documents pertaining to the study for a period of at least 2 years after Food and Drug Administration (FDA) approval of the drug or at least 2 years after withdrawal of the investigational new drug (IND) under which this study was conducted, whichever is longer. In countries outside the US, records must be kept for the period of time required by the US FDA as a minimum, and record retention should also comply with the local country regulatory requirements, if longer retention times are required than in the US. For example, study data for participants from New Zealand will be stored for 10 years after the youngest participant turns 16. Mandatory documentation includes copies of study protocols and amendments, financial disclosures, each FDA Form 1572, IRB/IEC approval letters, signed informed consent form (ICFs), drug accountability records, SAE forms transmitted to the Sponsor, subject files (source documentation) that substantiate entries in case report form/electronic case report form (CRF/eCRFs), all relevant correspondence, and other documents pertaining to the conduct of the study. These records must remain in each subject's study file and be available for verification by study monitors at any time.

The Investigator must inform the Sponsor immediately if any documents are to be destroyed, transferred to a different facility, or transferred to a different owner. The Sponsor should be given the option of collecting the documents before destruction.

13.9 Interim Analysis

An interim analysis of all available data will be conducted after 40 subjects have completed Month 6. The purpose of this interim analysis is to evaluate the safety and continued growth response in the 6 to 12-month period.

14.0 STUDY DURATION AND TERMINATION

The expected study duration is through completion of Month 24 or withdrawal of consent. The study started in 2020.

15.0 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

15.1 Compliance Statement

The study will be conducted in accordance with the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, principles enunciated in the Declaration of Helsinki, and all human clinical research regulations in countries where the study is conducted.

15.2 Informed Consent

The ICFs used for the study must comply with the Declaration of Helsinki, federal regulations US 21 CFR Part 50, and ICH GCP guidelines, and any other local regulations. The Investigator, or a person delegated by the Investigator, must explain the medical aspects of the study, including the nature of the study and the treatment, orally and in writing, in such a manner that the subject is aware of potential benefits and risks. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects, or a legal guardian if the subject is unable to, must give informed consent in writing.

The informed consent process must be conducted, documented in the source document (including the date), and the form must be signed, before the subject undergoes any study-specific procedures.

15.3 Institutional Review Board or Independent Ethics Committee

The Investigator must submit the protocol, protocol amendments, and the ICF for the proposed study, along with any other documents required by the center's IRB/IEC to the center's duly constituted IRB/IEC for review and approval. The Investigator must also ensure that the IRB/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of each IRB/IEC approval letter must be forwarded to the Sponsor or its authorized representative before the study is implemented. Documentation of subsequent reviews of the study must also be forwarded to the Sponsor or its authorized representative.

16.0 ADMINISTRATIVE PROCEDURES

16.1 Sponsor Responsibilities

Lumos Pharma, Inc. reserves the right to terminate the study and remove all study materials from a study center at any time. The Sponsor and the Investigators will assure that adequate consideration is given to the protection of the subjects' interests. Specific circumstances that may precipitate such termination are:

- Request by Health Authority to terminate the study.
- Unsatisfactory subject enrollment with regard to quality or quantity.
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects, maintain adequate study records or inaccurate, incomplete or late data recording on a recurrent basis.

- The incidence or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment.

16.1.1 Study Supplies

The Sponsor will supply sufficient quantities of the following materials to each clinical center:

- LUM-201 and rhGH as described in Section 9.0.
- IB for LUM-201.
- Approved prescribing information for Norditropin[®] (25).
- CRFs or data collection tools (e.g., laboratory kits, ECG machines).

16.1.2 Investigator Training

All study centers will have a center-specific study initiation meeting to ensure the center staff understands the protocol, study requirements, and data capture processes. This training will take place before the first subject is enrolled. Each study center will be provided with information regarding GCP and regulations specific to the conduct of clinical studies. Each center is responsible for ensuring that new team members are adequately trained, and the training is documented. Training may be conducted remotely.

16.1.3 Ongoing Communication of Safety Information During the Study

The Sponsor will provide the Investigator with documentation of SAEs, from this study and other studies, that are related to LUM-201 and unexpected (Section 12.3), as appropriate. The Investigator must forward this documentation to the IRB/IEC, as described in Section 12.3.

The Sponsor will also notify the Investigator about any other significant safety findings that could alter the safety profile of the Investigational Medicinal Product (IMP) from what is described in the protocol and significantly affect the safety of subjects, affect the conduct of the study, or alter the IRB/IEC's opinion about continuation of the study.

16.1.4 Study Monitoring

Representatives of the Sponsor will monitor the study. Routine monitoring visits will be conducted to:

- Assure compliance with the study protocol and appropriate regulations.
- Verify that (1) the informed consent process was conducted before initiation of any study-specific procedures (i.e., performed solely for the purpose of determining eligibility for the study) and before provision of study treatment, and (2) this process is adequately documented.

- Verify that the protocol, protocol amendments, and safety information are submitted to the IRB/IECs and approved by the IRB/IECs in a timely manner.
- Review the CRF/eCRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Verify that study treatments are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of LUM-201 and Norditropin® at the study centers are controlled and documented adequately.
- Verify that the Investigator and study center personnel remain adequately qualified throughout the study.
- Verify that the research facilities, including laboratories and equipment, are maintained adequately to conduct the study safely and properly.

16.1.5 Study Auditing and Inspecting

The Sponsor may audit the study conduct, compliance with the protocol and accuracy of the data in one or more centers.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, and inspections by the Sponsor, IRB/IEC, government regulatory bodies, and Sponsor Quality Assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from the Sponsor.

16.2 Investigator Responsibilities

16.2.1 Subject Screening Log

The Investigator must keep a record that lists all subjects who signed an informed consent and the reason for non-inclusion if they were not ultimately randomized or treated.

16.2.2 LUM-201 Accountability

An initial supply of LUM-201 will be shipped to each study center's pharmacy when all the initiation documents, including IRB/IEC approvals, IRB/IEC approved ICF, and business agreements, have been received and reviewed by the Sponsor and upon activation of the study center by the Sponsor or its authorized representative. Thereafter, the study pharmacist or authorized site personnel is responsible for ensuring adequate resupply of study drug and ancillary materials is available.

Keep the IMP in a locked, limited-access room. The study treatment must not be used outside the context of the protocol. Under no circumstances should the Investigator or other study center personnel supply IMP to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from the Sponsor.

The monitor will regularly review and verify all IMP supplies and associated documentation.

Maintain an accurate accounting of the study treatments. These records must show dates, lot numbers, quantities received, dispensed and returned, and must be available for monitoring by the Sponsor. The Investigator will ensure that any used and unused IMP and other study material is destroyed or returned to the Sponsor on completion of the study. If the IMP is destroyed at the study center, there should be documentation of destruction at the study center. The Sponsor and/or their representatives will verify final drug accountability. IMP accountability records must be maintained and readily available for inspection by representatives of the Sponsor and are open to inspections by regulatory authorities at any time.

16.2.3 Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the Sponsor or their representatives. Clearly record all requested study data on the CRF/eCRF and other study forms as required. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study personnel responsibility/signature log may enter or correct data in the CRF/eCRF. Incomplete or inconsistent data on the CRF/eCRFs will result in data queries that require resolution by the Investigator or designee.

For returning results and incidental findings such as laboratory results received at site, the PI and site staff will inform the participants and arrange for further follow up or counselling as deemed necessary. To ensure confidentiality of the participant's identity, any data or samples of the participant's sent to the Sponsor will be coded with a unique number. The PI will keep a list linking the codes to the participant's name, so that they can be identified by their coded data if needed (e.g., emergency reasons). This list will be kept at site in a secure location and will not be shared with the Sponsor.

The Investigator must assure subject anonymity and protection of identities from unauthorized parties. On CRF/eCRFs or other documents or subject records provided to the Sponsor, identify subjects by code (subject number, initials, date of birth, where allowed by local regulations) and not by names. The PI should maintain documents not for submission to the Sponsor (e.g., subjects' signed informed consent) in strict confidence.

16.2.4 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which CRF/eCRFs for each subject are based. They are to be separate and distinct from CRF/eCRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's CRF/eCRF is appropriate. These records should include detailed notes on:

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). Record the date of informed consent in the source documentation.

- The subject's medical history before participation in the study.
- The subject's basic identifying information, such as demographics, that links the subject's source documents with the CRF/eCRFs.
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
- The subject's exposure to study treatment.
- All AEs.
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage).
- All relevant observations and data on the condition of the subject throughout the study.

16.2.5 Tissue and Blood Sample Collection/Storage

Tissue and blood components samples which are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for additional PK or PD analyses.

No whole genome or other genetics testing will be performed on any of the residual samples.

16.3 Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating study centers upon request.

16.4 Study Administrative Letters and Protocol Amendments

The Sponsor may issue Study Administrative Letters (1) to clarify certain statements or correct obvious errors/typos/inconsistencies in the study protocol, (2) to change the logistical or administrative aspects of the study, such as study personnel or contact information, or (3) to instruct Investigators of DSMB safety decisions for immediate implementation for safety reasons (Section 6.11).

For all other changes, the Sponsor will initiate any change to the protocol in a protocol amendment document. The study center will submit the amendment to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject, information on the increased risk must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the study.

The Investigator must obtain IRB/IEC approval before any protocol amendment can be implemented, except for administrative changes or changes necessary to eliminate an immediate risk to study subjects, as outlined above.

17.0 POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The Sponsor encourages the scientific publication of data from clinical research studies. However, Investigators may not present or publish partial or complete study results individually without review by the Sponsor. The PIs and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. The Sponsor must review and comment on all proposed publications before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the Sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all Investigators and Sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

Qualification of authorship will follow the requirements of the International Committee of Medical Journal Editors (www.icmje.org). In most cases, the PIs at the centers with the highest participation in the study shall be listed as lead authors on manuscripts and reports of study results. In addition, other than clinical pharmacology studies in healthy volunteers or Phase 1 studies, all clinical studies must be registered with ClinicalTrials.gov.

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19.0 APPENDICES

19.1 Appendix 1: Birth weights (grams) for the 3rd percentile gestational age^a

Gestational age weeks	3 rd percentile birth weight
35	1870
36	2020
37	2167
38	2308
39	2440
40	2562
41	2671

^a WHO Int, et al. 2022 ³²

19.2 Appendix 2: Concomitant Medications

LUM-201 is primarily metabolized by CYP3A/4 and has been shown *in vitro* to induce CYP3A4, CYP2C8, CYP2C9 and CYP2C19, under conditions that may be clinically relevant. Thus, potential study subjects receiving medications that are primarily metabolized by either CYP3A/4, CYP2C8, CYP2C9 or CYP2C19 (< 5 % contribution by other isoforms) or are strong inducers or moderate or strong inhibitors of CYP3A/4 should not be screened. Subjects commencing these medications during the study may be withdrawn at the discretion of the PI and the MM.

Select examples of drugs and other items interacting with CYP3A/4 include:

Midazolam
Triazolam
Clarithromycin
Itraconazole
Ketoconazole
Phenytoin
Rifampin
Carbamazepine
Guanfacine hydrochloride
Protease inhibitors used as anti-viral agents
Grapefruit and grapefruit juice should also be avoided

In vitro experiments also indicate LUM-201 is substrate of P-gp and inhibits P-gp and MATE1, under conditions that may be clinically relevant. Thus, potential study subjects receiving medications that are strong inhibitors of P-gp or are potent substrates of P-gp or MATE1 should not be screened. Subjects commencing these medications during the study may be withdrawn at the discretion of the PI and the MM. Select examples of these items include:

P-gp substrate prescribed in children: fexofenadine (Allegra®).
P-gp inhibitor: clarithromycin.
MATE1 substrate: metformin.

The PI should consult with the MM regarding concomitant medication use while on study. Study participants will be given a letter they should share with their primary physician to inform them of study participation and concomitant medication restrictions.

19.3 Appendix 3: Rationale for Predictive Enrichment Marker (PEM) Test

A test of a drug's mechanism of action may provide information on longer-term treatment responses. When successful, these test results are termed predictive enrichment markers (PEM)^a.

LUM-201 is an oral agonist of the GH secretagogue receptor (GHSR1) that augments endogenous GH pulsatility. The GH peak in response to a single dose of LUM-201 (0.8 mg/kg) was evaluated as one aspect of a PEM using data from a clinical study of naïve-to-treatment children with GHD who were treated with LUM-201 or rhGH for 6 months. The ability of GH peak to predict 6-month HVs was evaluated by receiver operating characteristic (ROC) analyses. ROC is a 2×2 subject-level analysis that segregates subjects with positive tests that respond (true positive [TP]) or don't respond (false positive [FP]), and those with a negative test who respond (false negative [FN]) or don't respond (true negative [TN]). The number of TP, FP, FN, and TN were computed for each level of peak GH to identify the optimal GH cut-off value to maximize true predictions and minimize false predictions.

Five main ROC parameters were analyzed: true and false positive rates, predictive accuracy, critical success index, and positive predictive values. All analyses suggested a peak GH response to a single 0.8 mg/kg LUM-201 dose of ≥ 5 ng/mL as an optimal value for the main ROC parameters analyzed. A process of iterative filtering was then used to determine if baseline IGF-1 could enhance predictions as a second aspect of the PEM test. Among subjects with peak GH ≥ 5 ng/mL, the HV for LUM-201 increased and HV for rhGH decreased as baseline IGF-1 value approached 30 ng/mL (> 3.92 nmol/L). The use of GH peak in response to a single dose of LUM-201 combined with the baseline IGF-1 value can act as a PEM strategy intended to enrich a subject population for LUM-201 responders and exclude those better served with rhGH.

The PEM stimulation test consists of a one-time oral administration of 0.8 mg/kg LUM-201 dose. Blood samples for the test are collected pre-dose (time 0), 30 and 60 minutes post-dose. A baseline IGF-1 level is also drawn. Based on the ROC analysis described above, the combination of both baseline IGF-1 concentration of > 30 ng/mL (> 3.92 nmol/L) and peak GH response of ≥ 5 ng/mL meet the requirements to classify a subject as PEM positive and satisfy inclusion criteria for the Treatment portion of the study.

^a March 2019 FDA Guidance: Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products Guidance for Industry
<https://www.fda.gov/media/121320/download>

19.4 Appendix 4: Specialty Laboratory Testing (Serum GH and Plasma LUM-201 samples collected for subjects randomized to LUM-201 arms)

Matrix/ Analyte	Screening Visit		Day 1 (Baseline)		Month 1		Month 3		Month 6	
	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times
Serum/ IGF-1	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)
Serum/ GH	3	0, 30, 60 min	3	0, 30, 60 min	0	–	0	–	3	0, 30, 60 min
Serum/ IGFBP-3	0	–	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)
Plasma/ LUM-201	2	30, 60 min	0	–	1	30 min	1	Pre-dose (0 min)	3	0, 30, 60 min

Matrix/ Analyte	Month 9		Month 12		Month 15		Month 18		Month 21		Month 24	
	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times
Serum/ IGF-1	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)
Serum/ GH	0	–	3	0, 30, 60 min	0	–	0	–	0	–	0	–
Serum/ IGFBP-3	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)	1	Pre-dose (0 min)
Plasma/ LUM-201	0	–	1	Pre-dose (0 min)	0	–	0	–	0	–	0	–

19.5 Appendix 5: Clinical Analytes

Hematology	Serum Chemistry	Urinalysis	Other Tests
- Complete blood count (CBC)	- Alkaline phosphatase	- Dipstick	Thyroid function tests
- Hemoglobin	- ALT	- Specific gravity	- T3
- Hematocrit	- AST	- pH	- T4
- RBC counts	- Bilirubin	- Protein	- TSH
- RBC indices	- GGT	- Glucose	- HbA1c
- WBC counts	- Glucose	- Ketones	- Turner Syndrome*
- WBC differential	- LDL	- Leukocyte esterase	
- Platelets	- HDL	- Blood	
	- Cholesterol	- Pregnancy test (if applicable)	
	- Triglycerides		
	- Insulin		
	- Sodium		
	- Potassium		
	- Chloride		
	- Calcium		
	- Phosphate		
	- CO2		
	- BUN		
	- Creatinine		
	- Total protein		
	- Albumin		
	- Globulin		

* As needed

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; HbA1c = hemoglobin A1c; CO2 = bicarbonate; HDL = high density lipoprotein; LDL = low density lipoprotein; RBC = red blood cell; T3 = triiodothyronine; T4 = free thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell

19.6 Appendix 6: Growth Charts

19.6.1 BMI 5th Percentile^{a,b}

5th Percentile BMI Chart

Gender	Age (months)	5th percentile	Gender	Age (months)	5th percentile
Male	36	13.7	Female	36	13.5
Male	37	13.7	Female	37	13.4
Male	38	13.7	Female	38	13.4
Male	39	13.6	Female	39	13.4
Male	40	13.6	Female	40	13.4
Male	41	13.6	Female	41	13.3
Male	42	13.6	Female	42	13.3
Male	43	13.5	Female	43	13.3
Male	44	13.5	Female	44	13.3
Male	45	13.5	Female	45	13.3
Male	46	13.5	Female	46	13.2
Male	47	13.5	Female	47	13.2
Male	48	13.4	Female	48	13.2
Male	49	13.4	Female	49	13.2
Male	50	13.4	Female	50	13.2
Male	51	13.4	Female	51	13.2
Male	52	13.4	Female	52	13.1
Male	53	13.3	Female	53	13.1
Male	54	13.3	Female	54	13.1
Male	55	13.3	Female	55	13.1
Male	56	13.3	Female	56	13.1
Male	57	13.3	Female	57	13.1
Male	58	13.3	Female	58	13.1
Male	59	13.3	Female	59	13.1
Male	60	13.3	Female	60	13.1
Male	61	13.384	Female	61	13.133
Male	62	13.38	Female	62	13.126
Male	63	13.377	Female	63	13.12
Male	64	13.374	Female	64	13.114
Male	65	13.373	Female	65	13.109
Male	66	13.373	Female	66	13.104
Male	67	13.374	Female	67	13.1
Male	68	13.376	Female	68	13.097
Male	69	13.379	Female	69	13.094
Male	70	13.382	Female	70	13.091
Male	71	13.387	Female	71	13.09
Male	72	13.393	Female	72	13.089
Male	73	13.399	Female	73	13.088
Male	74	13.406	Female	74	13.088
Male	75	13.413	Female	75	13.089
Male	76	13.422	Female	76	13.09
Male	77	13.43	Female	77	13.093
Male	78	13.439	Female	78	13.096
Male	79	13.449	Female	79	13.099

Male	80	13.459	Female	80	13.104
Male	81	13.47	Female	81	13.11
Male	82	13.481	Female	82	13.116
Male	83	13.492	Female	83	13.123
Male	84	13.504	Female	84	13.131
Male	85	13.516	Female	85	13.14
Male	86	13.528	Female	86	13.15
Male	87	13.54	Female	87	13.16
Male	88	13.553	Female	88	13.172
Male	89	13.567	Female	89	13.184
Male	90	13.58	Female	90	13.197
Male	91	13.594	Female	91	13.211
Male	92	13.608	Female	92	13.226
Male	93	13.622	Female	93	13.241
Male	94	13.636	Female	94	13.257
Male	95	13.651	Female	95	13.275
Male	96	13.666	Female	96	13.293
Male	97	13.681	Female	97	13.312
Male	98	13.697	Female	98	13.331
Male	99	13.712	Female	99	13.352
Male	100	13.728	Female	100	13.373
Male	101	13.745	Female	101	13.395
Male	102	13.761	Female	102	13.418
Male	103	13.778	Female	103	13.441
Male	104	13.795	Female	104	13.465
Male	105	13.812	Female	105	13.489
Male	106	13.83	Female	106	13.514
Male	107	13.848	Female	107	13.54
Male	108	13.866	Female	108	13.566
Male	109	13.885	Female	109	13.592
Male	110	13.904	Female	110	13.62
Male	111	13.924	Female	111	13.647
Male	112	13.944	Female	112	13.675
Male	113	13.965	Female	113	13.704
Male	114	13.986	Female	114	13.733
Male	115	14.008	Female	115	13.762
Male	116	14.031	Female	116	13.792
Male	117	14.054	Female	117	13.823
Male	118	14.078	Female	118	13.854
Male	119	14.102	Female	119	13.886
Male	120	14.127	Female	120	13.919
Male	121	14.152	Female	121	13.952
Male	122	14.178	Female	122	13.986
Male	123	14.205	Female	123	14.02
Male	124	14.232	Female	124	14.055
Male	125	14.259	Female	125	14.092
Male	126	14.287	Female	126	14.128

Male	127	14.316	Female	127	14.165
Male	128	14.346	Female	128	14.204
Male	129	14.376	Female	129	14.242
Male	130	14.406	Female	130	14.282
Male	131	14.437	Female	131	14.322
Male	132	14.469	Female	132	14.363
Male	133	14.501	Female	133	14.405
Male	134	14.533	Female	134	14.447
Male	135	14.566	Female	135	14.49
Male	136	14.6	Female	136	14.533
Male	137	14.634	Female	137	14.578
Male	138	14.669	Female	138	14.623
Male	139	14.704	Female	139	14.668
Male	140	14.741	Female	140	14.714
Male	141	14.777	Female	141	14.76
Male	142	14.814	Female	142	14.807
Male	143	14.852	Female	143	14.855
Male	144	14.891	Female	144	14.902
Male	145	14.93	Female	145	14.95
Male	146	14.97	Female	146	14.999
Male	147	15.01	Female	147	15.047
Male	148	15.051	Female	148	15.096
Male	149	15.093	Female	149	15.145
Male	150	15.136	Female	150	15.193

* PI should contact MM if a child with HT > 121.5 cm is to be screened

^a WHO Int, et al. 2021²⁸

^b WHO Int, et al. 2022²⁹

19.6.2 95th Percentile BMI Chart^{a,b}

95th Percentile BMI Chart					
Gender	Age (months)	95th percentile	Gender	Age (months)	95th percentile
Male	36	17.8	Female	36	17.8
Male	37	17.8	Female	37	17.8
Male	38	17.8	Female	38	17.8
Male	39	17.7	Female	39	17.8
Male	40	17.7	Female	40	17.8
Male	41	17.7	Female	41	17.8
Male	42	17.7	Female	42	17.8
Male	43	17.7	Female	43	17.8
Male	44	17.7	Female	44	17.8
Male	45	17.6	Female	45	17.8
Male	46	17.6	Female	46	17.8
Male	47	17.6	Female	47	17.9
Male	48	17.6	Female	48	17.9
Male	49	17.6	Female	49	17.9
Male	50	17.6	Female	50	17.9
Male	51	17.6	Female	51	17.9
Male	52	17.6	Female	52	17.9
Male	53	17.6	Female	53	17.9
Male	54	17.6	Female	54	18
Male	55	17.6	Female	55	18
Male	56	17.6	Female	56	18
Male	57	17.6	Female	57	18
Male	58	17.6	Female	58	18
Male	59	17.7	Female	59	18.1
Male	60	17.7	Female	60	18.1
Male	61	17.656	Female	61	18.103
Male	62	17.665	Female	62	18.124
Male	63	17.677	Female	63	18.145
Male	64	17.689	Female	64	18.167
Male	65	17.704	Female	65	18.189
Male	66	17.721	Female	66	18.212
Male	67	17.739	Female	67	18.237
Male	68	17.759	Female	68	18.262
Male	69	17.78	Female	69	18.289
Male	70	17.804	Female	70	18.316
Male	71	17.828	Female	71	18.344
Male	72	17.854	Female	72	18.373
Male	73	17.882	Female	73	18.403
Male	74	17.911	Female	74	18.434
Male	75	17.941	Female	75	18.466
Male	76	17.972	Female	76	18.5
Male	77	18.004	Female	77	18.534
Male	78	18.038	Female	78	18.57
Male	79	18.073	Female	79	18.607

Male	80	18.108	Female	80	18.645
Male	81	18.145	Female	81	18.685
Male	82	18.183	Female	82	18.726
Male	83	18.221	Female	83	18.768
Male	84	18.261	Female	84	18.812
Male	85	18.301	Female	85	18.857
Male	86	18.343	Female	86	18.903
Male	87	18.385	Female	87	18.951
Male	88	18.428	Female	88	19
Male	89	18.472	Female	89	19.05
Male	90	18.517	Female	90	19.102
Male	91	18.562	Female	91	19.154
Male	92	18.609	Female	92	19.208
Male	93	18.656	Female	93	19.264
Male	94	18.704	Female	94	19.321
Male	95	18.753	Female	95	19.379
Male	96	18.802	Female	96	19.438
Male	97	18.852	Female	97	19.498
Male	98	18.904	Female	98	19.56
Male	99	18.956	Female	99	19.623
Male	100	19.008	Female	100	19.687
Male	101	19.061	Female	101	19.752
Male	102	19.115	Female	102	19.818
Male	103	19.17	Female	103	19.885
Male	104	19.225	Female	104	19.953
Male	105	19.281	Female	105	20.022
Male	106	19.338	Female	106	20.092
Male	107	19.395	Female	107	20.162
Male	108	19.453	Female	108	20.233
Male	109	19.513	Female	109	20.305
Male	110	19.573	Female	110	20.378
Male	111	19.634	Female	111	20.451
Male	112	19.696	Female	112	20.524
Male	113	19.759	Female	113	20.598
Male	114	19.823	Female	114	20.673
Male	115	19.887	Female	115	20.749
Male	116	19.953	Female	116	20.825
Male	117	20.02	Female	117	20.902
Male	118	20.087	Female	118	20.979
Male	119	20.155	Female	119	21.058
Male	120	20.225	Female	120	21.137
Male	121	20.294	Female	121	21.217
Male	122	20.365	Female	122	21.298
Male	123	20.436	Female	123	21.379
Male	124	20.509	Female	124	21.462
Male	125	20.581	Female	125	21.545
Male	126	20.656	Female	126	21.629

Male	127	20.73	Female	127	21.714
Male	128	20.805	Female	128	21.8
Male	129	20.881	Female	129	21.887
Male	130	20.958	Female	130	21.974
Male	131	21.035	Female	131	22.063
Male	132	21.113	Female	132	22.152
Male	133	21.191	Female	133	22.242
Male	134	21.27	Female	134	22.333
Male	135	21.35	Female	135	22.424
Male	136	21.43	Female	136	22.516
Male	137	21.51	Female	137	22.609
Male	138	21.591	Female	138	22.703
Male	139	21.673	Female	139	22.797
Male	140	21.756	Female	140	22.892
Male	141	21.838	Female	141	22.987
Male	142	21.922	Female	142	23.082
Male	143	22.006	Female	143	23.178
Male	144	22.09	Female	144	23.275
Male	145	22.175	Female	145	23.371
Male	146	22.261	Female	146	23.467
Male	147	22.347	Female	147	23.564
Male	148	22.434	Female	148	23.66
Male	149	22.521	Female	149	23.756
Male	150	22.609	Female	150	23.853

^a WHO Int, et al. 2021²⁸

^b WHO Int, et al. 2022²⁹

19.6.3 Height Standard Deviation Score (-2.0): Females, Computed from WHO Growth Charts^{a,b}

Height Standard Deviation Score (-2.0)					
FEMALES					
Age (months)	Height (cm) for SDS = -2.0	Age (months)	Height (cm) for SDS = -2.0	Age (months)	Height (cm) for SDS = -2.0
36	87.4	81	108.628	126	128.736
37	88	82	109.043	127	129.227
38	88.6	83	109.459	128	129.719
39	89.2	84	109.877	129	130.213
40	89.8	85	110.294	130	130.707
41	90.4	86	110.713	131	131.202
42	90.9	87	111.13	132	131.7
43	91.5	88	111.551	133	132.198
44	92	89	111.974	134	132.695
45	92.5	90	112.396	135	133.193
46	93.1	91	112.819	136	133.688
47	93.6	92	113.245	137	134.183
48	94.1	93	113.672	138	134.675
49	94.6	94	114.101	139	135.164
50	95.1	95	114.53	140	135.653
51	95.6	96	114.961	141	136.134
52	96.1	97	115.393	142	136.612
53	96.6	98	115.828	143	137.085
54	97.1	99	116.265	144	137.552
55	97.6	100	116.703	145	138.015
56	98.1	101	117.143	146	138.467
57	98.5	102	117.584	147	138.914
58	99	103	118.029	148	139.349
59	99.5	104	118.475	149	139.777
60	99.9	105	118.92	150	140.196
61	100.055	106	119.371	151	140.605
62	100.514	107	119.822	152	141.006
63	100.968	108	120.273	153	141.393
64	101.418	109	120.728	154	141.769
65	101.865	110	121.185	155	142.138
66	102.306	111	121.643	156	142.492
67	102.745	112	122.101	157	142.838
68	103.181	113	122.564	158	143.172
69	103.612	114	123.025	159	143.496
70	104.04	115	123.49	160	143.805
71	104.464	116	123.959	161	144.105
72	104.885	117	124.427	162	144.395
73	105.306	118	124.896	163	144.673
74	105.724	119	125.369	164	144.941
75	106.139	120	125.843	165	145.194
76	106.557	121	126.322	166	145.441
77	106.971	122	126.799	167	145.677
78	107.385	123	127.281	168	145.903
79	107.8	124	127.764	169	146.12
80	108.213	125	128.249	170	146.324

WHO Int, et al. 2021²⁸

^b WHO Int, et al. 2022²⁹

19.6.4 Height Standard Deviation Score (-2.0): Males, Computed from WHO Growth Charts^{a,b}

Height Standard Deviation Score (-2.0)

MALES

Age (months)	Height (cm) for SDS = -2.0	Age (months)	Height (cm) for SDS = -2.0	Age (months)	Height (cm) for SDS = -2.0
36	88.7	81	109.919	126	127.29
37	89.2	82	110.335	127	127.673
38	89.8	83	110.75	128	128.062
39	90.3	84	111.162	129	128.453
40	90.9	85	111.573	130	128.848
41	91.4	86	111.983	131	129.247
42	91.9	87	112.39	132	129.651
43	92.4	88	112.796	133	130.057
44	93	89	113.2	134	130.47
45	93.5	90	113.602	135	130.887
46	94	91	114.002	136	131.312
47	94.4	92	114.399	137	131.738
48	94.9	93	114.795	138	132.173
49	95.4	94	115.188	139	132.612
50	95.9	95	115.58	140	133.058
51	96.4	96	115.969	141	133.509
52	96.9	97	116.357	142	133.969
53	97.4	98	116.743	143	134.436
54	97.8	99	117.127	144	134.909
55	98.3	100	117.51	145	135.392
56	98.8	101	117.892	146	135.879
57	99.3	102	118.27	147	136.38
58	99.7	103	118.65	148	136.884
59	100.2	104	119.03	149	137.399
60	100.7	105	119.408	150	137.921
61	101.082	106	119.786	151	138.452
62	101.555	107	120.164	152	138.986
63	102.026	108	120.542	153	139.531
64	102.496	109	120.918	154	140.077
65	102.96	110	121.295	155	140.629
66	103.42	111	121.67	156	141.187
67	103.875	112	122.048	157	141.747
68	104.329	113	122.422	158	142.307
69	104.777	114	122.795	159	142.867
70	105.22	115	123.17	160	143.428
71	105.662	116	123.542	161	143.989
72	106.097	117	123.916	162	144.544
73	106.529	118	124.286	163	145.098
74	106.96	119	124.659	164	145.65
75	107.387	120	125.032	165	146.197
76	107.812	121	125.405	166	146.737
77	108.237	122	125.779	167	147.269
78	108.659	123	126.154	168	147.797
79	109.079	124	126.53	169	148.318
80	109.499	125	126.907	170	148.827

WHO Int, et al. 2021²⁸

^b WHO Int, et al. 2022²⁹

19.7 Appendix 7: Blood volume collection

Table 4 Blood Volume Collection rhGH Arm

Study Visit	Screening visit	Day 1 visit	Month 1 visit	Month 3 visit	Month 6 visit	Month 9 visit	Month 12 visit	Total volume (mL)
Volume/Visit(mL)	~22.5 ml	~22.5 ml	~ 14.0 ml	~ 14.0 ml	~17.5 ml	~7.0 ml	~17.5 ml	~115 ml
Volume/Visit (tsp)	~ 4.6 tsp	~ 4.6 tsp	~ 2.8 tsp	~ 2.8 tsp	~ 3.6 tsp	~ 1.4 tsp	~ 3.6 tsp	~23.3 tsp

mL=Milliliter; tsp=teaspoon

Table 5 Blood Volume Collection LUM-201 Arms

Study Visit	Screening visit	Day 1 visit	Month 1 visit	Month 3 visit	Month 6 visit	Month 9	Month 12 visit	Month 15 visit	Month 18 visit	Month 21	Month 24 visit	Total volume (mL)
Volume/Visit(mL)	~22.5 ml	~22.5 ml	~ 16.0 ml	~ 16.0 ml	~25.5 ml	~7.0 ml	~25.5 ml	~7.0 ml	~ 14.0 ml	~7.0 ml	~14.0 ml	~177 ml
Volume/Visit (tsp)	~ 4.6 tsp	~ 4.6 tsp	~ 3.2 tsp	~ 3.2 tsp	~ 5.2 tsp	~ 1.4 tsp	~ 5.2 tsp	~ 1.4 tsp	~ 2.8 tsp	~ 1.4 tsp	~ 2.8 tsp	~35.9 tsp

mL=Milliliter; tsp=teaspoon

19.8 Appendix 8: Running Summary of Changes

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
Version 5.1, dated 30 July 2021	1.0 Title Page (1 – 3)	Revision of study length and phase. This revision is reflected throughout the protocol.	A Multicenter, 6 12 -Month, Randomized, Open-Label, Active Control, Parallel Arm, Phase 2b Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal Children with Growth Hormone Deficiency (GHD)
	2.0 Synopsis (4 – 14)	Revision of primary, key secondary, and other secondary objectives	Removal of LTES language throughout. Revision to all sections within the synopsis detailing: <ul style="list-style-type: none"> - updates to objectives to align with revised study length - defined PEM test description - a modified schedule of assessments to include revised and additional study visits, and procedures to occur therein
	5.0 Study Objectives (29-30)	Revision of secondary objectives	clarification on study drug administration herein and throughout <ul style="list-style-type: none"> • To assess the reproducibility of the LUM-201 strategy in the PEM positive classification of subjects as PEM positive or PEM-negative • To assess additional clinical parameters of efficacy (at Month 6 and Month 12) including: <ul style="list-style-type: none"> • Change in height standard deviation score (HT-SDS) from Day 1 (Visit 3) to Month 6 (Visit 10) • Change in height velocity standard deviation score (HV-SDS) • Change in weight and weight SDS from Day 1 (Visit 3) to Month 6 (Visit 10) • Change in body mass index (BMI) and BMI SDS from Day 1 (Visit 3) to Month 6 (Visit 10) • Change in predicted adult height Change in Bone Age (Only Month 6)

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
	6.0 Investigational Plan (30 – 38)	Revision of Schema of Study Design (Figure 1)	The following sentence was added:
		Rationale for Study Design: rationale for comparator	Norditropin® was selected as the comparator drug because it is available in all study locations.
		Stopping Rules	Revised to reflect stopping rules based on drug-related SAFEs and QtcB guidelines.
		Provide clarification of revised study design	This study was designed for 6 months of treatment to allow the necessary minimum of time to assess change in height in this population. Norditropin® was selected as the comparator drug because it is available in all study locations.
			This study is designed to confirm the ability of the PEM test to select for subjects who will respond to LUM-201 treatment, and the reproducibility of the positive PEM test result. The response to LUM-201 will be based on the annualized height velocity at Month 6. An additional 6 months of study treatment will be used to further characterize overall safety and growth response to LUM-201.

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		Revised Clinical Outcome Measurements to align with revised Schedule of Assessments.	<ul style="list-style-type: none"> Height collected in triplicate at all clinic visits (except Week 2 [Visit 3]) HV from Day 1 (Visit 3) to Month 6 (Visit 10) Weight collected at all clinic visits Change in HT SDS from Day 1 (Visit 3) to Month 6 (Visit 10) (Error! Reference source not found.) Change in height-velocity-standard deviation score (HV-SDS) Change in weight and weight SDS from Day 1 (Visit 3) to Month 6 (Visit 10) (Error! Reference source not found.) Change in body mass index (BMI) and BMI SDS from Day 1 (Visit 3) to Month 6 (Visit 10) (Error! Reference source not found.) Change in Bone Age collected at baseline (Screening Day 1 [Visit 1]) and Month 6 (Visit 9)
	7.0 Selection and Withdrawal of Subjects (38 – 41)	Removal of bone age evaluation exception	<p>Consent may be withdrawn at any time for any reason by the subject or subject caregiver without prejudice to further treatment. The MM, PI or DSMB may withdraw a subject (Section 6.11). If possible, subjects who withdraw early should complete the activities of Month 12 (Visit 11) (except for the bone age evaluation, if a prior bone age evaluation was completed within the past 3 months) and return at the scheduled Month 12 (Visit 11) (6 visit for a final evaluation of the endpoints.</p>

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	9.0 Study Treatments (42-45)	Clarification of treatment description concerning the PEM test	<p>All subjects will receive a single oral 0.8 mg/kg dose of LUM-201 twice, at Screening Visit 1 and Screening Visit 2 as part of the PEM strategy. All subjects will receive a single oral 0.8 mg/kg dose of LUM-201 at Screening (Visit 1). Subjects who test PEM positive will receive a second PEM test at Day 1 (Visit 2). Subjects who test PEM negative will not be included in the treatment period of the study.</p> <p>All randomized subjects will commence their assigned dose on Day 1 (Visit 23) for those randomized to rhGH and the day following Day 1 for those randomized to LUM-201 and continue treatment until Month 126 (Visit 1120) Visit.</p>
	11.0 Study Assessments and Procedures (45 – 57)	Included detailed description of Predictive Enrichment Markers (PEMs)	Detailed description provided based on global changes to the protocol, relating to length of study and revised procedures
		Revision and addition of study procedures to align with revised Schedule of Assessments	Applicable revisions are described in the Schedule of Assessments and reflected in detail in this section.
	13.0 Statistics (62-69)	Clarification of PEM Reproducibility calculation throughout.	
		Addition of 12 months per protocol population language	The 12 month Per Protocol Population includes all randomized subjects who complete Month 12 and have not missed more than 10% of scheduled doses over the 12-month Treatment portion or more than 20% of the intended doses over any 30-day interval, and who do not have any significant protocol deviations. The Per Protocol Population will be used for the primary evaluation of treatment response.

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		Clarification of Additional Analyses	The data from Month 6 to Month 12 will be summarized to allow for assessments of growth response to 12 months of treatment.
		Inclusion of interim analysis plan	An interim analysis of all available data will be conducted after 40 subjects have completed Month 6 (Visit 9). The purpose of this interim analysis is to evaluate the safety and continued growth response in the 6 to 12-month period.
			No interim analyses of the primary endpoint are planned for this study.
	19.4 Appendix 4: Specialty Laboratory Testing (Serum GH and Plasma LUM-201 samples collected for subjects randomized to LUM-201 arms only from Week 2 [Visit 3] through Month 12 [Visit 11])(82)	Addition of Visit 11 (Month 12) sample collection information, and revision of other sample collections per the Schedule of Assessments.	
	19.7 Appendix 7: Blood Volume Collection (92)	Revision of blood volume collection based on revised study visit procedures per the Schedule of Assessments.	
	19.8 Appendix 8: Running Summary of Changes (93-102)	Update to running summary of changes	Inclusion of summary of changes from Protocol Version 3 to Version 4.1.

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
Version 4.1, dated 29 April 2021	1.0 Title Page (1 – 3)	Removal of Lumos's previous Chief Medical Officer. Addition of Lumos's Chief Scientific and Chief Operating Officer.	<div>████████████████████</div> Chief Medical Officer <div>████████████████████</div> Lumos Pharma, Inc.
	2.0 Synopsis (5 – 14)	Revision of synopsis to reflect additional sites (countries) and updated primary and secondary objectives	Addition of 10 planned sites, and inclusion of study locations: Russia, Ukraine, and Israel Revision to all sections within the synopsis detailing: - updates to inclusion/exclusion criteria a modified schedule of assessments including clarification of screening procedures
	4.0 Introduction and Background (26-28)	Inclusion of newly published background information from Blum manuscript. Addition of Section 4.5 Mitigation Procedures for Public Health Emergency	“Baseline IGF-1 and GH response to standard of care GH stimulation tests have also found to be independent predictors of 12-month growth response to rhGH (24).” Addition of mitigation procedures (throughout) in the event of a pandemic, epidemic, or natural disaster.
	6.0 Investigational Plan (29 – 35)	Revision of stopping rules to include expansion of age range for QTcB interval prolongation criteria Addition to Clinical Outcome Measurements:	Addition of ages ≥ 12 and < 16 ; values of > 449 in males and > 457 in females.
			Addition of: Change in height velocity standard deviation score (HV-SDS)

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	7.0 Selection and Withdrawal of Subjects (36 – 39)	Revisions to reflect the updated inclusion/exclusion criteria and subject withdrawals and replacements	<p>Updates to inclusion criteria, including:</p> <ul style="list-style-type: none"> - clarification of established diagnosis of PGHD - At screening visit 1 or in the past 12 months have a random morning cortisol test meeting given inclusion criteria - increase in age range for boys and girls - Revision to body measurement criteria <p>Updates to exclusions criteria, including:</p> <ul style="list-style-type: none"> - clarification of absent pituitary function by “standard of care” GH test - Stipulation of ADHD treatment, within three months of Screening Visit 1 <p>Updates to subject withdrawals and replacements, including: revision of “the height endpoint” to “the endpoints”</p>
		Conditions of administration of treatment during a pandemic, epidemic, or natural disaster.	Inclusion of language concerning Mitigation Procedures for Public Health Emergency . Language includes safety measures such as remote monitoring and home healthcare visits, as permitted by local health authorities.
	9.0 Study Treatments (40 – 43)	Deletion of Table 4 and associated language	Deletion of Table 4 and associated tablet selection language.
		Removal of language regarding rhGH administration.	Administration of all LUM 201 or rhGH doses will be performed by health care professionals or the caregiver. The time, date, dose volume, and site of administration will be recorded.
		Revision of investigational drug packaging information.	LUM-201 will be supplied in polypropylene, foil sealed bottles with desiccant-high-density polyethylene (HDPE) bottles with an induction seal and a polypropylene child-resistant closure. Each bottle is packaged with a 1-gram desiccant and may include polyester coil.
		Specification of excluded ADHD drugs while on trial.	If a subject needs to start medications capable of altering the safety or efficacy of study drug (e.g., drugs guanfacine hydrochloride or methylphenidate) to treat ADHD)

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
	11.0 Study Assessments and Procedures (43 – 53)	Conditions of administration of treatment during a pandemic, epidemic, or natural disaster.	Inclusion of language concerning Mitigation Procedures for Public Health Emergency . Language includes safety measures such as remote monitoring and home healthcare visits, as permitted by local health authorities.
		Revision to Assessments of Pharmacokinetic (PK) and Pharmacodynamic (PD)	In consideration of the “Ethical considerations for clinical trials on medicinal products conducted with the pediatric population, 2008” document and protocol requirements, language was added to reflect minimal blood samples will be drawn while allowing for adequate evaluation of PK characteristics and PD response. Revision allows for certain samples to be omitted if blood collection exceeds limit per visit.
		Addition of language specifying where certain blood and urine samples will be analyzed	Addition of Clinical laboratory tests information: “Clinical laboratory tests were implemented to allow adequate surveillance of subject safety throughout the study duration. All blood samples will be shipped to a central laboratory as described in the Laboratory Manual. Urine samples will be analyzed locally. Repeat laboratories, if needed, may be analyzed locally per site’s standard procedures.”
	19.1 Appendix 1: Birth weights (grams) for the 5th percentile by gender and gestational age (73) 19.2 Appendix 2: Concomitant Medications (74) 19.6.3 Height Standard Deviation Score (-2.0): Females (83-84)	Revisions to Screening Procedures	Revisions and additions to Screening Procedures as reflected in the Schedule of Assessments
		Addition of Appendix	
		Addition of ADHD drug to concomitant medications	Addition of “Guanfacine hydrochloride” to list of drugs that interact with CYP3A/4
		Replacement of table	

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
Version 3.0, dated 18 December 2020	19.6.4 Height Standard Deviation Score (-2.0): Males (85-86)	Replacement of table	
	19.6.5 25th Percentile Height Velocities (87)	Addition of Appendix	
	19.7 Appendix 7: Blood volume collection (88)	Addition of Appendix	
	19.8 Appendix 8: Running Summary of Changes (89-95)	Update to running summary of changes	Inclusion of summary of changes from Protocol Version 2 to Version 3.
	1.0 Title Page (1 – 3)	Update Title Page to include NCT Number and EudraCT Number. Add “Name and Title” to include Lumos’s current Vice President, Clinical Operations	Update Clinical Study Protocol informational table to include “NCT NUMBER 04614337” and “EUDRACT NUMBER 2020-000874-92” [REDACTED] Vice President, Clinical Operations Lumos Pharma, Inc.
	2.0 Synopsis (5 – 13)	Revision of synopsis to reflect updated primary and secondary objectives	Revision to all sections within the synopsis detailing: - updates to inclusion/exclusion criteria - clarification of assays used in PEM test a modified schedule of assessments including the removal of cortisol testing from Treatment Portion of study
	5.0 Study Objectives (27-28)	Revisions to clarify definition of “responders”	Revisions include: - Clarifying definition of “responders” Updated text to reflect addition of visit numbers for clarity
	6.0 Investigational Plan (28 – 34)	Revisions to reflect the visit numbers of Clinical Outcome Measurements	Revisions include: Updated text to reflect addition of visit numbers for clarity

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
	7.0 Selection and Withdrawal of Subjects (34 – 37)	Revisions to reflect the updated inclusion/exclusion criteria and subject withdrawals and replacements	<p>Updates to inclusion criteria, including:</p> <ul style="list-style-type: none"> - diagnosis made by standard of care, including radiographic data - have historical (within past 6 months) cortisol testing meeting given inclusion criteria - addition of IGF-1 and GH response criteria from the first of two screening PEM tests <p>Updates to exclusions criteria, including:</p> <ul style="list-style-type: none"> - clarification of absent pituitary function by “standard of care” GH test <p>Updates to subject withdrawals and replacements, including: revision of “the endpoints” to “the height endpoint”</p>
	9.0 Study Treatments (37 – 41)	Revisions to concomitant medications and restrictions	<p>Revisions include:</p> <ul style="list-style-type: none"> - Clarification of concomitant medications criteria: Hypothyroidism Other pituitary hormone deficiencies discovered at during the Screening Visit Portion requires treatment for a minimum of 30 days for hypothyroidism or 3 months for any other pituitary axis deficiency prior to administration of study drug randomization. <p>Updates to restrictions, including: Addition of fasting requirement for Visit 7</p>

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
	11.0 Study Assessments and Procedures (41 – 50)	Revision to Electrocardiograms (ECGs), Clinical Laboratory Tests, and Study Activities	<p>Updates to Electrocardiograms (ECGs), including:</p> <ul style="list-style-type: none"> - Clarification of triplicate ECGs to be recorded as described in Table 1 - Addition of “ECGs collected prior to study drug administration at Screening Visit 1 will be used as baseline.” <p>Updates to Clinical Laboratory Tests, including:</p> <ul style="list-style-type: none"> - removal of cortisol analysis from Treatment Portion of study - clarification of tests to be considered baseline. <p>Updates to Study Activities, including:</p> <p>Addition and removal of screening procedures as reflected in Table 1</p>
	12.0 Adverse Event Assessment and Reporting (50-55)	Revision and clarification to Serious Adverse Event occurrence and Expected Adverse Events	<p>Revisions include:</p> <ul style="list-style-type: none"> - Instruction on treatment and follow-up of a Serious Adverse Event (SAE) - Addition of language: “All expected AEs (if untoward reactions) should be reported as AEs.”
	13.0 Statistics (55 – 61)	Revisions to statistics to reflect definition of “response” and clarity regarding repeatability and PEM classification	<p>Revisions include:</p> <ul style="list-style-type: none"> - Addition of clarifying language: “Positive growth response (“response”) is defined as ≥ 6.85 cm/yr AHV from Baseline (Day 1) to Month 6.” <p>Clarification of language concerning repeatability calculation and PEM classification</p>
	16.2.3 Reporting and Recording of Study Data (64-65)	Clarification of reporting results and incidental findings	Included instructional language on returning patient results and incidental findings in a confidential manner.

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	19.4 Appendix 4: Clinical Analytes (73)	Revisions to clinical analytes	Revisions include: - Addition of WBC differential to the hematology clinical analytes - Removal of HbA1c, fasting glucose, and cortisol, and addition of total protein to the serum chemistry and addition of HbA1c and Turner Syndrome to other tests Addition of HbA1c and Turner Syndrome to other tests Addition of appendix to include running summary of changes.
	19.6 Appendix 6: Running Summary of Changes (80)	Addition of appendix	
Version 2.0, dated 05 August 2020	1.0 Title Page (1 – 3)	Revision to title to reflect the updated primary objective to validate predictive the predictive enrichment marker (PEM) strategy	Title updated to state: A Multicenter, 6-Month, Randomized, Open-Label, Active Control, Parallel Arm, Phase 2b Dose-Selection Study of Daily Oral LUM-201 in Naïve-to-Treatment, Prepubertal Children with Growth Hormone Deficiency (GHD) Selected by Predictive Enrichment Markers
		Update “Name and Title” to reflect current Lumos Chief Medical Officer	Clinical Development [REDACTED] Lumos Pharma, Inc.
	2.0 Synopsis (4 – 13)	Revision of synopsis to reflect updated primary and secondary objectives	Revision to all sections within the synopsis detailing: - updates to inclusion/exclusion criteria, including new PEM-positive enrollment criterium - updated primary and secondary objectives - statistical methods that now include a power and repeatability analyses a modified schedule of assessments including the addition of a second screening visit and remote 2, 4, and 5-month assessments
	4.0 Introduction and Background (22 – 24)	Additional background information provided	Updates to align with current available clinical data and proposed PEM strategy

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	5.0 Study Objectives (24 – 25)	Revisions to reflect updated primary and secondary objectives	<p>Revisions include:</p> <ul style="list-style-type: none"> - New primary objective to validate the PEM strategy to select subjects likely to respond to therapy with LUM-201 - Movement of the objective to select a pediatric dose of LUM-201 from a primary to a secondary objective - Additional secondary objective to assess additional clinical parameters of efficacy <p>Additional secondary objective to assess the repeatability of the PEM-bases subject classification</p>
	6.0 Investigational Plan (25 – 32)	Revisions to reflect the updated PEM strategy and stopping rules	<p>Revisions include:</p> <ul style="list-style-type: none"> - Updated text to reflect updated primary objective to validate predictive the predictive enrichment marker (PEM) strategy <p>Updated stopping rules, including addition of rules regarding new intracranial tumors, new malignancies, plasma glucose levels, QTcB interval prolongation criteria, and other laboratory abnormalities</p>
	7.0 Selection and Withdrawal of Subjects (33 – 36)	Revisions to reflect the updated PEM strategy and updated inclusion/exclusion criteria	<p>Updates to inclusion criteria, including:</p> <ul style="list-style-type: none"> - new PEM-positive enrollment criterium - Peak cortisol > 20 µg/dL on the glucagon, ACTH or insulin test - height minus arm span difference < 3 cm <p>Updates to exclusions criteria, including: uncontrolled diabetes mellitus or diabetes insipidus</p>
	8.1 Randomization (36)	Revisions to reflect the updated PEM strategy for randomization	<p>Revision to include the addition of a second screening visit</p>

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	9.0 Study Treatments (36 – 40)	Revisions to the schedule of assessments to reflect the updated PEM strategy and adherence criteria	Revisions include: - A modified schedule of assessments including the addition of a second screening visit with treatment Clarification of treatment adherence criteria: A subject who misses more than 20% of the intended doses over any 30-day interval, or more than 10% of the intended doses over the entire Treatment period without good reason such as meeting a stopping rule or the treatment of an intercurrent illness will be considered non-compliant
	11.0 Study Assessments and Procedures (40 – 49)	Revision to assessments	Revisions include: - Addition of description of arm span measurement - Description of assessments at 2 screening visits - Description of additional 2, 4, and 5-month assessments Addition of EGC test at 1 hour post-dose at Month 3 (Visit 7)
	12.2.3 Expected Adverse Event (52)	Removal of expected adverse event	Expected AEs include injection site reactions, increased appetite, and joint pain and carbohydrate intolerance.
	13.0 Statistics (53 – 59)	Revisions to statistics to reflect the updated PEM strategy for randomization	Revisions include: Addition of description of statistical methods that now include a power and PEM Classification – Treatment Response Rate repeatability analyses Updated per protocol population description
	16.2.5 Tissue and Blood Sample Collection/Storage (63)	Clarification of allowable analyses on residual samples	Replaced text describing applicable regulations on testing of residual samples with “No whole genome or genetics testing will be performed on any of the residual samples.”
	19.2 Appendix 2: Rationale for PEM Test (69)	Reflect the updated primary objective to validate PEM strategy	Revisions to align with the PEM strategy

Protocol Version and Date	Section (Page[s]) Affected	Change	Summary
	19.3 Appendix 3: Specialty Laboratory Testing (71)	Revision to schedule of testing to reflect PEM strategy	Revision to include the addition of a second screening visit and remote 2, 4, and 5-month assessments
	19.4 Appendix 4: Clinical Analytes (72)	Revisions to clinical analytes	Revisions include: - Addition of RBC indices to the hematology clinical analytes Addition of sodium, potassium, chloride, calcium, phosphate, CO ₂ , BUN, creatine, albumin, globulin, and cortisol to serum chemistry clinical analytes