Statistical Analysis Plan

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)

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Summary of Changes from Version 2.0 to 3.0.

Section	Update
2	Objective for correlation between PD response and AHV was removed.
4.1	Updated to include changes from SAP version 2.0 to version 3.0.
4.3.3	Added AHV to the variables for SDS.
4.3.7	Remove section. Renumber subsequent sections (PEM Test Results and Tanner Stage)
4.5.2	Removed section describing visit windows for unscheduled lab visits. Section 4.5.3 (Height and Height Related Data) renumbered to 4.5.2. Section 4.5.3.1 (LOCF imputation) renumbered to 4.5.2.1.
4.5.3	Added section to describe LOCF imputation of planned dose also described in section 5.8.
4.6	Added section to describe ET visit windows for ADHT/ADDA.
4.7	Added section to define Study Day 1.
5.8	Updated dosing compliance calculation to match use all dosing data.
6.2	Updated terms for ANCOVA model, non-convergence plan, and inclusion of Month 24 AHV as an endpoint.
6.2.1	Updated Multiple Imputation sensitivity analysis plan.
7.2.1	Added AHV SDS to Clinical Parameters of Efficacy in other secondary endpoint analyses.
8.1	Section removed “PD Response and AHV Correlation”. Renumbered 8.2 to 8.1 and 8.3 to 8.2.
8.2	Updated exploratory analysis of AHV relationship with baseline characteristics.
Appendix 2	Added AHV SDS reference.

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ABBREVIATION	DEFINITION
AE	adverse event
AESI	adverse event of special interest
AHV	annualized height velocity
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BA	Bone age
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CA	chronological age
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
EDC	electronic data capture
FAS	Full Analysis Set Population
GGT	gamma glutamyl transferase
GH	growth hormone
GHD	growth hormone deficiency
HR	heart rate
HT SDS	height standard deviation score
HV	height velocity
ICH	International Council for Harmonization
IGFBP-3	insulin-like growth factor binding protein 3
IGF-1	insulin-like growth factor 1
IGF-1 SDS	insulin-like growth factor 1 standard deviation score
IRT	interactive response technology
ITT	Intent-to-Treat Population
LC/MS	liquid chromatography–mass spectrometry
LLQ	lower limit of quantification
LOCF	last observation carried forward
LSM	least square means
MAR	missing at random
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities

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ABBREVIATION	DEFINITION
min	minimum
MM	medical monitor
MPH	mid-parental height
MPH SDS	mid-parental height standard deviation score
msec	millisecond
PD	pharmacodynamic(s)
PEM	predictive enrichment marker
PK	pharmacokinetic(s)
PP6	Per Protocol Month 6 Population
PP9	Per Protocol Month 9 Population
PP12	Per Protocol Month 12 Population
PP18	Per Protocol Month 18 Population
PP24	Per Protocol Month 24 Population
PR	PR interval
PT	preferred term
QT	absolute QT interval
QTcB	absolute QT interval corrected for heart rate by Bazett formula
QTcF	absolute QT interval corrected for heart rate by Fridericia's formula
rhGH	recombinant human growth hormone
RR	RR interval
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
SEM	standard error of the mean
SOC	system organ class
SUSAR	serious unexpected suspected adverse reaction
TBL	total bilirubin
TEAE	treatment-emergent adverse events
ULN	upper limit of normal
yr	year
WHO	World Health Organization

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1 Introduction/Background

This statistical analysis plan (SAP) describes data analysis specifications for the LUM-201-01 protocol (version 7.0, dated 28 April 2022) entitled "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)." The SAP follows the International Council on Harmonisation (ICH) Guidelines E3 and E9. All statistical analyses will be performed using SAS®, Version 9.4 or higher. In cases in which the analyses in this SAP differ from those in the study protocol, the analyses in the SAP supersede those in the protocol. Should differences exist, these will be described in section 4.1 of this document.

1.1 Study Overview

This study is a multicenter, up to 24 months, randomized, open-label, active control, parallel arm, Phase 2 study of daily oral LUM-201 in naïve-to-treatment, prepubertal children with idiopathic GHD.

This study is designed to confirm the ability of the clinical predictive enrichment marker (PEM) strategy to select subjects likely to respond to LUM-201 treatment, and the reproducibility of the positive PEM test result.

Subjects will receive PEM tests prior to randomization, consisting of a single dose of LUM-201 (0.8 mg/kg), and blood samples for IGF-1 and GH predose, and GH post-dose. A subject is considered "PEM positive" if the following criteria are met: IGF-1 concentration > 30 ng/mL (> 3.92 nmol/L) and peak serum GH concentration ≥ 5 ng/mL observed following the single dose of LUM-201. Subjects who meet both criteria are "PEM positive".

Preliminary clinical validation of predictive enrichment marker (PEM) strategy intended to select subjects likely to respond to therapy with LUM-201 will be evaluated by the proportion of treatment responders (Month 6 AHV ≥ 6.85 cm/yr); dose selection for future studies will be supported by the comparison of the annualized height velocity (AHV) at Month 6 in the LUM-201 treatment groups and the rhGH treatment group. Up to an additional 18 months of study treatment will be used to further characterize overall safety and growth response to LUM-201.

Other study assessments are employed as standard pediatric practice for the evaluation of growth and growth promoting treatments.

The Schedule of Assessments is presented in Appendix 4.

1.2 Changes to Study Design in Protocol Amendments

Prior to Protocol version 5.1, the Screening portion of the study consisted of two visits (Screening 1 and Screening 2). All screened subjects completed two PEM tests, one at each screening visit. Starting with Protocol version 5.1, the Screening portion of the study is reduced to one visit (Screening 1). Only subjects that are "PEM positive" at the

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screening visit, and were determined to be eligible for the Treatment portion of the study, complete a second PEM test on Day 1.

To maintain consistency in visit naming, and for ease of summarizing study data, the screening visit for subjects entering under Protocol version 5.1 and beyond will be referred to as Screening 1. Subjects entering prior to Protocol version 5.1 will have Screening 1 and Screening 2 visits, while the comparable PEM test visits for subjects entering under Protocol version 5.1 and beyond will be Screening 1 and Day 1 visits.

Prior to Protocol version 7.0, GH samples following the PEM dose were collected at 30, 60, and 90 minutes post-dose. Starting with Protocol version 7.0, the 90-minute post-dose sample is no longer collected. In addition, the Week 2 in-clinic visit was eliminated; results for assessments that were previously made at this visit will not be available for subjects enrolling under Protocol version 7.0 and beyond.

1.3 Treatment Administration

1.3.1 PEM Dose

All screened subjects will receive a single oral 0.8 mg/kg dose of LUM-201 during the PEM test at Screening 1.

For subjects who were enrolled in the Screening portion of the study prior to Protocol version 5.1, all screened subjects took a second PEM test at Screening 2 (which occurred at least one week, but not later than 13 days after Screening 1).

For subjects entering under Protocol version 5.1 and beyond, only subjects who are "PEM positive" at Screening 1 will be given a second PEM test on Day 1 (which will occur within 30 days after Screening 1 for subjects enrolled prior to Protocol version 7.0, or within 56 days for subjects enrolled under Protocol version 7.0 and beyond).

1.3.2 Randomized Treatment Dose

For subjects who entered the Treatment portion prior to Protocol version 5.1, all randomized subjects commenced their treatment on Day 1, which occurred at least one week after Screening 2. For Subjects who entered the Treatment portion under Protocol version 5.1 and beyond, subjects randomized to LUM-201 will commence their treatment the day following Day 1, and subjects randomized to rhGH will commence their treatment in the evening on Day 1. LUM-201 treatment is administered as an oral dose taken in the morning, without regard to meals. rhGH treatment is administered as a daily SC injection; the dose of rhGH used in this study is 34 μg/kg.

The quantity of study drug administered will be adjusted based on body weight at Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, and Month 21 visits at the instruction of the study staff to the subject caregiver. Subject's weight should be rounded to the nearest kilogram.

All subjects will continue their randomized treatment until the Month 12 visit. Subjects randomized to rhGH will be offered the option to transition to a LUM-201 extension

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study. Subjects randomized to LUM-201 who have AHV≥ 6.7 cm/yr at Month 12 may continue their same LUM-201 treatment for up to an additional 12 months, with an option to transition into LUM-201-02 long-term safety extension trial at Month 18 or Month 24 visit. Subjects randomized to LUM-201 who have AHV < 6.7 cm/yr at Month 12 will be withdrawn from the trial and may be switched to standard of care treatment at the discretion of the principal investigator and subject [1].

1.4 Treatment Blinding and Randomization

This is an open-label study, except for the medical monitors (MMs) who are blinded to treatment allocation.

The randomization to the treatment groups will be centralized across all sites, and will be stratified by age (< 90 months, ≥ 90 months) and Screening 1 height (HT) standard deviation score (HT SDS) (< -2.5, ≥ -2.5). The randomization will be assigned by an electronic system after approval by the MMs. Around eighty “PEM Positive” subjects will be randomized at a 1:1:1:1 ratio to the following four daily treatment groups: LUM-201 0.8 mg/kg, LUM-201 1.6 mg/kg, LUM-201 3.2 mg/kg, rhGH 34 µg/kg.

1.5 Sample Size Calculation

Sample size calculations were made in consideration of the ability for the PEM test to select for LUM-201 treatment response (“responders”). The null hypothesis is a responder proportion of ≤ 50%, with the alternative hypothesis of > 50%. Assuming a population responder rate of 70%, a sample size 60 LUM-201 subjects, 20 in each of three dose levels, will provide > 85% power for a one-sided test of this hypothesis with alpha of 0.025.

An additional 20 subjects will be randomized to daily rhGH treatment.

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2 Study Objectives and Endpoints (Protocol 7.0)

Objectives	Endpoints
Primary	
• Preliminary clinical validation of predictive enrichment marker (PEM) strategy intended to select subjects likely to respond to therapy with LUM-201	• Positive growth response rate: proportion of "responders", defined as PEM positive subjects, who received randomized LUM-201 doses, and achieved an AHV ≥ 6.85 cm/yr from Day 1 to Month 6 [2]
Primary Clinical	
• To select a pediatric dose of LUM-201 for use in future studies including Phase 3 trial(s)	• Comparison of Month 6 AHVs achieved by daily rhGH and the dose levels of LUM-201 treatment
Key Secondary	
• To assess the reproducibility of the "PEM positive" classification of subjects	• Positive agreement rate: the number of subjects with two positive PEM tests, divided by the number of subjects with two PEM tests, one of which was positive
Other Secondary	
• To assess additional clinical parameters of efficacy (at Month 6 and Month 12)	• Change in height standard deviation score (HT SDS) • Change in height velocity (HV) • Change in weight and weight SDS • Change in body mass index (BMI) and BMI SDS • Change in Bone Age (BA) compared to Chronological Age (CA) (ie, BA/CA) ratio
• To assess the safety and tolerability of oral LUM-201	• AEs, SAEs, SUSARs • Clinical Laboratory Safety Events • ECGs
• To further explore pharmacokinetics (PK) of LUM-201	• Plasma LUM-201 concentrations

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Objectives	Endpoints
• To determine acute and chronic pharmacodynamic (PD) responses to daily LUM-201	• Growth hormone (GH) • Insulin-like growth factor 1 (IGF-1) • Insulin-like growth factor 1 Standard Deviation Score (IGF-1 SDS) • Insulin-like growth factor binding protein 3 (IGFBP-3) • Molar IGF-1/IGFBP-3 ratio
• To characterize variance in AHVs of subjects treated with rhGH and LUM-201 to enable sample size estimates for future trials	• AHV change from baseline
Exploratory	
• Comparison of PD responses to LUM-201 and rhGH	• IGF-1 • IGF-1 SDS • IGFBP-3 • Molar IGF-1/IGFBP-3 ratio
• Explore the relationship of AHV and Baseline characteristics	• P-values for baseline characteristics in the AHV ANCOVA models.

3 Analysis Populations

Membership of subjects in the analysis sets will be determined prior to database closure.

3.1 Enrolled Population

The Enrolled Population includes subjects who signed informed consent.

3.2 Intent-to-treat (Full Analysis Set) Population

The Full Analysis Set (FAS) Population includes subjects who received at least one dose of LUM-201 or rhGH during the Treatment portion of the study.

3.3 Safety Population

The Safety Population includes subjects who received at least one dose of LUM-201 during the Screening portion of the study.

3.4 Per Protocol Population

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A total of five Per Protocol Populations will be created: Month 6, Month 9, Month 12, Month 18, and Month 24.

3.4.1 Per Protocol Month 6 Population (PP6)

The Per Protocol Month 6 Population includes subjects who complete Month 6 and have not missed more than 20% of scheduled doses between Day 1 and Month 6, and who do not have any major protocol deviations likely to impact efficacy.

3.4.2 Per Protocol Month 9 Population (PP9)

The Per Protocol Month 9 Population includes subjects who complete Month 9 and have not missed more than 20% of scheduled doses between Day 1 and Month 9, and who do not have any major protocol deviations likely to impact efficacy.

3.4.3 Per Protocol Month 12 Population (PP12)

The Per Protocol Month 12 Population includes subjects who complete Month 12 and have not missed more than 20% of scheduled doses between Day 1 and Month 12, and who do not have any major protocol deviations likely to impact efficacy.

3.4.4 Per Protocol Month 18 Population (PP18)

The Per Protocol Month 18 Population includes subjects who complete Month 18 and have not missed more than 20% of scheduled doses between Day 1 and Month 18, and who do not have any major protocol deviations likely to impact efficacy.

3.4.5 Per Protocol Month 24 Population (PP24)

The Per Protocol Month 24 Population includes subjects who complete Month 24 and have not missed more than 20% of scheduled doses between Day 1 and Month 24, and who do not have any major protocol deviations likely to impact efficacy.

3.5 24-month Completer Population

Subjects that completed 24 months of treatment, regardless of compliance or protocol deviations.

4 Statistical Methodology

4.1 Changes from Protocol-Specified Analyses

For all analyses and summaries involving LC/MS IGF-1 and IGFBP-3 results, Molar LC/MS IGF-1/IGFBP-3 ratio will also be included.

Section 2: Other secondary objective “Change in predicted adult height” will be replaced by the “Change in (HT SDS - MPH SDS).”

Section 4.5.2.1: Missing height and derived height parameters up to 12 months will be imputed by LOCF of the parameter directly, instead of derived from LOCF of height measurement with estimated interval between two missing visits. Missing height and height related data after Month 12 will not be imputed.

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Section 4.5.3: Missing Study Drug Administration doses will be imputed by LOCF in order to compute compliance.

Section 4.6: Early Termination visit windowing for height and drug administration analysis datasets.

Section 5.3: Screening BA has been replaced by BA delay, and predicted adult height has been replaced by (HT SDS - MPH SDS).

Section 5.8: Updated dosing compliance calculation.

Section 6.1: The primary endpoint will be tested using a binomial test, instead of Chi-square, due to small sample size.

Section 6.2: ANCOVA model was updated to include following covariates: baseline age, sex, treatment group, peak GH response to PEM LUM-201 test at screening, baseline HT SDS, baseline BMI SDS, baseline LC/MS IGF-1 SDS, baseline bone age delay, and the difference between height SDS and mid-parental height SDS.

Formerly section 8.1: The exploratory analysis of correlation between PD response and AHV (Protocol Section 13.7.4) will not be performed.

Section 8.2: The ANCOVA model specified to explore the relationship of AHV and Baseline characteristics will be the same as in section 6.2.

Section 9.1.2.1: A subgroup analysis for subjects with 'true' iGHD, of the primary endpoint will be performed during the first interim analysis.

Section 9.2.1: A subgroup analysis for subjects with standard GH stimulation test response between 7 and 10 ng/mL, exclusive, of the primary endpoint will be performed during the second interim analysis.

4.2 Statistical Notation and Presentation

For continuous variables, the following descriptive statistics will be provided: number of subjects, mean, standard error of the mean (SEM), standard deviation (SD), minimum (min), maximum (max), and median. For categorical variables, descriptive statistics will include the number and percentage of subjects in each category, using either the number of subjects in the treatment group or the number of subjects with non-missing values as the denominator for the percentages.

In general, min and max values will be rounded to the precision of the original value. Mean and median values will be rounded to one decimal place greater than the precision of the original value. SD and SEM values will be rounded to two decimal places greater than the precision of the original value. Additional truncation on rounding may be applied to parameters that contain too many decimal places for table presentation. Percentages for summarizing categorical data will be rounded to one decimal place. p-values will be presented with four decimal places, and values less than

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0.0001 will be presented as <0.0001. Unless specified otherwise, all inferential statistical testing will be two-sided.

When summarizing laboratory assays, values below the lower limit of quantification (LLQ) will be imputed as LLQ/2; values reported as "≥ x" or "≤ x" will be imputed as the value of x; values reported as "< x" will be imputed as a value one digit less than the reported value, relative to the precision of the lab measurement (ex. "x < 10" imputed as 9, " x < 9.5" imputed as 9.4, and "x < 0.11" imputed as 0.10); values reported as "> x" will be imputed as a value. In listings, data will be presented as recorded, with the sign.

Analysis of safety laboratory post-baseline minimum and maximum values will consider results from scheduled and unscheduled visits. For all other data summary and analysis, only data used for protocol scheduled visits will be included.

Unless specified, all listings will be presented by randomized treatment group, subject, and visit (if applicable), for the Safety Population. All values, scheduled or unscheduled, will be presented in data listings.

4.3 Derivations

4.3.1 HV and AHV

The HV (height velocity) at the timepoint t_2 is derived as follows, where h_2 and h_1 are the heights (in cm) measured at t_2 and t_1 (in days), respectively:

$$HV = \left(\frac{h_2 - h_1}{t_2 - t_1}\right)$$

The AHV (annualized height velocity) is derived as follows:

$$AHV = HV * 365.25$$

Baseline will be calculated where h_1 and t_1 are the prior height measurement and date of the prior visit, respectively, as recorded in the electronic data capture (EDC); h_2 and t_2 are the height measurement reported on Day 1 and the date of Day 1, respectively. Prior height data was not required for subjects enrolled prior to Protocol v7.0. As such, baseline HV and AHV will only be calculated for subjects enrolled under Protocol v7.0 and beyond.

4.3.2 Body Mass Index (BMI)

BMI is reported in EDC only at Screening 1. For all visits after Screening 1, if both weight and height are reported, BMI will be derived as follows:

$$BMI = \frac{weight\ (kg)}{height\ (m)^2}$$

The resulting value will be rounded to one decimal place.

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4.3.3 Standard Deviation Scores

Standard deviation scores (also called z-scores) for height, weight, and BMI will be computed using percentile, and z-score data files from the World Health Organization (WHO) Child Growth Standards [3-9]. Standard deviation scores for annualized height velocity will be computed using percentile and z-score data files from the Journal of Clinical Endocrinology and Metabolism. [10] Standard Deviation Scores will be derived using the LMS method, such that for any value X, the corresponding z-score (Z) will be calculated by:

$$Z = \frac{\left[\left(\frac{X}{M}\right)^{L} - 1\right]}{LS};\ L \neq 0 \qquad \text{or} \qquad Z = \frac{ln\left(\frac{X}{M}\right)}{S};\ L = 0$$

It should be noted that weight-for-age reference data are not available beyond age 10 because this indicator does not distinguish between height and body mass in an age period where many children are experiencing the pubertal growth spurt and may appear as having excess weight (by weight-for-age) when in fact they are just tall. For this reason, weight SDS values will be missing for subjects once they are beyond 10 years of age.

Likewise, AHV-for-age reference data are only available for ages 5.5 to 17.5 years. AHV SDS values will be missing for subjects outside of this age range.

4.3.4 Birth Weight percentile

Birth Weight percentile for gestational age will be computed using the Fenton method [11].

4.3.5 IGF-1 iSYS

IGF-1 SDS values based on the iSYS method will be derived using iSYS IGF-1 concentration data provided by the central lab, and CRF based sex and age at sampling date, as described in Appendix 1.

4.3.6 Mid-parental Height (MPH)

Mid-parental height (MPH) will be calculated by taking the average of the parents' heights, and adding 6.5 cm for male subjects or subtracting 6.5 cm for female subjects [12]. MPH SDS will be calculated by the LMS method using WHO growth chart values by subject's sex at age = 228 months.

4.3.7 PEM Test Results

The results of the PEM tests will be derived as follows: if, after receiving a single dose of LUM-201 (0.8 mg/kg), a subject has peak serum GH concentration ≥ 5 ng/mL, and either iSYS IGF-1 concentration > 3.92 nmol/L (> 30 ng/mL), and/or LC/MS IGF-1 concentration > 3.92 nmol/L (> 30 ng/mL), then the subject is considered "PEM positive" for that PEM test.

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4.3.8 Tanner Stage

Tanner Stage for male subjects will be derived from testicular volume data as follows: Stage 1 = < 4 ml; Stage 2 = 4 ml to 8 ml; Stage 3 = 9 ml to 12 ml; Stage 4 = 15 to 20 ml; Stage 5 = greater than 20 ml [12]. Breast development in females is in direct alignment with Tanner stage, thus breast development stage will determine the Tanner stage.

4.4 Baseline and Change from Baseline

Unless specified otherwise, baseline is considered to be the last non-missing result prior to the first randomized dose.

For height, weight, and arm span, time was not collected. If the date for measurements on Day 1 is the same date as the first randomized dose, then Baseline will be defined as the measurement on Day 1. If the date for measurements on Day 1 is missing, or is after the date of the first randomized dose, then the next prior measurement value will be used as Baseline.

For IGF-1 concentration and IGF-1 SDS (LC/MS and iSYS), baseline will be calculated as the average of the values reported at the two visits in the Screening portion of the study (Screening 1, and Screening 2 or Day 1). Values derived using LC/MS and iSYS methods will be averaged separately.

Calculations of baseline AHV and HV are detailed in SAP section 4.3.1.

For BA, the Screening 1 result will be considered baseline.

4.5 Handling of Missing or Partial Data

4.5.1 Adverse Events and Concomitant Medications

No missing data will be imputed for the safety analysis, except for missing or partial start dates of adverse events (AEs) with the imputation rule that missing component(s) will be assumed as the most conservative value(s) as possible. For example, AEs with missing start dates will be assumed as treatment-emergent adverse events (TEAEs), and will be conservatively captured as follow:

- If “day” is the only missing field, impute the “day” as the first randomized dose date if their “month” and “year” are the same; otherwise, if lab results are missing for a given visit, but unscheduled results are available within two weeks of the scheduled visit, then the unscheduled results will be used for that visit. first day of the non-missing month.
- If “day” and “month” are the only missing fields, impute the “day” and “month” as the first randomized dose date if their “year” are the same; otherwise, January 1 of the non-missing year.

Missing or partial dates for non-study medications will be imputed similarly. If the start date is unknown and end date is “ongoing” then the non-study medication will be considered a concomitant medication, but not new concomitant medication.

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Date imputation will only be used for computational purposes e.g., defining the treatment-emergent status. Actual data values as they appear in the original CRFs will be shown in data listings.

4.5.2 Height and Height Related Data

4.5.2.1 LOCF Imputation

Missing post-baseline height related parameters (AHV, HV, HT SDS, [HT SDS-MPH SDS], and height) will be imputed up to, and including, Month 12 by the last observation carried forward (LOCF) method, of each parameter. Results from scheduled and unscheduled visits will be considered for the imputation. No imputation will be performed for missing data beyond Month 12. All associated analyses will use data imputed with the LOCF method, except the sensitivity analysis detailed in SAP section 6.2.1.

4.5.3 Study Drug Administration Dosing Data

In accordance with the method for deriving dosing compliance described in section 5.8, if a subject is missing the prospectively planned daily dose for a given visit in the study drug administration data, and if that subject has an actual dose recorded for the corresponding period between visits, then LOCF imputation will be used on the prospective daily dose in order to calculate the dosing compliance.

4.6 Early Termination Visit Windows

Early Termination visits will be mapped to scheduled visits for analyzing drug administration and height parameters. Unscheduled visits will not be considered for visit windowing. Scheduled visits will be mapped to their nominal visit. Early Termination visits will be mapped to scheduled visits if the ET visit falls within 14 days (inclusive) of the target study day for Month 1 (Day 30), Month 3 (Day 91), Month 6 (Day 183), Month 9 (Day 274), Month 12 (Day 365), Month 18 (Day 548), or Month 24 (Day 730). This will be done prior to LOCF imputation.

4.7 Definition of Study Day 1

Study Day 1 is defined as the date of first exposure to the study treatment. For purposes of this definition, PEM dosing is not considered study treatment.

5 Study Subjects Analyses

5.1 Analysis Populations

The number and percentage of subjects in each analysis population will be summarized for the Safety Population. A listing of analysis sets will also be presented.

5.2 Subjects Disposition

Subject disposition will be summarized for the Safety Population. The number and percent of subjects who were enrolled in the Screening portion of the study, treated with LUM-201 PEM dose, enrolled in the Treatment portion of the study, treated with

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randomized study drug, completed, or discontinued from the study, as well as the reason for discontinuation will be tabulated. A listing of subject disposition will also be presented.

5.3 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized, for the FAS Population, and each Per-Protocol Population:

- Age
- Sex
- Race/Ethnicity
- Bone Age (BA) (years), BA Delay (CA – BA)
- Time from BA assessment to Screening 1
- Birth weight, gestational age, birth weight percentile
- Peak GH (μg/L) response to historical stimulation test(s)
- Peak GH (μg/L) response to PEM at Screening 1
- AHV
- Height and HT SDS
- Weight and weight SDS
- BMI and BMI SDS
- Baseline IGF-1, IGF-1 SDS (LC/MS and iSYS), IGFBP-3, and Molar LC/MS IGF-1/IGFBP-3 ratio
- Midparental height (MPH), MPH SDS, (HT SDS - MPH SDS)

Listings for demographics and baseline characteristics, and growth baseline characteristics will also be provided.

In addition, the demographics and baseline characteristics will be summarized for the following subgroups in the FAS Population:

- Subjects entering puberty (i.e., Tanner Stage 2) by Month 12
- Subjects who did not meet the 6.7 cm/yr threshold for AHV at Month 12

5.4 Medical History

Medical history will be coded using version 23.1 or later of the Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Analysis Population. Multiple histories in a summary level will be counted only once per subject. A listing of medical history will also be presented.

5.5 Subjects Violating Eligibility Criteria

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Subjects violating eligibility criteria, e.g., inclusion and exclusion criteria failures, will be listed for all screened subjects.

5.6 Protocol Deviations

The number and percent of subjects with major protocol deviations will be summarized by treatment group, for the FAS Population. Subjects will only be counted once for each deviation category.

All protocol deviations (major and minor) will be listed by subject, including if the protocol deviation resulted in exclusion from one or more Per Protocol Populations.

5.7 Study Drug Exposure

Extent of exposure will be assessed as the total number of days each subject was administered a randomized dose of study drug (LUM-201 or rhGH). Duration of study drug exposure for subjects, and the total days of exposure for all subjects will be summarized by treatment group, for the FAS Population. Duration of exposure to study drug is calculated as (date of last dose – date of first randomized dose + 1).

A listing of in-clinic study drug exposure will be presented, including PEM doses.

5.8 Study Drug Accountability and Dosing Compliance

Study drug accountability and dosing compliance will be derived using data from the EDC, and interactive response technology (IRT) systems. For the purpose of calculating compliance, "number of doses" is interpreted as number of tablets for subjects assigned to LUM-201 and mL of rhGH for the subjects assigned to rhGH. The actual number of doses taken is recorded in the IRT data. The planned number of doses is calculated as the product of the number of days between visits and the prospective daily dose recorded at each visit. When the prospective dose is not recorded at a subject visit, LOCF imputation will be used to determine the prospective daily dose for the period to the next visit.

Number of missed doses will be summarized by treatment group and visit range, for LUM-201 subjects in the FAS Population. Number of missed doses will be analyzed as continuous and categorical type variable (0-10, 11-20, 21-30, >30). Visit range will be between consecutive study visits.

Percent dosing compliance will be summarized by treatment group and visit range, for the FAS Population. Dosing compliance will be analyzed as continuous and categorical type variable (>100%, 90-100%, 80-<90%, 70-<80%, <70%). Visit range will be from Day 1 to study visit. Percent dosing compliance is calculated as follows:

$$LUM: \frac{number\ of\ tablets\ taken\ in\ visit\ range}{planned\ number\ of\ tablets\ in\ visit\ range} * 100$$

$$GH: \frac{planned\ mL\ of\ rhGH\ in\ visit\ range - mL\ of\ residual\ rhGH}{planned\ mL\ of\ rhGH\ in\ visit\ range} * 100$$

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Listings for study drug accountability and dosing compliance will also be presented, for the FAS Population.

5.9 Concomitant Medication

The WHO Drug B3 Global 2020 Q3 will be used to categorize verbatim descriptions of non-study medications into the anatomical therapeutic chemical (ATC) classification system. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and trade name.

Prior medication is defined as any medication with a stop date prior to the date/time of the first dose of study drug. Prior medication will not be summarized but will be provided in a listing. Concomitant medications refer to non-study medications used after the date/time of the first dose of study drug. Among concomitant medications, those with a start date after the date/time of the first dose of study drug will be defined as new concomitant medication.

Concomitant medications, and new concomitant medications, will be summarized by ATC classification (ATC level 3 and preferred term), separately for the Screening, and Treatment portions of the study. The Safety Population will be used for the Screening portion of the study; the PEM dose of LUM-201 administered at Screening 1 will be considered the first dose of study drug. The FAS Population will be used for the Treatment portion of the study; the first dose of randomized treatment (LUM-201 or rhGH) will be considered the first dose of study drug.

All prior and concomitant medications will be presented in a listing. Flags for prior vs concomitant, and new concomitant, in the Screening, and Treatment portions of the study will be included.

5.10 Month 12 AHV Threshold

As mentioned in SAP section 1.3.2, subjects randomized to receive LUM-201 who have AHV < 6.7 cm/yr at Month 12 will be withdrawn from the trial. The incidence of subjects who did not meet the threshold will be summarized for each LUM-201 treatment group, and all LUM-201 subjects.

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6 Primary Objectives Analyses

6.1 Primary Objective Analysis

To evaluate the PEM strategy to select subjects likely to respond to LUM-201, the proportion of treatment responders (i.e. subjects with a positive growth response from Day 1 to Month 6 of AHV ≥ 6.85 cm/yr) will be presented, along with the two-sided 95% confidence interval (CI) (equivalent to one-sided 97.5% CI), for the FAS Population and PP6 Population. Analysis will be performed for LUM-201 1.6 mg/kg and 3.2 mg/kg LUM-201 treatment groups combined, overall LUM-201 (all treatment groups combined), and each LUM-201 treatment group separately. The PEM response rate of the LUM-201 1.6 mg/kg and 3.2 kg/mg LUM-201 treatment groups combined is expected to be ≥ 70%.

The lower bound of the two-sided 95% CI (equivalent to one-sided 97.5% CI) will be derived based on the binomial method, and will be used to reject the null hypothesis of responder rate ≤ 50%. The one-sided p-value will also be reported.

6.2 Primary Clinical Objective Analysis

To support the clinical objective of selecting a pediatric dose of LUM-201 for use in future studies, the AHV related values in Appendix 3 will be summarized by treatment group, including overall LUM-201, for the FAS Population.

For the FAS Population, an ANCOVA model, with Month 6 AHV as the dependent variable, and model terms for baseline age, sex, treatment group, peak GH response to PEM LUM-201 test at screening, baseline HT SDS, baseline BMI SDS, baseline LC/MS IGF-1 SDS, baseline bone age delay, and the difference between height SDS and mid-parental height SDS will be used to compare the LUM-201 treatment groups and the rhGH treatment group. In the case of model non-convergence, the terms listed above (excluding treatment group) will be removed one at a time from the model in reverse order, beginning with the difference between height SDS and mid-parental height SDS, until convergence is attained. The least square means (LSM), and associated 2-sided 95% CIs, for AHV will be presented for each treatment group. The same analyses will be done using Month 12 AHV and Month 24 AHV as the dependent variable. No multiplicity adjustment will be applied for this phase 2 study.

As baseline AHV was not a required until protocol version 7.0, not all subjects will have accurate baseline AHV values. A listing of AHV values, change from Baseline AHV, and percent change from Baseline AHV will also be presented, for the protocol v 7.0 population.

Mean and individual AHV over time will be presented graphically for the FAS Population. Data will be plotted using scheduled visits. Mean plots will be presented ± standard deviation (SD). For individual subject plots, spaghetti plots (all subjects in one

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plot per treatment group) will be created. In addition, a mean plot will be presented for the 24-month Completer Population.

Additional plots may be presented to graphically display the difference in growth between Year 1 vs Year 2.

6.2.1 Multiple Imputation Sensitivity Analysis of Primary Clinical Objective

Sensitivity analysis will be performed for analysis of Month 6 and Month 12 AHV ANCOVA modeling, for the FAS population.

Multiple imputation under the assumption of missing at random (MAR) will be applied to the observed data (prior to the LOCF imputation described in SAP section 4.5.3), to impute missing AHV up to Month 12, for the FAS Population. The imputation will be performed using the fully conditional specification method which will include terms for treatment group, and the randomization stratification factors (i.e., Age < 90 months, ≥ 90 months; screening HT SDS < -2.5, ≥ -2.5).

In a separate analysis, multiple imputation will be performed under the assumption of missing not at random (MNAR). For this imputation method, the imputed value for the LUM-201 subjects will be adjusted by a penalty of -1.8 cm/year at the analysis visit. Thus, for Month 6 AHV ANCOVA, the penalty will be applied only to the LUM-201 treatment arms and only to the Month 6 visit. For Month 12 AHV ANCOVA, the penalty will be applied only to the LUM-201 treatment arms and only to the Month 12 visit.

For each imputation method (MAR, MNAR for Month 6, MNAR for Month 12), a total of 100 imputed datasets will be created using SAS PROC MI. The ANCOVA analysis (described above) will be performed on each imputed dataset to obtain LS means at Month 6 and Month 12 under MAR and MNAR methods. The results will then be combined using SAS PROC MIANALYZE, and LS means, their standard errors and 95% confidence intervals will be reported.

As a supportive analysis, unadjusted sample means by visit up to Month 12 will be generated for the MAR imputation method only. The results will then be combined using SAS PROC MIANALYZE, and means and their standard errors will be reported by visit.

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7 Secondary Objectives Analyses

7.1 Key Secondary Endpoint Analyses

To assess the reproducibility of the PEM positive classification of subjects, the proportion of subjects with positive agreement rate (i.e., got a positive result on both PEM tests) will be calculated along with the 2-sided 95% CI, for the Safety Population. The lower limit of the CI of positive agreement rate is expected to be greater than 80%. Subjects with only one PEM test, and subjects with two negative PEM tests will not be included in the analysis.

The following PEM test results will be summarized for each PEM test, for the Safety Population:

- IGF-1 (LC/MS and iSYS)
- IGF-1 SDS (LC/MS and iSYS)
- GH by timepoint
- Peak GH (post-dose)
- Change from pre-dose GH to Peak GH

Listings for PEM test results, and historical standard GH stimulation tests will also be presented.

7.2 Other Secondary Endpoint Analyses

7.2.1 Clinical Parameters of Efficacy

To assess additional clinical parameters of efficacy, baseline, post-baseline, and change from baseline values for the following parameters will be summarized by treatment group, including overall LUM-201, for the FAS Population: height, HT SDS, weight, weight SDS, BMI, BMI SDS, (HT SDS – MPH SDS), BA, and BA/CA. Week 2, Month 1, and unscheduled visits will be excluded from the summary.

Listings for growth data (result, change from baseline, and percent change from baseline), (HT SDS – MPH SDS), and bone age will also be presented. Growth data listing will include Tanner stage (results only), AHV, height, HT SDS, HV, weight, weight SDS, BMI, and BMI SDS. (HT SDS - MPH SDS) listing will include MPH, MPH SDS, height, HT SDS, and (HT SDS - MPH SDS). Bone age listing will include BA, chronological age (CA), BA delay (CA - BA), and BA/CA ratio. Another listing will report AHV SDS.

Mean and individual height, HT SDS, HV, BA/CA, and (HT SDS - MPH SDS), over time will be presented graphically for the FAS Population. Data will be plotted using scheduled visits. Mean plots will be presented ± standard deviation (SD). For individual subject plots, spaghetti plots (all subjects in one plot per treatment group) will be created.

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7.2.2 Safety and Tolerability of LUM-201

The Safety Population will be used for all safety listings, and adverse event summary tables. The FAS Population will be used for all other safety summary tables.

7.2.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject, temporally associated with the use of study product, whether or not considered related to study drug. All AEs will be coded using MedDRA version 23.1 or later.

If an AE has missing causality, it is assumed to be related to the study drug for analysis purposes.

AE severity will be classified using the Common Terminology Criteria for Adverse Events (CTCAE). Any AE that has worsened in the severity will be recorded as a separate AE. AEs with missing severity will be classified as "Severe."

A treatment-emergent adverse event (TEAE) is defined as any AE with an onset on or after receiving a Screening PEM dose of LUM-201, through 30 days after the last dose of study drug (LUM-201 or rhGH). TEAEs will be separated into those that occurred prior to the first randomized dose, and those that occurred on or after the first randomized dose. TEAEs will be summarized by the following treatment groups:

- Prior to Randomized Dose
    - PEM Dose LUM-201 – 0.8 mg/kg
- On or After Randomized Dose
    - LUM-201 – 0.8 mg/kg
    - LUM-201 – 1.6 mg/kg
    - LUM-201 – 3.2 mg/kg
    - All LUM-201
    - rhGH – 34 μg/kg

The total number of TEAEs will be summarized by treatment group. For each system organ class (SOC) and preferred term (PT), the number and percentage of subjects who experienced at least one TEAE in the summary level, will be summarized by the treatment groups described above.

Percentages for the PEM Dose LUM-201 – 0.8 mg/kg treatment group will be based on the total number of subjects in the Safety Population. Percentages for all other treatment groups will be based on the number of subjects in each randomized treatment group in the FAS Population.

Subjects will be counted once per summary level. When summarizing by maximum severity, subjects will be counted once per summary level, at the highest severity.

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All TEAEs will be sorted in descending order of the incidence rate of SOC summary levels, and then within each SOC by descending order of incidence rate of the PT summary levels.

The sponsor and MMs will review the data, and determine if any adverse events of special interest (AESIs) occurred.

An overall summary table of TEAEs will include:

- Any TEAEs
- Serious TEAEs (SAE)
- TEAEs related to the study drug
- TEAEs resulting in discontinuation of study drug
- TEAEs resulting in discontinuation from the study
- TEAEs resulting in death

TEAEs will also be summarized for:

- TEAEs by maximum severity
- TEAEs related to the study drug
- Serious TEAEs (SAE)
- Serious TEAEs related to study drug
- Serious Unexpected Suspected Adverse Reaction TEAEs (SUSAR)
- Serious Unexpected Suspected Adverse Reaction TEAEs related to study drug
- TEAEs with CTCAE Grade ≥ 3
- TEAEs resulting in discontinuation of study drug
- TEAEs resulting in discontinuation from the study
- TEAEs resulting in death
- TEAEs of Special Interest (AESI)
- TEAEs with Incidence > 5% up to Month 12

AEs listings will be presented by treatment group, subject, start date, SOC and PT for:

- All Adverse Events
- Serious Adverse Events
- Adverse Events Related to Study Treatment
- Adverse Events Resulting in Discontinuation of Study Treatment
- Adverse Events CTCAE Grade ≥ 3

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- Adverse Events of Special Interest
- Adverse Events Special Interest Related to Study Treatment

In addition, a listing of all adverse events will be presented for all enrolled subjects.

7.2.2.2 Safety Clinical Laboratory Parameters

Clinical laboratory data will be presented using the standard unit of measurement as reported by the laboratory. Each measurement will be classed as below, within, or above normal range, based on ranges supplied by the laboratory.

For clinical laboratory (hematology, chemistry, urinalysis, chemistry-lipids, hemoglobin, serology, thyroid, and special) parameters with continuous results, baseline, post-baseline, and change from baseline values will be summarized by treatment group and visit. The post-baseline minimum and maximum values will also be summarized.

For clinical laboratory parameters with categorical results, the number and percentage of subjects with results in each category will be summarized by treatment group and visit. The denominator is the number of subjects with non-missing values for the given parameter and visit. The post-baseline minimum and maximum values will also be summarized.

The number and percentage of subjects with abnormal laboratory results (i.e. those that are outside of normal ranges) will also be summarized by treatment group and visit, for all non-urinalysis laboratory parameters. In addition, change from baseline to post-baseline visit will be presented in a shift table; the denominator is the number of subjects with non-missing value at baseline and the visit for the given parameter.

All laboratory (hematology, chemistry, urinalysis, chemistry-lipids, hemoglobin, serology, thyroid, special, and other) listings will be presented by treatment group, subject and visit (both scheduled and unscheduled). Abnormal laboratory results and/or with clinical significance will be flagged, when applicable.

In addition, incidence of the following will be summarized:

- AST ≥ 3 x ULN
- ALT ≥ 3 x ULN
- ALP ≥ 2 x ULN
- GGT ≥ 2 x ULN
- AST or ALT ≥ 2 x ULN and TBL ≥ 1.5 x ULN
- AST or ALT ≥ 3 x ULN and TBL ≥ 1.5 x ULN

Separate listings will also be presented for the following:

- Subjects with ALT or AST ≥ 2 x ULN and Total Bilirubin ≥ 1.5 x ULN
- Subjects with ALT or AST ≥ 3 x ULN and Total Bilirubin ≥ 1.5 x ULN, will also be presented.
- Subjects with ALT or AST ≥ 2

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7.2.2.3 Physical Examinations

All physical examination results, including details of clinically significant findings, will be presented in by-subject listings.

7.2.2.4 Vital Signs

Vital signs will include body temperature, resting respiration rate, and sitting blood pressure (BP, systolic and diastolic) and heart rate (HR).

Baseline, post-baseline, and change from baseline values will be summarized by treatment group and visit. A listing of vital sign data for all subjects will also be provided.

Mean and individual vital signs over time will be presented graphically for the FAS Population. Data will be plotted using scheduled visits. Mean plots will be presented ± standard deviation (SD). For individual subject plots, vital signs will be presented graphically, all measurement will be displayed on one plot, by subject.

7.2.2.5 ECGs

ECGs are recorded in triplicate for all subjects at Screening visit, Day 1 visit, Month 3 visit, Month 6 visit, and Month 12 visits. The average of triplicate the results at each visit will be used in data summary at these visits. Single ECG recording will be performed for subjects on the LUM-201 arms that continued after Month 12, at Month 18 visit and Month 24 visit.

ECG parameters will include PR, QT, QTcB, QTcF and RR intervals, QRS duration, heart rate (HR), and T wave amplitude, as well as the interpretation. Baseline, post-baseline, and change from baseline values summarized by treatment group and visit.

For overall interpretation at baseline, the most conservative (best case) of the respective readings will be reported; at post baseline, the most severe (worst case) of the respective readings will be reported. Change from baseline to post-baseline visit will be summarized by treatment group, in a shift table. The denominator will be the number of subjects with non-missing interpretations at baseline and the given visit. If the ECG is uninterpretable, the result will be considered missing, and not considered for summary analysis.

In addition, the incidence of the following ECG results of interest will be summarized by treatment group and visit:

- HR < 50 bpm, or ≥ 100 bpm
- HR ≥ 100 bpm and HR percent change from baseline ≥ 25%
- HR < 50 bpm and HR percent change from baseline ≤ -25%
- PR < 120 msec, or ≥ 200 msec
- PR ≥ 200 msec and PR percent change from baseline ≥ 25%

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- PR < 120 msec and PR percent change from baseline ≤ -25%
- QRS duration ≥ 120 msec
- QRS duration ≥ 110 msec and QRS duration percent change from baseline ≥ 25%
- QTcB > 450 msec, or > 480 msec, or > 500 msec
- QTcB change from baseline > 30 msec, or > 60 msec
- QTcF > 450 msec, or > 480 msec, or > 500 msec
- QTcF change from baseline > 30 msec, or > 60 msec

Parameters QTcB and QTcF are corrected QT parameters which will be provided by the laboratory.

A listing of ECG data for will also be presented. In addition, a listing of QT, QTcB and QTcF results and change from baseline (of average measurement) will be presented.

7.2.3 Pharmacokinetics of LUM-201

Details of the PK analysis will be presented in a separate PK Analysis Plan.

7.2.4 Acute and Chronic Pharmacodynamic Responses to LUM-201

PD parameters include peak GH (only LUM-201 subjects), IGF-1 and IGF-1 SDS (iSYS and LC/MS), IGFBP-3, and LC/MS molar IGF-1/IGFBP-3 ratio. Peak GH will only be evaluated for LUM-201 subjects. Baseline, post-baseline, and change from baseline values of PD parameters will be summarized by treatment group and visit, for the FAS Population. In addition, change from baseline values will be evaluated using a Wilcoxon Signed Rank Test.

In addition, the incidence of LC/MS IGF-1 SDS > 2 and > 3 will be summarized by treatment group and visit. The denominator is the number of subjects with non-missing value at the visit.

Listings for GH, IGF-1 and IGFBP-3 data will also be presented. The IGF-1 and IGFBP-3 data listing will include results and change from baseline for the following: IGF-1 and IGF-1 SDS (iSYS and LC/MS), IGFBP-3, and Molar LC/MS IGF-1/IGFBP-3 ratio. In addition, listings of IGF-1 and IGFBP-3 parameters will be presented for observations where either LC/MS IGF-1 SDS or iSYS IGF-1 SDS are greater than 2, and similarly where either LC/MS IGF-1 SDS or iSYS IGF-1 SDS are greater than 3. Mean and individual IGF-1 SDS (iSYS and LC/MS) over time will be presented graphically for the FAS Population. Data will be plotted using scheduled visits. Mean plots will be presented ± standard deviation (SD). For individual subject plots, spaghetti plots (all subjects in one plot per treatment group) will be created.

7.2.5 Sample Size Estimation for Future Trials

To support sample size estimation for future trials, the AHV related values in Appendix 3 will be summarized by treatment group and visit, for the following:

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- FAS Population: Subjects Who Remained in Tanner 1 by Month 12
- FAS Population: Subjects Who Transitioned from Tanner 1 to Tanner 2 by Month 12
- FAS Population: LUM-201 Subjects Who Met the 6.7 cm/yr Threshold for AHV
- FAS Population: LUM-201 Subjects Who Did not Meet the 6.7 cm/yr Threshold for AHV
- FAS Population: LUM-201 Subjects Reaching 24 Months of Treatment
- PP6 Population: study visits up to Month 6
- PP12 Population: study visits up to Month 12, and Month 6 to Month 12
- PP18 Population: study visits up to Month 18, Month 6 to Month 12, and Month 12 to Month 18
- PP24 Population: study visits up to Month 12, Month 6 to Month 12, and Month 12 to Month 24

The same ANCOVA model used for the primary clinical objective analysis, as described in SAP section 6.2, will be applied to the populations below:

- PP6 Population: Month 6 AHV
- PP12 Population: Month 12 AHV
- PP24 Population: Month 24 AHV

8 Exploratory Analyses

8.1 Comparison of PD Responses to LUM-201 and rhGH

Responses to LUM-201 and rhGH will be compared for the following PD parameters: IGF-1 (LC/MS and iSYS), IGF-1 SDS (LC/MS and iSYS), IGFBP-3, and molar LC/MS IGF-1/IGFBP-3 ratio.

ANCOVA models, with model terms for treatment group and parameter baseline value, will be used to compare the LUM-201 treatment groups and the rhGH treatment group, for the FAS Population. The rhGH treatment group will be designated as the reference group for pair-wise comparisons. The LSM will be presented for each treatment group. Additionally, the difference between LSMs of each LUM-201 treatment group and the rhGH treatment group will be calculated, along with the two-sided 95% CIs. No multiplicity adjustment will be applied for this phase 2 study.

8.2 Relationship between AHV and Baseline Characteristics

The relationship of Month 6 AHV and baseline characteristics will be explored by statistical modeling methods. Month 12 AHV and Month 24 AHV will also be modeled

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separately to explore relationship with baseline characteristics. To achieve this, p-values will be added to the model output from the analysis described in section 6.2.

9 Interim Analyses

9.1 First Interim Analysis: Safety and Growth Response

An interim analysis of all available data will be conducted after 40 subjects have completed the Month 6 Visit. At the time of the interim analysis, some subjects who were early enrollers will have data through Month 12, while others will have data only through Month 6 or Month 9. The purpose of this interim analysis is to evaluate the safety and continued growth response in the 6- to 12-month period.

9.1.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group, for the FAS, as well as separately for each of the subgroups of subjects who have completed Month 6, Month 9, and Month 12. A by-subject listing of demographics and baseline characteristics will be provided to supplement the tabulated results.

9.1.2 AHV

The primary focus will be on the AHVs at Month 6. However, AHVs at Months 9 and 12 will also be summarized for those subjects who have Month 9 and Month 12 data. Based on data for all subjects who have completed Month 6, descriptive statistics for Month 6 AHV will be presented by treatment group, as well as for all LUM-201 subjects combined. The summary will be repeated for the subset of subjects who have completed Month 9, and will include descriptive statistics for the Month 6 and Month 9 timepoints. The summary will be repeated again for the subset of subjects who have completed Month 12, and will include descriptive statistics for the Month 6, Month 9, and Month 12 timepoints.

By-subject listing of AHV based on all data will be provided to supplement the tabulated results. In addition, a by-subject listing of AHV data will be provided for subjects who did not meet the 6.7 cm/yr threshold for AHV at Month 6, Month 9, and/or Month 12.

9.1.2.1 Subgroup Analysis

During early enrollment, some subjects were allowed to enter the study who may not have presented with 'true' idiopathic GHD, as the protocol did not include an inclusion criterion for either IGF-1 SDS or (HT SDS - MPH SDS). While still blinded to treatment allocation, the MMs will review the demographics and baseline characteristics of all enrolled subjects to assess any who might not technically have iPGHD. All subgroup assignments will be made prior to interim database lock.

A subgroup analysis of the AHV results at Months 6, 9, and 12 will be performed as described above for subjects in the FAS Population who have been determined to have true idiopathic PGHD. This analysis will only be performed in the first interim analysis.

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9.1.3 Clinical Parameters of Efficacy

Tables summarizing the results and changes from Day 1 to Months 6, 9, and 12 will be provided for height, HT SDS, weight, weight SDS, BMI, BMI SDS, IGF-1 (both LC/MS and IDS iSYS results), IGF-1 SDS (LC/MS only), IGFBP-3. These summaries will be presented by treatment group, as well as for all LUM-201 subjects combined. If there are any subjects with IGF-1 SDS excursions greater than 2 and/or greater than 3, they will be tabulated at each visit by treatment group and for all LUM-201 subjects combined.

By-subject listings of all growth data and IGF-1/IGFBP-3 data will be provided to supplement the tabulated results.

9.1.4 Adverse Events

TEAEs will be summarized by treatment group, for the Safety Population. TEAEs related to study drug, and SAEs will also be summarized. By-subject listings of all TEAEs, related TEAEs, and SAEs will be provided.

9.1.5 Safety Clinical Laboratory

A summary of the largest laboratory shifts from baseline to on-study result will be presented by treatment group and for all LUM-201 subjects combined. The largest shift from baseline indicates the largest absolute shift in the numeric result (positive or negative). In cases where subjects have multiple visits with the same magnitude of shift, the earliest visit will be selected. For each lab test, the number and percentage of subjects with the largest on-study shift from baseline (e.g., Low to Normal, Low to High, Normal to Low, etc.) will be tabulated. A by-subject listing of all safety laboratory abnormal results will also be provided.

9.1.6 Study Drug Accountability and Dosing Compliance

A summary of study drug accountability will be presented by treatment group and for all LUM-201 subjects combined. This tabulation will include summary statistics of the number of doses missed over time, as well as the number and percentage of subjects with missed doses.

Listings of drug accountability data for LUM-201 and rhGH subjects will also be provided to supplement the tabulated results. These will include information on whether subjects missed any doses of study drug, and if so, when they were missed, if these details are available.

9.2 Second Interim Analysis:

A second interim analysis for this study is scheduled to occur when all subjects have completed the Month 6 visit. This analysis will serve as the read-out for the primary objective endpoints and will serve to provide information for the end of phase 2 (EOP2) meeting with the FDA and other regulatory agencies.

Analysis will be based on a clean and stable snapshot of the database as described in the main body of this document. This is an open-label study so unblinding

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considerations are not applicable. However, prior to performing the analysis, protocol deviation information will be provided in a manner that allows for incorporation into the CDISC datasets to allow for proper determination of the subject-level per-protocol populations.

9.2.1 Primary Endpoint Subgroup Analysis

A subgroup analysis will be performed as described in SAP section 6.2 for subjects in the FAS Population who have standard GH stimulation test response between 7 and 10 ng/mL, exclusive. This analysis will only be performed in the second interim analysis.

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10 References

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3. "Body mass index-for-age (BMI-for-age)" World Health Organization, https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age. Accessed July 10, 2023.
4. "BMI-for-age (5-19 years)" World Health Organization, https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age. Accessed July 10, 2023.
5. "Length/height-for-age" World Health Organization, https://www.who.int/tools/child-growth-standards/standards/length-height-for-age. Accessed July 10, 2023.
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11 Appendices

11.1 Appendix 1 – Derivation of iSYS IGF-1 SDS values

IDSYS iSYS IGF-1 SDS values will be derived as follows:

Inputs:

1. iSYS IGF-1 concentration values from the central lab.
2. CRF collected sex and age in months at the screening visit and date of the screening visit.
3. Date at which the IGF-1 sample was drawn.
4. LMS tables (Supplemental Tables 15 and 16) from https://academic.oup.com/jcem/article/99/5/1712/2537423?login=false

Method:

1. Determine iSYS IGF-1 concentration in units of ng/mL from the laboratory results in original results. If the original results are in nmol/L, convert to ng/mL using the conversion calculation below. DO NOT round the result value.

$$X\ ng/mL\ =\ Y\ nmol/L\ *\ 7.63.$$

2. Derive Age at Visit in Half Years using the calculations below.

$$age\ at\ visit = \frac{(age\ at\ screening * 30.44) + (visit\ date – screening\ date + 1)}{365.25}$$

$$age\ at\ visit\ in\ half\ years\ = \frac{floor(age\ at\ visit * 2)}{2}$$

3. Merge data with LMS tables by sex and age at visit in half years, to obtain values for the following LMS parameter: lambda (λ), mu (μ), and sigma (σ).

4. Calculate SDS values from the LMS parameter values using calculation below.

$$SDS = round\left(\frac{((X\ ng/mL)/\mu)^{\lambda} - 1}{\lambda * \sigma}, 0.001\right)$$

5. Incorporate normal ranges for the SDS values:
    a. X < -2.0 = Low
    b. -2.0 < X <2.0 = Normal
    c. X > 2.0 = High

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11.2 Appendix 2 – WHO Child Growth Standards

"Body mass index-for-age (BMI-for-age)" World Health Organization, *https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age* Accessed July 10, 2023.

- bmi_girls_2-to-5-years_zscores.xlsx
- bmi_boys_2-to-5-years_zscores.xlsx

"BMI-for-age (5-19 years)" World Health Organization, *https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age* Accessed July 10, 2023.

- bmi-boys-z-who-2007-exp.xlsx
- bmi-girls-z-who-2007-exp.xlsx

"Length/height-for-age" World Health Organization, *https://www.who.int/tools/child-growth-standards/standards/length-height-for-age* Accessed July 10, 2023.

- lhfa_boys_2-to-5-years_zscores.xlsx
- lhfa_girls_2-to-5-years_zscores.xlsx

"Height-for-age (5-19 years)" World Health Organization, *https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/height-for-age* Accessed July 10, 2023.

- hfa-boys-z-who-2007-exp.xlsx
- hfa-girls-z-who-2007-exp.xlsx

"Weight-for-age" World Health Organization, *https://www.who.int/tools/child-growth-standards/standards/weight-for-age* Accessed July 10, 2023.

- wfa_boys_0-to-5-years_zscores.xlsx
- wfa_girls_0-to-5-years_zscores.xlsx

"Weight-for-age (5-10 years)" World Health Organization, *https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years* Accessed July 10, 2023.

- hfa-boys-z-who-2007-exp_0ff9c43c-8cc0-4c23-9fc6-81290675e08b.xlsx
- hfa- girls-z-who-2007-exp_0ff9c43c-8cc0-4c23-9fc6-81290675e08b.xlsx

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"Age-Based Reference Ranges for Annual Height Velocity in US Children." Andrea Kelly, Karen K. Winer, Heidi Kalkwarf, Sharon E. Oberfield, Joan Lappe, Vicente Gilsanz, and Babette S. Zemel. *J Clin Endocrinol Metab*, June 2014, 99(6):2104–2112

- Reference Ranges and L, M, S values for Height Velocity for Males and Females without Reference to Timing of Pubertal Onset (Supplemental Table 2a.)

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11.3 Appendix 3 – AHV Related Derivations

AHV	Derivation
Baseline	$(HT\ at\ D1 - HT\ at\ prior\ visit)/(Date\ of\ D1 - date\ of\ prior\ visit) * 365.25$
Month 6	$(HT\ at\ M6 - HT\ at\ D1)/(Date\ of\ M6 - date\ of\ D1) * 365.25$
Month 9	$(HT\ at\ M9 - HT\ at\ D1)/(Date\ of\ M9 - date\ of\ D1) * 365.25$
Month 12	$(HT\ at\ M12 - HT\ at\ D1)/(Date\ of\ M12 - date\ of\ D1) * 365.25$
Month 18	$(HT\ at\ M18 - HT\ at\ D1)/(Date\ of\ M18 - date\ of\ D1) * 365.25$
Month 24	$(HT\ at\ M24 - HT\ at\ D1)/(Date\ of\ M24 - date\ of\ D1) * 365.25$
Month 6 to Month 12	$(HT\ at\ M12 - HT\ at\ M6)/(Date\ of\ M12 - date\ of\ M6) * 365.25$
Month 12 to Month 18	$(HT\ at\ M18 - HT\ at\ M12)/(Date\ of\ M18 - date\ of\ M12) * 365.25$
Month 12 to Month 24	$(HT\ at\ M24 - HT\ at\ M12)/(Date\ of\ M24 - date\ of\ M12) * 365.25$

AHV	Change from	Derivation
Month 6	Baseline	$M6\ AHV - Baseline\ AHV$
Month 9	Baseline	$M9\ AHV - Baseline\ AHV$
Month 12	Baseline	$M12\ AHV - Baseline\ AHV$
Month 12	Month 6	$M12\ AHV - M6\ AHV$
Month 18	Baseline	$M18\ AHV - Baseline\ AHV$
Month 18	Month 12	$M18\ AHV - M12\ AHV$
Month 24	Baseline	$M24\ AHV - Baseline\ AHV$
Month 24	Month 12	$M24\ AHV - M12\ AHV$
Month 6 to Month 12	Baseline	$M6\ to\ M12\ AHV - Baseline\ AHV$
Month 6 to Month 12	Month 6	$M6\ to\ M12\ AHV - M6\ AHV$
Month 12 to Month 18	Baseline	$M12\ to\ M18\ AHV - Baseline\ AHV$
Month 12 to Month 18	Month 12	$M12\ to\ M18\ AHV - M12\ AHV$
Month 12 to Month 24	Baseline	$M12\ to\ M24\ AHV - Baseline\ AHV$
Month 12 to Month 24	Month 12	$M12\ to\ M24\ AHV - M12\ AHV$

AHV	Percent Change from	Derivation
Month 6	Baseline	$(M6\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 9	Baseline	$(M9\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 12	Baseline	$(M12\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 12	Month 6	$(M12\ AHV - M6\ AHV)/(M6\ AHV)$
Month 18	Baseline	$(M18\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 18	Month 12	$(M18\ AHV - M12\ AHV)/(M12\ AHV)$
Month 24	Baseline	$(M24\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 24	Month 12	$(M24\ AHV - M12\ AHV)/(M12\ AHV)$
Month 6 to Month 12	Baseline	$(M6\ to\ M12\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 6 to Month 12	Month 6	$(M6\ to\ M12\ AHV - M6\ AHV)/(M6\ AHV)$
Month 12 to Month 18	Baseline	$(M12\ to\ M18\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 12 to Month 18	Month 12	$(M12\ to\ M18\ AHV - M12\ AHV)/(M12\ AHV)$
Month 12 to Month 24	Baseline	$(M12\ to\ M24\ AHV - Baseline\ AHV)/(Baseline\ AHV)$
Month 12 to Month 24	Month 12	$(M12\ to\ M24\ AHV - M12\ AHV)/(M12\ AHV)$

AHV	Percent Difference in Growth from	Derivation
Month 6 to Month 12	Month 6	$(M6\ to\ M12\ AHV)/(M6\ AHV)$
Month 12 to Month 18	Month 12	$(M12\ to\ M18\ AHV)/(M12\ AHV)$
Month 12 to Month 24	Month 12	$(M12\ to\ M24\ AHV)/(M12\ AHV)$

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11.4 Appendix 4 – Table 1: Schedule of Assessments

Visit	S1	S2[a]	D1	W2[b]	M1	M2[c]	M3	M4[c]	M5[c]	M6	M9	M12[d]	M15[e]	M18[e]	M21[e]	M24[e]	FU[c]
Scheduled Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Informed consent/assent	X																
Inclusion/exclusion criteria review	X	X															
Medical history[f]	X																
Physical examination[g]	X		X	X	X		X			X	X	X	X	X	X	X	
Interval history[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior medications	X																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs and weight[i]	X	X	X	X	X		X			X	X	X	X	X	X	X	
Stadiometer height[j]	X		X		X		X			X	X	X	X	X	X	X	
Arm span	X																
Fundoscopy	X											X					
GH Stimulation Test Confirmation[k]	X																
Confirmation of normal adrenal function	X																
Bone Age[l]	X									X				X			
ECG[m]	X		X	X			X			X		X		X		X	
Laboratory assessments																	
Hematology, CBC	X		X	X	X		X			X		X		X		X	
Serum chemistry panel	X		X	X	X		X			X		X		X		X	
HbA1c	X						X			X		X		X		X	
Fasting serum glucose, insulin concentrations[n]	X						X			X		X					

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Visit	S1	S2[a]	D1	W2[b]	M1	M2[c]	M3	M4[c]	M5[c]	M6	M9	M12[d]	M15[e]	M18[e]	M21[e]	M24[e]	FU[c]
Scheduled Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Fasting cortisol[o]	x									x							
Thyroid panel (TSH, Free T_4, T_3)	X				X					X		X		X		X	
Lipids[p]	X									X		X		X		X	
Urinalysis	X		X	X	X		X			X		X					
PK: Plasma LUM-201 (LUM-201 subjects only, except at screening)[q]	X			X	X		X			X		X					
PD: GH (LUM-201 subjects only)[r]										X		X					
PD: IGF-1 (all subjects)	X	X	X	X	X		X			X	X[o]	X	X	X	X	X	
IGFBP-3 (all subjects)[s]			X		X[o]		X[o]			X	X[o]	X	X	X	X	X	
PEM test[t]	X[t]	X[a,t]	X[t]														
Karyotype test[u]	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[v]			X														

Abbreviations: S = Screening; D = Day; W = Week; M = Month; FU = Follow-up Contact; 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

NOTE: Protocol v5.1 extended the study from 6 months to 12 months for all treatment groups. Protocol 7.0 extended the study from 12 months to 24 months for LUM-201 treatment groups.

a. Screening 2 visit removed with Protocol 5.1, see SAP section 1.2.
b. Week 2 visit eliminated with Protocol 7.0, see SAP section 1.2.
c. Month 2, Month 4, Month 5, and Follow-up Contact were remote visits.
d. Subjects on the rhGH arm will end treatment in the LUM-201-01 protocol after the completion of the Month 12 visit.
e. 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.

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f. 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.
g. Complete physical examination at Screening visit. Physical examination focused on changes from prior visit is acceptable for all other clinic visits. Physical examination to include Tanner staging at Screening, Month 6, Month 12, and for subjects on the LUM-201 arms at Month 18 and Month 24. Fundoscopy is required at the Screening, Month 6 (prior to Protocol v5.1), Month 12 (after Protocol v5.1, prior to Protocol 7.0), and for all 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.
h. Interval history includes evaluation of general health status since the last visit and query for headache, visual disturbance, joint pain, and change in eating behavior. If present, these events should be recorded.
i. Vital signs include temperature, respiratory rate, pulse rate, and blood pressure. Body weight, in kg, taken in light clothing without shoes or socks.
j. 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.
k. 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 (added Protocol v7.0). 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.
l. 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 12 months (prior to Protocol v7.0) or 9 months (after Protocol v7) 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.
m. Triplicate ECGs will be performed for all subjects at Screening, Day 1, Month 3, Month 6, and Month 12. 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.
n. Fasting glucose and insulin may be repeated if indicated by a suspicion of evolving glucose intolerance.
o. Added with Protocol v7.0
p. Fasting LDL, HDL, total cholesterol, and triglycerides for the first 12 months. Non-fasted in the second 12 months (Months 13-24).
q. 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: 30 and 60 minutes post-dose
    - Month 1: single sample 30 minutes post-dose
    - Week 2 (prior to Protocol v5.1), Month 3 and Month 12: only a pre-dose (trough) collection
    - Month 6: pre-dose and at 30 and 60 minutes post-dose collection
r. Serum GH samples will be collected at Month 6 visit and Month 12 visit pre-dose and 30, 60, and 90 (removed with Protocol v7.0) minutes post-dose for subjects randomized to LUM-201. ±10-minute window is allowed for post-dose PD sample collections.
s. Serum IGF-1 and IGFBP-3 samples will be collected pre-dose at Day 1, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, and Month 24 visit.
t. The PEM test will be done in the fasting state at the Screening 1, and Screening 2 (prior to Protocol v5.1) or Day 1 (on or after Protocol v5.1). 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, 60, and 90 (removed with Protocol v7.0) minutes post LUM-201 dose. Symptoms occurring during the test will be reported as Adverse Events.
u. Karyotype for female subjects may be obtained at screening if not already available.
v. 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 µg/kg/day SC.
w. Study drug dispensed as needed. Dose adjustment is based on subject's weight.

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