Protocol Title:

An Open-Label, Multicenter, Phase 2 Study to Evaluate Growth and Safety of LUM-201 Following 12 Months of Daily rhGH Treatment in Children with Idiopathic Growth Hormone Deficiency who have Previously Completed the LUM-201-01 Trial

NCT #: 05250063

Date: 19 January 2022

1.0 TITLE PAGE

Clinical Study Protocol

OraGrowtH213 TRIAL

STUDY NUMBER:	LUM-201-04
PROTOCOL TITLE:	An Open-Label, Multicenter, Phase 2 Study to Evaluate Growth and Safety of LUM-201 Following 12 Months of Daily rhGH Treatment in Children with Idiopathic Growth Hormone Deficiency who have Previously Completed the LUM-201-01 Trial
SPONSOR:	Lumos Pharma, Inc. 4200 Marathon Blvd. Suite 200 Austin, Texas 78756 Telephone: [redacted]
SPONSOR CONTACT:	Name: [redacted] Title: Chief Medical Officer
MEDICAL MONITOR:	Name: [redacted] Medical Monitor WuXi Clinical Development, Inc. Telephone: [redacted]
PROTOCOL VERSION:	2.0
PROTOCOL DATE:	19 January 2022

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: An Open-Label, Multicenter, Phase 2 Study to Evaluate Growth and Safety of LUM-201 Following 12 Months of Daily rhGH Treatment in Children with Idiopathic Growth Hormone Deficiency who have Previously Completed the LUM-201-01 Trial

Protocol Date: 19 January 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
[redacted] Chief Medical Officer Lumos Pharma, Inc.	[redacted] Signing Reason: I approve this document Signing Time: 1/20/2022 | 12:27 CST 77A652CA01374FDB9BDDE1C3DE79E760	1/20/2022 | 12:27 CST
[redacted] Vice President, Clinical Operations Lumos Pharma, Inc.	[redacted] Signing Reason: I approve this document Signing Time: 1/20/2022 | 13:01 CST E9955E80205E48E3B27801BBDC5DC9AA	1/20/2022 | 13:01 CST

INVESTIGATOR'S AGREEMENT

An Open-Label, Multicenter, Phase 2 Study to Evaluate Growth and Safety of LUM-201 Following 12 Months of Daily rhGH Treatment in Children with Idiopathic Growth Hormone Deficiency who have Previously Completed the LUM-201-01 Trial

Protocol Date: 19 January 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-201-04, 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 Council for Harmonisation (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 PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Lumos Pharma, Inc.

Name of Investigational Product:
LUM-201

Name of Active Ingredient:
Ibutamoren mesylate

Title of Study: An Open-Label, Multicenter, Phase 2 Study to Evaluate Growth and Safety of LUM-201 Following 12 Months of Daily rhGH Treatment in Children with Idiopathic Growth Hormone Deficiency who have Previously Completed the LUM-201-01 Trial

Study Centers and Principal Investigators: Multicenter study, with up to 20 sites planned in the United States (US), Poland, New Zealand, Australia, Ukraine, Russia and Israel

Study Period (Years):	**Phase of development:**
Estimated date first subject enrolled: January 2022 Estimated date last subject completed: January 2024	Phase 2

Objectives:

Primary Objective

- Assess the growth response to LUM-201 administration in children with idiopathic growth hormone deficiency (GHD) previously treated with daily rhGH for 12 months in the LUM-201-01 trial.

Secondary Objective(s)

- Assess safety in response to LUM-201 treatment.

Study Design and Methodology:

Study Design

This is an open-label, multicenter, safety and efficacy study. Subjects may enter onto this trial if they have completed 12 months of treatment with rhGH in the LUM-201-01 trial. Subjects will receive approximately 3.2 mg/kg of LUM-201 as a daily oral dose each morning. Subject's dose may be decreased once to a lower LUM-201 dose, such as the 1.6 mg/kg/day dose, if they show a confirmed IGF-1 SDS value > +2.0 SDS at any assessment post Screening/Baseline visit, or if subject has demonstrated safety and tolerability issues to 3.2 mg/kg/day dose administration. Total duration of LUM-201 administration will be 12 months.

Study Procedures

There will be six clinic visits. The screening/baseline visit can coincide with the Month 12 visit in the LUM-201-01 trial. If the Baseline/Screening visit doesn't take place at the LUM-201-01 Month 12 visit, the Baseline/Screening visit should be completed within 30 days of the LUM-201-01 Month 12 visit. If the Baseline/Screening visit is not scheduled within 30 days of the LUM-201-01 Month 12 visit, a discussion needs to take place with the Medical Monitors. Adverse events, concomitant medications, height and weight will be collected at each clinic visit. Baseline electrocardiograms (ECGs) will be performed at the Screening/Baseline Day 1 visit prior to and one hour after LUM-201 administration. ECGs will also be performed one hour after LUM-201 administration at Month 3, Month 6, and Month 12 visits.

Bone age assessment will be performed at the Month 6 visit (12 months after the bone age assessment in the LUM-201-01 Trial); complete physical examinations will be performed at Baseline and Month 12 visits. Tanner staging will be performed at Baseline, Month 3, Month 6, Month 9, and Month 12.

All subjects will have 0 (pre-dose) and 60 ± 10 minutes post-dose GH samples collected at Baseline, Month 6 and Month 12 visits. Collection of GH samples will be done in the fasting state. Pre-dose IGF-1 and IGFBP-3 samples will be collected at Baseline, Month 3, Month 6 and Month 12 visits. Safety laboratory samples will be collected at the Baseline, Month 1, Month 3, Month 6 and Month 12 visits.

LUM-201 will be adjusted for body weight increments at each clinic visit, as applicable.

Safety Surveillance

Appropriate surveillance, monitoring, and intervention will be performed to ensure subject safety, as necessary. Ongoing safety review of adverse events (AEs) and serious adverse events (SAEs) will be performed by the Medical Monitor (MM) and Sponsor. All AEs assessed by the Investigator as severe in intensity and possibly related to study drug will be discussed with Lumos and the Investigator and may result in the subject discontinuing study drug.

Inclusion Criteria

Potential study subjects must meet all the inclusion criteria listed below to be eligible for study participation:

1. Parent/caregiver must sign the informed consent, and the subject must sign the assent, as applicable.
2. Must have previously completed 12 months of daily rhGH treatment as part of the LUM-201-01 PGHD trial.
3. Is eligible for study participation as confirmed by the principal investigator (PI).

Exclusion Criteria

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

1. Has a medical condition that, in the opinion of the PI and/or MM, adds unwarranted risk to use of LUM-201.
2. Uses any medication that, in the opinion of the PI and/or MM, can independently cause short stature or limit the response to exogenous growth factors.
3. Has planned or is receiving current long-term treatment with medications known to act as substrates, inducers, or inhibitors of the cytochrome system CYP3A4 that metabolizes LUM-201 (see Appendix 1 for list of example medications). Subjects receiving shorter-term (two weeks or less) treatment with these medications should be evaluated on case-by-case basis by the PI in consultation with the MM.
4. Has been randomized to LUM-201 in the LUM-201-01 trial.

Number of Subjects (Planned):

Up to 20 subjects may enter this study.

Investigational Product, Dosage and Mode of Administration:

Subjects will receive approximately 3.2 mg/kg of LUM-201 as a daily oral dose each morning. The LUM-201 dose will be administered in clinic at all visits with the pharmacodynamic (PD) sample collections. Remaining LUM-201 doses will be administered at home. A subject's dose may be decreased if they demonstrate an IGF-1 SDS > +2.0 SDS at any visit that is confirmed by a follow-up (unscheduled) lab, or if safety and tolerability data support a dose decrease.

Duration of Treatment:

LUM-201 treatment will be offered on a continuous basis as medically appropriate for 12 months. The Sponsor retains the right to cancel this study at any time. If the Long-Term Safety Extension (LTSE) Study is opened at a study site, subjects may be allowed to enroll into the LTSE Study.

Criteria for Evaluation:

Safety:

Safety assessments will include collection of AEs and SAEs, routine laboratory tests (hematology, chemistry panel including liver enzymes, and urinalysis), hemoglobin A1c (HbA1c), thyroid panel, lipid panel, interval history, concomitant medications, physical examinations, ECGs and vital signs.

Clinical Outcome Measurements:

Annualized height velocity (AHV). Efficacy endpoints will be calculated at six-month intervals. Standard Deviation Scores (SDS) for growth parameters will be calculated using international reference data from the World Health Organization (WHO).

Additional Efficacy Endpoints:

- Change in HT-SDS.
- Change in Weight and Weight-SDS.
- Change in BMI and BMI-SDS.
- Change in Bone Age (Only Month 6).

PD:

Serum LUM-201 PD markers including GH, IGF-1, and IGFBP-3 concentrations. IGF-1 SDS will be calculated from measured IGF-1 concentrations

Statistical Methods:

Statistical Hypotheses:

No formal hypotheses will be tested in this trial.

Sample Size Calculation:

No formal calculation of power or sample size will be performed.

Clinical Efficacy Analyses:

Descriptive statistics will be compiled for each of the efficacy and PD parameters. Although not powered a priori, AHV at Month 12 that is < 70% of the 1st year growth on rhGH will be summarized

Safety Analyses:

Adverse events and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 23.1). Summary tables of treatment-emergent AEs (TEAEs) will be provided. Laboratory, ECG parameters and vital signs will be summarized.

Table 1 Schedule of Assessments

Visit	Screening/ Baseline + 30 Days from end of prior study	Month 1 (± 3 days)	Month 3 (± 7 days)	Month 6 (± 7 days)	Month 9 (± 7 days)	Month 12/ Early Term (± 7 days)	Follow-up Contact
Scheduled Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	
Informed consent/assent	X						
Inclusion/exclusion criteria review	X						
Medical history	X						
Physical examination[b]	X[a]					X	
Tanner staging	X[a]		X	X	X	X	
Adverse events	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	
Stadiometer height and weight	X[a]	X[c]	X	X	X	X	
Bone age				X			
ECG[d]	X		X	X		X	
Enrollment	X						
Laboratory assessments							
Hematology, CBC	X[a]	X	X	X		X	
Serum chemistry panel	X[a]	X	X	X		X	
HbA1c	X[a]			X		X	
Fasting glucose	X[a]			X		X	
Thyroid panel (TSH, T_4, T_3)	X[a]			X		X	
Lipids	X[a]			X		X	
Urinalysis (Dipstick)	X[a]			X		X	
IGF-1 sample	X[a]		X	X		X	
IGFBP-3 sample	X[a]		X	X		X	
GH sample[e]	X			X		X	
Drug accountability/ Compliance check		X	X	X	X	X	
Study drug dispensed	X	X	X	X	X		
Commence daily treatment with LUM-201	X						
Dose adjustment, when applicable		X	X	X	X		

Abbreviations: CBC = complete blood count; ECG = electrocardiogram; GH = growth hormone; HbA1c = hemoglobin A1c; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth binding protein 3; T3 = triiodothyronine; T4 = free thyroxine; TSH = thyroid stimulating hormone

[a] Screening/Baseline visit of this study can coincide with the last visit of the LUM-201-01 study. Therefore, overlapping assessments, such as vital signs, safety labs, Tanner staging and stadiometer height and weight, may be

completed only once to satisfy both protocol requirements. If the Baseline/Screening visit occurs within 30 days of the LUM-201-01 Month 12 visit, repeat assessments are not necessary. If the Baseline/Screening visit is not scheduled within 30 days of the LUM-201-01 Month 12 visit, a discussion needs to take place with the Medical Monitors.

[b] Complete physical examination will be performed at Baseline and Month 12 visits. For any patients complaining of headache, fundoscopy examination should be performed per investigator's judgment.

[c] At Month 1 visit, only weight will be collected. Height will not be collected.

[d] ECGs will be performed pre-dose for all subjects at Screening/Baseline Day1 (Visit 1), and 1 hour ± 10 min at Screening/Baseline Day 1, Month 3 (Visit 3), Month 6 (Visit 4), and Month 12 (Visit 6). ECGs will be interpreted by a central reader using age-related normative data.

[e] GH sample should be collected at 0 (pre-dose) and 60 ± 10 minutes after LUM-201 administration.

SUMMARY OF CHANGES

Amendment Rationale

The primary purpose of this amendment is to: include periodic ECG monitoring, and to include prolongation of QTc interval as a subject level stopping criterion.

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 201-04 Version 2.0 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
2.0 Synopsis (4 – 8)	Revision of Study Procedures	Revision to all sections within the synopsis, and applicably throughout the protocol, detailing: - Baseline ECGs to be performed at Screening, Month 3, Month 6, and Month 12 visits, and subsequent assessments thereof. - Alignment of assessment description with the Table 1 Schedule of Assessments
6.8.1 (Stopping Rules) Individual Subjects (20 – 21)	Addition of QTcB stopping criterion	Addition of the following individual subject stopping rule: - **8. QTcB interval increase of ≥ 60 msec from baseline or QTcB value ≥ 500 msec**
6.8.2 (Stopping Rules) LUM-201 Treatment Arms (21)	Clarification of dose reduction language	Addition of the following individual subject stopping rule: - Although at start of treatment this is a single arm study, as subjects may **have a single dose reduction to a 1. 6 mg/kg/day** ~~transition to a lower~~ LUM-201 dose during the course of the study, there may be more than one treatment arm at the end of the trial.
11.3.1 Electrocardiograms (ECGs) (27)	Addition of ECG language	Addition of the following section: - **11.3.1 Electrocardiograms (ECG)** **A 12-lead ECG (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, QT/QTc, morphology, and overall interpretation) will be recorded as described in Table 1, and as described in the Medpace Core Laboratories Site Acquisition Manual. Results will be interpreted by a central reader. ECGs collected prior to study drug administration at Screening/Baseline Day 1 (Visit 1) will be used as baseline.**
11.5 Study Activities (28-33)	Addition of ECG language	Addition of periodic ECG monitoring at applicable visits, as described in the Synopsis and Table 1 Schedule of Assessments.

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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 transaminase (serum glutamic pyruvic transaminase [SGPT])
ANCOVA	analysis of covariance
AST	aspartate transaminase (serum glutamic oxaloacetic transaminase [SGOT])
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
CI	confidence interval
CFR	Code of Federal Regulations
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
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 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
LDL	low-density lipoprotein
LTSE	Long-Term Safety Extension
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor
MRI	magnetic resonance imaging
PD	pharmacodynamic(s)
PGHD	pediatric growth hormone deficiency
PI	Principal Investigator
rhGH	recombinant human growth hormone
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
SST	somatostatin
SUSAR	serious unexpected suspected adverse reaction
T3	triiodothyronine
T4	free thyroxine
TEAE	treatment-emergent adverse events
TSH	thyroid-stimulating hormone
US	United States
WBC	white blood cell

4.0 WHO WORLD HEALTH ORGANIZATION INTRODUCTION AND BACKGROUND

Patients with untreated growth hormone deficiency (GHD) frequently attain adult heights less than 5 feet and have abnormal body composition (1). Treatment with recombinant human growth hormone (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, are now in clinical trials or have recently been approved in some regions, 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 lead to a pulsatile release of GH. LUM-201, binding to its receptors in the hypothalamus, not only stimulates the secretion of GHRH, but also suppresses the secretion of SST.

Lumos Pharma, Inc. (Sponsor) initiated a Phase 2 trial of LUM-201 in December 2020 in 80 children diagnosed with GHD (NCT04614337). In that ongoing clinical trial, approximately 20 patients are being randomized to 12-month treatment with rhGH. The current protocol aims to provide a 12-month LUM-201 treatment option for those 20 patients. If the Long-Term Safety Extension (LTSE) Study is open to enrollment at study sites, subjects may be allowed to enroll into the LTSE Study.

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. 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. The numerous causes include neoplasia, trauma, inflammation, surgery, and/or irradiation of the central nervous system and genetic causes. 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). PGHD is usually subcategorized as either organic (including both congenital and acquired), which is usually associated with an

inability to make GH and is a more severe form of GHD, or idiopathic GHD. Of the approximately 60-70% of the PGHD population identified as having idiopathic GHD, most are felt to have hypothalamic dysregulation as the cause of their GHD, as most of this population tests as GH-sufficient after completion of puberty.

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.

4.2 Background of Treatment Options

Current treatment of GHD children is limited to subcutaneous (SC) injections of rhGH. Treatment is required for an average of approximately 7 years, but in cases of organic GHD treatment may persist throughout adult life.

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 use of LUM-201 in the pediatric population.

To date, LUM-201 has been studied in more than 1200 people (~200 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.

4.4 Potential Risks and Benefits to Human Subjects

The main risk of LUM-201 in children is increased appetite.

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

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

5.0 STUDY OBJECTIVES

5.1 Primary Objective

- Assess the growth response to LUM-201 administration in children with idiopathic growth hormone deficiency (GHD) previously treated with daily rhGH for 12 months in the LUM-201-01 trial.

5.2 Secondary Objective

- To assess safety of LUM-201 administration in children with PGHD previously treated with daily rhGH for 12 months.

6.0 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a multiple center, 12-month, open-label in children with GHD who completed 12 months of rhGH treatment in the LUM-201-01 Trial. Up to 20 subjects will be enrolled.

Following successful screening, subjects will be assigned to the 3.2 mg/kg daily oral dose of LUM-201. IGF-1 samples will be collected throughout the study. If an IGF-1 SDS value > +2.0 is confirmed by a follow-up (unscheduled) lab, the LUM-201 dose may be reduced to 1.6 mg/kg/day.

The follow-up safety history of subjects will be collected by telephone visit 30 days after their final visit.

6.2 Rationale for the Study

This study investigates how children respond to daily LUM-201 after 12 months of treatment with daily injectable rhGH. In healthy children, GH is secreted in an ultradian pattern of discrete pulses (25). Secreted GH stimulates synthesis and release of IGF-1. Together, GH and IGF-1 signal the numerous intracellular mechanisms that culminate in physical growth during childhood (26). Children with GHD have diminished endogenous GH pulses, diminished IGF-1 and in consequence have inadequate growth. Growth can be restored with injections of rhGH but rhGH injections are associated with sustained and pharmacologically elevated levels of GH and, occasionally, of IGF-1. This study will evaluate growth and IGF-1 concentrations while on LUM-201 treatment in children previously treated with rhGH, who have previously demonstrated that they are able to secrete endogenous GH upon treatment with LUM-201 through the results of their PEM (Predictive Enhancement Marker) results in the LUM-201-01 Trial.

6.3 Rationale for Selection of the Treatment Population

The study population is limited to children who were assigned to rhGH comparator arm in the LUM-201-01 Trial and have completed that clinical trial, and thus have previously demonstrated that they are capable of responding to LUM-201 with an increase in GH as part of the PEM assessment.

6.4 Rationale for Selection of LUM-201 Dose

A dose-finding study of LUM-201 was conducted in naïve-to-treatment, pre-pubertal children with GHD 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 annualized height velocities (AHV) for these groups are shown in Table 2 and demonstrate a dose-related increase in AHV in response to treatment with LUM-201. Greater growth responses with rhGH than LUM-201 in a carefully stratified population of GHD subjects indicate a need to increase LUM-201 dose in order to achieve maximum GH release from the pituitary. Modeling of PD (GH and IGF-1) response to increasing doses of LUM-201 across the dose range of 1 mg to 200 mg demonstrates that 25 mg (equivalent to a daily dose of about 0.8 mg/kg/day) is about 30% up the GH-release dose-response curve, and that 100 mg (equivalent to a daily dose of about 3.2 mg/kg/day) is at the top of the GH-release dose-response curve, and suggests that maximal growth hormone response in children may be achieved with the 3.2 mg/kg dose. As this dose has thus far demonstrated acceptable safety and tolerability in the ongoing LUM-201-01 and LUM-201-03 trials, the dose of LUM-201 chosen for this study is 3.2 mg/kg/day.

Table 2 PEM Positive Subject Height Velocity at 6 Months in Merck Study 020

	Placebo n = 13	**LUM-201 0.4 mg/kg/d n = 12**	**LUM-201 0.8 mg/kg/d n = 15**	**rhGH 42 µg/kg/d n = 11**
Mean (SD) height velocity at 6 months (cm/yr)	5.09 (0.83)	6.2 (1.8)	7.7 (1.3)	8.8 (1.8)
P-value versus Placebo	N/A	0.0567	< 0.0001	< 0.0001

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

In summary, the rationale for the select dose is based on:

1. LUM-201 has been evaluated extensively in adults and has demonstrated an acceptable safety profile, at either single or prolonged exposures that are similar to or exceed those anticipated in children at the proposed dose of 3.2 mg/kg (27,31).

2. The safety margins defined by the toxicology studies in animals support exploration of the LUM-201 dose proposed for PGHD.

3. Data collected in LUM-201-01 and LUM-201-03 trials to date, in which several subjects have been receiving 3.2 mg/kg/day dose of LUM-201 for a period of several months, support safety and tolerability of this dose in children with GHD.

4. Examination of the LUM-201 dose and PD (GH release) relationship indicates that a plateau in GH response is anticipated to occur at a dose of approximately 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; however, a higher dose may not provide additional benefit.

6.5 Rationale for Study Design

This study is designed as a switch study for patients treated with rhGH in the LUM-201-01 Trial to generate initial data on the second year height velocity and safety of LUM-201 in children previously treated with rhGH for one year. Periodic safety laboratories will be drawn and height measurements will be obtained to gather information on how LUM-201 administration supports continued growth after the first year of catch-up growth attained under rhGH treatment in the LUM-201-01 Trial.

6.6 Study Duration and Dates

The total duration of treatment for each subject is 12 months.

The on-study time for each subject will be approximately 13-14 months, including Screening (up to 30 days), active treatment (12 months), and Follow up (30 days). If the LTSE Study is opened at a study site, subjects may be allowed to enroll into the LTSE Study. If a subject enrolls in the LTSE Study, the subject will not be required to have a post-treatment contact after Month 12 (visit 6).

6.7 Safety Reviews and Stopping Rules

The Medical Monitors (MMs) will monitor safety and clinical laboratory safety events on an ongoing basis. The MM will review data for any potential risks to subjects and 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, MM, and Sponsor.

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 >500 msec or uncorrected QT >600 msec, or QTc change from baseline of >60 msec, and > upper limit of normal (ULN).

9. Clinically relevant laboratory abnormalities, including serum ALT and/or AST > 3x 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, MMs, and 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.

6.8.2 LUM-201 Treatment Arms

Although at start of treatment this is a single arm study, as subjects may have a single dose reduction to a 1.6 mg/kg/day LUM-201 dose during the course of the study, there may be more than one treatment arm at the end of the trial. Given this, a 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 was designed for 12 months of treatment to allow the necessary minimum amount of time to assess change in height in this population.

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), PD markers, and bone ages are appropriate to the evaluation of a new investigational product (LUM-201).

6.10 Study Endpoints

6.10.1 Growth Endpoints

Growth parameters of efficacy (at Month 3 [visit 3], Month 6 [visit 4] and Month 12 [visit 6]) will be assessed based on:

- Annualized height velocity.
- Change in HT-SDS. (33)
- Change in Weight and Weight SDS. (33)
- Change in BMI and BMI SDS. (33)
- Change in Bone Age (Only Month 6 [visit 4]).

6.10.2 PD Endpoints

PD will be assessed by:

- GH, IGF-1 and IGFBP-3.

6.10.3 Safety Endpoints

Safety of LUM-201 will be assessed by AEs and SAEs, routine laboratory tests (hematology, chemistry panel including liver enzymes and urinalysis), HbA1c, blood glucose, free thyroxine (T4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), lipids, physical examinations, ECGs and vital signs.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

The Screening population will consist of children with PGHD who successfully completed 12 months of treatment with rhGH in LUM-201-01 study.

Approximately 20 subjects will be screened to allow enrollment of up to 20 subjects.

Following successful screening, subjects will be enrolled and commence their assigned 3.2 mg/kg daily oral LUM-201 treatment. Subjects may withdraw from the study at any time.

7.1 Inclusion Criteria

Potential study subjects must meet all the inclusion criteria listed below to be eligible for study participation:

1. Parent/caregiver must sign the informed consent, and the subject must sign the assent, as applicable.

2. Must have previously completed 12 months of daily rhGH treatment as part of the LUM-201-01 PGHD trial.

3. Is eligible for study participation as confirmed by the principal investigator (PI).

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. Has a medical condition that, in the opinion of the PI and/or MM, adds unwarranted risk to use of LUM-201.

2. Uses any medication that, in the opinion of the PI and/or MM, can independently cause short stature or limit the response to exogenous growth factors.

3. Has planned or is receiving current long-term treatment with medications known to act as substrates, inducers, or inhibitors of the cytochrome system CYP3A4 that metabolizes LUM-201 (see Appendix 1 for list of example medications). Subjects receiving shorter-term (two weeks or less) treatment with these medications should be evaluated on case-by-case basis by the PI in consultation with the MM.

4. Has been randomized to LUM-201 in the LUM-201-01 trial.

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. In addition, the MM or PI may withdraw a subject if medically necessary. If possible, subjects who withdraw early should complete the Month 12 visit (visit 6) activities and return at the scheduled Month 12 visit (visit 6) for a final evaluation of the growth endpoints.

8.0 ENROLLMENT AND BLINDING PROCEDURES

8.1 Methods of Subject Assignment

Each screened subject will enter the Subject Number previously assigned in the LUM-201-01 trial, at the Screening/Baseline visit (visit 1). Subject Numbers will not be reassigned.

8.2 Blinding

This study is an open-label study; no blinding is required.

9.0 STUDY TREATMENTS

9.1 Description of Treatments

All subjects will receive a single oral 3.2 mg/kg dose of LUM-201 at the Screening/Baseline visit (visit 1) which will include measurement of GH concentrations at baseline and 60 ± 10 minutes after dosing.

All subjects will commence their dosing at the Screening/Baseline visit (visit 1) and continue treatment until the Month 12 visit (visit 6).

9.1.1 LUM-201

Subjects will receive 3.2 mg/kg/day as an oral dose taken in the morning without regard to meals. If subject is not tolerating the 3.2 mg/kg/day dose, the PI and MM will determine if dose reduction would be appropriate on an individual basis.

9.2 Administration of Treatment

All subjects and their caregivers will receive instruction on the storage, handling, and administration of their assigned study drug at the Screening/Baseline (visit 1). 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.

The dose of study drug will only be adjusted based on body weight at Month 1 (visit 2), Month 3 (visit 3), Month 6 (visit 4) and Month 9 (visit 5). All changes in LUM-201 dosage will include instructions by the study staff to the subject caregiver.

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

9.2.1 Treatment Interruption

Study drug may be stopped temporarily for new medical events at the discretion of the PI and/or MM. Removal of subjects from the study or from a treatment arm are described in the Stopping Rules (Section 6.8).

9.2.2 Dose Reduction

Study drug dose may be reduced if the IGF-1 SDS is confirmed by a follow-up (unscheduled) laboratory testing to be > +2.0 at any visit after the Screening/Baseline visit (visit 1) or if the subject has demonstrated safety and tolerability issues to the 3.2 mg/kg/day dose administration. One dose reduction to 1.6 mg/kg is allowed. All dose reductions should be discussed with the Medical Monitors before implemented.

9.3 Concomitant Medications

Restrictions on concomitant medications are noted in the Inclusion and Exclusion Criteria (Sections 7.1 and 7.2) and in Appendix 1. Commencement of new medications that can influence the subject's safety or response to study drug are prohibited. Use of 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 LUM-201 administration paused, as needed. If illness persists past 2 weeks, the MM should be consulted, and the subject may need to terminate LUM-201 treatment.

9.4 Restrictions

All subjects must complete an overnight (after 10 p.m.) fast prior to Screening/Baseline (visit 1), Month 6 (visit 4) and Month 12 (visit 6). 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 will be performed by health care professionals or the caregiver. A subject who misses more than 10% of the intended doses 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.

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 polyester coil. All clinical supplies will be provided as 100-count bottles.

9.7 Storage, Transport, and Accountability:

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

All unused LUM-201 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 LUM-201 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. At the end of the Study, these materials will be destroyed or returned to the sponsor.

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 hydrocholoride to treat ADHD) while on trial, they may be excluded from continued trial participation. See Appendix 1 for complete details regarding prohibited medications and foods.

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 blood glucose abnormalities have been noted in patients treated with rhGH (1,3). It is not

known if this will be associated with LUM-201 treatment. The PI should contact the MM if signs or symptoms of IH occur, primarily headache or visual changes.

11.0 STUDY ASSESSMENTS AND PROCEDURES

11.1 Assessments of Efficacy

11.1.1 Height and Weight

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. Height should be measured during study visits at approximately the same time of day as the baseline height assessment (e.g., if the baseline is an AM height assessment, the clinic visits should be scheduled prior to noon, so that follow-up height assessments are also collected in the AM).

If not previously recorded in the LUM-201-01 trial, the heights of both parents should be measured. Reported heights should be recorded for parents unavailable for measurement.

11.1.2 Bone Age

Digitized radiographs of the left hand and wrist will be recorded at Month 6 visit (visit 4) and will be interpreted by the central reader to determine bone age.

11.2 Assessments of Pharmacodynamic (PD) Markers

Serum IGF-1, IGFBP-3 and GH are PD markers that will be evaluated in all subjects, as indicated in the Schedule of Assessments (Table 1).

PD markers concentration measurements will be performed by central laboratories.

11.3 Assessments of Safety

Safety assessments will be based on reports of AEs and SAEs (see Section 12.0 for full details), routine laboratory tests (hematology, chemistry panel including liver enzymes, and urinalysis), HbA1c, blood glucose, Free T4, T3, TSH, lipids, physical examinations, ECGs and vital signs.

11.3.1 Physical Examination

A complete physical examination will be performed at Screening/Baseline (visit 1) and at the Month 12 visit (visit 6) or Early Termination Visit for early study terminations. Fundoscopy may be performed at visits where headache is recorded as an AE, per PI's discretion. Signs of increased intracranial pressure should be confirmed by an ophthalmologist and lead to appropriate medical evaluation. Tanner staging of pubertal development will be performed at Screening/Baseline (visit 1), Month 3 (visit 3), Month 6 (visit 4), Month 9 (visit 5) and Month 12 (visit 6). Tanner staging to include breast development, pubic and axillary hair and, in males, testicular volumes.

11.3.2 Vital Signs

Vital signs should be recorded in the sitting position after approximately 5 minutes of rest. Vital signs include pulse, blood pressure, respiratory rate, and oral temperature.

11.3.1 Electrocardiograms (ECG)

A 12-lead ECG (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, QT/QTc, morphology, and overall interpretation) will be recorded as described in Table 1, and as described in the Medpace Core Laboratories Site Acquisition Manual. Results will be interpreted by a central reader. ECGs collected prior to study drug administration at Screening/Baseline Day 1 (Visit 1) will be used as baseline.

11.3.2 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the following time points. For more information, refer to the LUM-201-04 Laboratory Manual, and (Appendix 2) in this protocol.

- Complete blood count (CBC, including hemoglobin, hematocrit, red blood cell indices, white blood cell count [WBC], and platelet count), serum chemistry panel (including glucose, sodium, potassium chloride, bicarbonate, blood urea nitrogen [BUN], creatinine, alanine aminotransferase [AST], aspartate aminotransferase [ALT], and total bilirubin) will be performed at:
    - Screening/Baseline (visit 1) (results from the Month 12 visit [visit 11] on the LUM-201-01 Trial can be used)
    - Month 1 (visit 2)
    - Month 3 (visit 3)
    - Month 6 (visit 4)
    - Month 12 (visit 6)
- Lipid studies (low- and high-density lipoproteins [LDL and HDL, respectively], cholesterol, and triglycerides), thyroid function (T3, T4, and TSH), Urinalysis (specific gravity, pH, and Multi-stix readings), HbA1c, and Fasting glucose will be assessed at:
    - Screening/Baseline (visit 1) (results from the Month 12 visit [visit 11] on the LUM-201-01 Trial can be used)
    - Month 6 (visit 4)
    - Month 12 (visit 6)

11.4 Study Procedures

11.4.1 Informed Consent

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

11.4.2 Medical History and Genetic Testing

A complete medical history will be obtained at the Screening. No genetic testing will be required for this study.

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 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/Baseline (visit 1) +30 day window from LUM-201-01 Month 12 visit (visit 11)

Screening/Baseline (visit 1) will typically be conducted as specified in the protocol for the LUM-201-01 Trial. Assessments completed for the LUM-201-01 Month 12 (visit 11) will not need to be repeated for the Screening/Baseline (visit 1).

The following procedures will also be conducted specifically for the LUM-201-04 trial:

- Obtain informed consent (and assent where applicable).
- Verify inclusion and exclusion criteria.
- Record medical history.
- Record any adverse events.
- Record prior and concomitant medications.
- Record vital signs (prior to LUM-201 administration and approximately 1 hour after the LUM-201 administration).

- Record ECG (1 hour ± 10 minutes after LUM-201 administration)
- Collect GH serum samples 0 (pre-dose) and 60 ± 10 minutes post-dose.
- Dispense study drug adequate to permit dosing through Month 1 (visit 2).
- Instruct caregivers on storage and administration of study drug.
- Remind caregiver to begin at-home administration of study drug on the following day.
- Schedule Month 1 (visit 2) for 30 ± 3 days from Screening/Baseline (visit 1).
- Remind subjects not to take their study drug prior to Month 1 (visit 2) clinic visit.

The following assessments completed for the LUM-201-01 Month 12 visit (visit 11) will not need to be repeated:

- Collect safety labs, IGF-1 and IGFBP-3 samples.
- Conduct physical examination (including Tanner pubertal staging).
- Record height and weight.
- Record ECG (prior to LUM-201 administration)

11.5.1.1 Month 1 ± 3 days (Visit 2)

Month 1 (visit 2) will be conducted 30 ± 3 days from the Screening/Baseline (visit 1). The following procedures will be conducted:

- Record AEs.
- Record concomitant medications.
- Record vital signs.
- Record weight.
- Collect samples for:
  - hematology/CBC.
  - serum chemistries.
- Study drug:
  - Complete drug accountability/compliance check.
  - Adjust drug dose to current body weight (if applicable).
  - Dispense study drug adequate to permit dosing through Month 3 (visit 3).
- Administer LUM-201.
- Answer any questions and encourage compliance with daily dosing.

- Schedule Month 3 (visit 3) for 3 months ± 7 days from Baseline (visit 1).
- Remind subjects not to take their study drug prior to Month 3 (visit 3) clinic visit.

11.5.1.2 Month 3 ± 7 days (visit 3)

Month 3 (visit 3) will be conducted 3 Months ± 7 days from Baseline (visit 1). The following procedures will be conducted.

- Record AEs.
- Record concomitant medications.
- Record vital signs.
- Record ECG 1 hour ± 10 minutes after LUM-201 administration
- Record height and weight.
- Conduct Tanner pubertal staging.
- Collect samples for:
  - hematology/CBC.
  - serum chemistries.
- Collect IGF-1 and IGFBP-3 serum samples (pre-dose).
- Study drug:
  - Complete drug accountability/compliance check.
  - Adjust drug dose to current body weight (if applicable).
  - Dispense study drug adequate to permit dosing through Month 6 visit (visit 4).
  - Administer LUM-201.
- Schedule Month 6 (visit 4) for 6 months ± 7 days from Baseline visit (visit 1).
- Remind subjects not to take their study drug prior to Month 6 (visit 4) clinic visit.

11.5.1.3 Month 6 ± 7 days (Visit 4)

Month 6 (visit 4) will be conducted after an overnight fast (beginning at 10 p.m.) 6 Months ± 7 days from Baseline (visit 1). The following procedures will be conducted.

- Conduct Tanner pubertal staging.
- Record AEs.
- Record concomitant medications.
- Record height and weight.
- Record vital signs.
- Record ECG 1 hour ± 10 minutes after LUM-201 administration

- Conduct X-ray to assess bone age (may be done within 7 days prior to or after the visit).
- Collect fasting samples for:
  - hematology/CBC.
  - serum chemistries.
  - HbA1c.
  - fasting glucose.
  - thyroid panel (TSH, T_4, T_3).
  - lipids.
  - urinalysis (dipstick).
- Collect IGF-1 and IGFBP-3 samples (pre-dose).
- Collect GH serum samples 0 (pre-dose) and 60 ± 10 minutes post-dose.
- Provide a snack after collection of fasting labs.
- Study drug:
  - Complete drug accountability/compliance check.
  - Adjust drug dose to current body weight (if applicable).
  - Dispense study drug.
  - Administer LUM-201.
- Schedule Month 9 (visit 5) for 9 Months ± 7 days after Baseline (visit 1).

11.5.1.4 Month 9 ± 7 days (Visit 5)

Month 9 (visit 5) will be conducted 9 Months ± 7 days from Baseline (visit 1). The following procedures will be conducted.

- Conduct Tanner pubertal staging.
- Record AEs.
- Record concomitant medications.
- Record height and weight.
- Record vital signs.
- Study drug:
  - Complete drug accountability/compliance check.
  - Adjust drug dose to current body weight (if applicable).
  - Dispense study drug.
  - Administer LUM-201.

- Schedule Month 12 (visit 6) for 12 Months ± 7 days after Baseline (visit 1).
- Remind subjects not to take their study drug prior to Month 12 (visit 6) clinic visit.

11.5.1.5 Month 12 ± 7 days (Visit 6) (Performed after an overnight [10 p.m.] fast) or Early Termination (ET) Visit

Month 12 (visit 6) will be conducted after an overnight fast (beginning at 10 p.m.). The following procedures will be conducted.

- Conduct physical exam with Tanner pubertal staging.
- Record AEs.
- Record concomitant medications.
- Record vital signs.
- Record ECG 1 hour ± 10 minutes after LUM-201 administration
- Record height and weight.
- Collect fasting samples for:
  - hematology/CBC.
  - serum chemistries.
  - HbA1c.
  - fasting glucose.
  - thyroid panel (TSH, T_4, T_3).
  - lipids.
  - urinalysis (dipstick).
- Collect IGF-1 and IGFBP-3 samples (pre-dose).
- Collect GH serum samples 0 (pre-dose) and 60 ± 10 minutes post-dose.
- Provide a snack after collection of fasting labs.
- Study drug:
  - Complete drug accountability/compliance check.

11.5.1.6 Post-treatment Follow-up Contact (approximately 30 ± 5 days after Month 12 [visit 6], by telephone) for subjects who don't transition to the LTSE Trial

The following procedures will be conducted.

- Record concomitant medications.
- Record AEs.

- Complete End of Study (EOS) Form.

11.5.1.7 Study Auditing and Inspecting

The Sponsor may audit the study conduct, compliance with the protocol and accuracy of the data.

The PI/institution will permit study-related monitoring, audits, and inspections by the Sponsor, Institutional Review Board/Independent Ethics Committee (IRB/IEC), government regulatory bodies and Lumos Pharma, Inc. personnel or its designees by providing direct access to source data/documents after appropriate notification from Sponsor.

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 PI 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 PI or 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 PI, or 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 or until the subject starts new GHD treatment, including new investigational treatment, whichever occurs earlier. Also record Screening/Baseline (visit 1) procedure-related AEs that occur before the start of study treatment. Other than study procedure-related AE, any other event that precedes the first exposure to study drug should be collected as a baseline condition on the Medical History form.

Record all AEs either observed by the PI 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 PI 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 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. The PI will assess the status of previously reported, and occurrence of new AEs and SAEs at all subject evaluation time points during the study.

12.2.1 Severity

Use the definitions found in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (November 2017) for grading the severity (intensity) of AEs. The CTCAE v5.0 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 v5.0, use the following grading system to assess severity:

- Grade 1 – Mild; asymptomatic or mild symptoms with no impact on activities of daily living (ADL); clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local or noninvasive intervention indicated; limiting some age-appropriate instrumental ADL, such as attending school, activities, etc.
- Grade 3 – Severe or medically significant but not immediately life-threatening; 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, the PI 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. (e.g., are not reasonably related to the drug, or are judged to likely related to some cause other than study drug.

12.2.3 Expected Adverse Events

Expected AEs include increased appetite.

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 PI to the MM within 24 hours through the 30-day period after the last dose of study treatment. The minimum data required for the initial SAE report includes the subject ID, the SAE term, the start date of the SAE, and the initial relatedness (either Drug-related or Drug-unrelated). 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, 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 PI (e.g., hospital admission or discharge notes, laboratory results). SAEs will be followed up through completion or treatment termination.

Drug Safety Contact Information	
Telephone Numbers	
Local Number:	[redacted] Sponsor MM: [redacted]
Fax Numbers	
Local Fax:	[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 the PI, according to regulatory requirements. The PI 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 PI 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 General Considerations

Summaries and descriptive statistics will be provided by treatment group, as applicable. 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.

The gender, age, height, weight, treatment group , and bone age of subjects will be described. Entrance into puberty is defined as Tanner Stage 2 breast development in girls and testicular volumes $\geq$ 4 mL in boys.

The AHV at the time point t2 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 at Baseline visit (visit 1).

Standard Deviation Scores for height, weight, and BMI will be computed using the WHO Child Growth Standards available from the World Health Organization (WHO) website (33).

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

Mean values and change from Baseline (visit 1) values will be compiled for all clinical laboratory tests. Shift tables may be employed to document treatment related changes.

All bone age results will be determined by a central reader using the Greulich and Pyle method (35). Change in Bone Age will be calculated. The ratios of bone age to chronological age (BA/CA) from LUM-201-01 Month 6 visit and this trial's Month 6 (visit 4), and the change in the ratio between the LUM-201-01 Month 6 visit and this trial's Month 6 (visit 4) 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, and the calculation method of Hermanussen and Cole (36).

A summary table of subjects with AHV at Month 12 (visit 6) < 70% of their AHV at the Month 12 visit in LUM-201-01 will be determined.

13.2 Determination of Sample Size

No formal calculation of power and sample size will be performed.

13.3 Analysis Populations

13.3.1 Intent-to-treat (Full Analysis Set)

The Full Analysis Set includes all enrolled subjects who have received at least one dose of study treatment. This set will be used for the safety analysis.

13.3.2 Per Protocol

The Per Protocol Population includes all enrolled subjects who complete Month 12 (visit 6) and have not missed more than 10% of scheduled doses and who do not have any significant protocol

deviations. The Per Protocol Population will be used for the primary evaluation, the growth response to treatment.

13.3.1 Safety Population

The Safety Population is defined as all subjects having at least one dose of study drug.

13.4 Demographics and Baseline Characteristics

Demographic and Baseline Characteristics include:

- Age.
- Gender.
- Race/Ethnicity.
- Birth weight and gestational age.
- Birth weight percentile for gestational age.
- Maternal and paternal heights for calculation of MPH.
- Bone age (as measured at Month 6 in LUM-201-01 Trial).
- Target HT-SDS (computed from maternal and paternal heights).
- Height and HT-SDS.
- Weight and weight SDS.
- BMI and BMI SDS.
- Tanner Stage.
- Baseline IGF-1, IGF-1 SDS.

13.5 Efficacy Analyses

13.5.1 Effects of LUM-201 on Growth

Descriptive statistics will be compiled for 6-month and 12-month AHV, change in HT-SDS, change in weight, weight SDS, BMI, and BMI SDS. These measures will be calculated from least square means from an analysis of covariance (ANCOVA) with age, Baseline HT-SDS, and bone age delay as covariates.

13.6 Safety Analyses

AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 23.1). Summary tables of treatment-emergent AEs (TEAEs) will be provided. Laboratory and vital sign 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 number and percentage of subjects with changes to or from the normal range (e.g., normal to low, normal to high, low to normal, etc.) from baseline to each subsequent visit

13.7 Missing and Spurious Data

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

For height related endpoints, 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 height after the last measurement.

13.8 Retention of Data

The PI 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 PI 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. 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 PI 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

No interim analysis is planned, but interim analyses may be performed at Sponsor discretion as described in the Statistical Analysis Plan (SAP).

14.0 STUDY DURATION AND TERMINATION

The expected study duration is through completion of Month 12 (visit 6) or withdrawal of consent. The study is expected to start in 2022.

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 PI, or a person delegated by the PI, 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 PI 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 PI 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 before the study is implemented. Documentation of subsequent reviews of the study must also be forwarded to the Sponsor.

16.0 ADMINISTRATIVE PROCEDURES

16.1 Sponsor Responsibilities

Lumos Pharma, Inc. reserves the right to terminate the study and remove all study materials from the study center at any time. Lumos Pharma, Inc. and the PI 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 the clinical center:

- LUM-201 as described in Section 9.0.
- IB for LUM-201.
- CRFs or data collection tools (e.g., laboratory kits, ECG machines).

Refer to the Study Manual for a list of additional Sponsor-provided supplies for this study.

16.1.2 Investigator Training

The study site will have a study initiation meeting to ensure the center staff understand the protocol, study requirements, and data capture processes. This training will take place before the first subject is enrolled. Study center staff will be provided with information regarding GCP and regulations specific to the conduct of clinical studies. The study center is responsible for ensuring that new team members are adequately trained and the training is documented.

16.1.3 Ongoing Communication of Safety Information During the Study

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

The Sponsor will also notify the PI 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/IEC and approved by the IRB/IEC 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 at the study center are controlled and documented adequately.
- Verify that the PI 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 PI/institution will permit study-related monitoring, audits, and inspections by the Sponsor, IRB/IEC, government regulatory bodies, and Lumos Pharma, Inc. Quality Assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from Sponsor.

16.2 Investigator Responsibilities

16.2.1 Subject Screening Log

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

16.2.2 LUM-201 Accountability

An initial supply of LUM-201 will be shipped to the study center's pharmacy when all the initiation documents, including IRB/IEC approval, 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 ordering a resupply.

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 PI or other study center personnel supply IMP to other 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 PI 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 PI or designee.

The PI 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) 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 PI 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 that are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for additional PD analyses.

After the study, samples may be used for additional investigation to help identify factors that may influence response to therapy. Such samples will be used in compliance with guidelines defined by FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable (issued 25 April 2006) and European Agency for the Evaluation of Medicinal Products (EMEA)'s Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA 2007). No DNA will be collected.

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 PI of MM’s safety decisions for immediate implementation for safety reasons.

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 PI 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, the PI may not present or publish partial or complete study results individually without review by the Sponsor. The PI 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 the PI 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). The site PI shall be listed as lead author 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.

18.0 REFERENCES

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19.0 APPENDICES

19.1 Appendix 1: 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

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.

19.2 Appendix 2: Laboratory Testing

Table 3 Specialty Laboratory Tests

Matrix/ Analyte	Screening/Baseline (Visit 1)		Month 3 (Visit 3)		Month 6 (Visit 4)		Month 12 (Visit 6)	
	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times	No. of Samples	Collection Times
IGF-1	0*	–	1	0 min	1	0 min	1	0 min
IGFBP-3	0*	–	1	0 min	1	0 min	1	0 min
GH	2	0, 60 min	0	–	2	0, 60 min	2	0, 60 min

Note: Time "0" is pre-dose

*: These samples are collected at the Month 12 visit on the LUM-201-01 study.

19.3 Appendix 3: Clinical Laboratory Analytes

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; 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