STATISTICAL ANALYSIS PLAN

Version 3.0

Date: 24 June 2024

For the Open Label Extension (OLE) of

Protocol: CP-4-004

Safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children

OPKO Biologics Ltd.
16 Ashlagan St.
Kiryat Gat, Israel

Date of the Protocol: CP-4-004 Version 10, 03 October 2017 (Global Amendment 9)

Prepared by:

OPKO Health, Inc
4400 Biscayne Blvd.
Miami, FL 33137, USA

DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Change
1.0	31 May 2019	Original final.
2.0	03 Oct 2019	Added baseline summaries for Height (HT) standard deviation score (SDS), insulin like growth factor-1 (IGF-1) SDS, Bone Age (BA), and Height Velocity (HV). Added the calculation of cumulative change in HT SDS from year 1 baseline, based on original dosing group. Added the classification of antibody status as determined from year 1 results, in addition to the classification based only on OLE results. HV and HT SDS will be presented at each year based on original dosing group, in addition to the summary across dosing groups. Pubertal status will be summarized for each year.
3.0	24 June 2024	Updated to include data from all visits to end of study (EOS) closure. Updated relevant table and listing titles to reflect all additional years of data to EOS closure. Prepared by, on the title page, update to OPKO Health, Inc.

SIGNATURE FORM

DOCUMENT NAME: Statistical Analysis Plan, CP-4-004 Open Label Extension

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PROTOCOL IDENTIFIER: CP-4-004

PROTOCOL TITLE: Safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children

We, the undersigned, have read this Statistical Analysis Plan (SAP) and agree that it contains all necessary information required to analyze the data and generate the tables, listings and figures for this study and that the SAP is in consistent with the clinical study protocol, reporting obligations as per International Council of Harmonisation guidelines and previous clinical study reports for this study.

Signature	Date
[redacted]	25 Jun 2024
Manager, Statistical Programming	
See electronic signature	
[redacted], OPKO Health, Inc.	
Associate Director, Clinical Data Management	
See electronic signature	
[redacted] Transition Therapeutics Corp, ULC	
Sr. Director of Strategic Initiatives and Data Management	
See electronic signature	
[redacted] OPKO Health, Inc.	
Sr. Director, Clinical Operations	
See electronic signature	
[redacted] OPKO Pharmaceuticals, LLC.	
Sr. Director, Chemistry and Regulatory Affairs	

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1 LIST OF ABBREVIATIONS

ADA: Anti-somatrogon antibodies
AE: Adverse Event
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
ATC: Anatomical Therapeutic Chemical code
BA: Bone Age
BM: Bone Maturation
BMI: Body Mass Index
CA: Chronologic Age
ECG: Electrocardiogram
EOS: End of Study
FSH: Follicle Stimulating Hormone
FT4: Free Thyroxin
GGT: Gamma-Glutamyl Transferase
HDL: High Density Lipoprotein
hGH: Human Growth Hormone
HLT: Highest Level Term
HT: Height
HV: Height Velocity
IGF-1: Insulin-like Growth Factor – 1
IMP: Investigational Medicinal Product
ISR: Injection Site Reaction
kg: kilograms
LDH: Lactate Dehydrogenase
LDL: Low Density Lipoprotein
LH: Lutinizing Hormone
ml: Millilitre
MCH: Mean Corpuscular Hemoglobin
MCHC: Mean Corpuscular Hemoglobin Concentration
MCV: Mean Corpuscular Volume
MedDRA: Medical Dictionary for Drug Regulatory Activities

mg:	milligram
MRI:	Magnetic Resonance Imaging
ng:	nanogram
No:	Number
OLE:	Open Label Extension
PEN:	Single patient multidose pen delivery device
PT:	Preferred Term
rhGH:	Recombinant Human Growth Hormone
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SD:	Standard Deviation
SDS:	Standard Deviation Score
SGOT:	Serum Glutamic Oxaloacetic Transaminase
SGPT:	Serum Glutamic Pyruvic Transaminase
SMQ:	Standardized MedDRA Queries
SOC:	System Organ Class
T3:	Triiodothyronine
T4:	Free Thyroxine
TEAE:	Treatment Emergent Adverse Event
TSH:	Thyroid Stimulating Hormone
UA:	Urinalysis
ULN:	Upper Limit of Normal
WHO:	World Health Organisation
wk:	Week

2 INTRODUCTION

This statistical analysis plan (SAP) details data analysis of the OLE periods of protocol CP-4-004, version 10, 3 Oct 2017 ([redacted]). The first 12 months of this study consisted of two periods, Periods I and II, with the primary objective of evaluating three doses of somatrogon to a commercially available standard daily recombinant human growth hormone (rhGH) formulation. The ongoing long-term open-label treatment covered by this plan starts with Period III (after the completion of Period II), through Period V (treatment with PEN formulation) to the end of study for all patients. This plan provides more specific details for the analysis than in the protocol, and any differences from the analysis as outlined in the protocol will be documented in this plan. Any difference from this plan that arise during the actual analysis of the data will be documented in the study report.

The International Nomenclature Name for MOD-4023 is somatrogon, which will be used subsequently throughout this document. The somatrogon designation was assigned after the commencement of CP-4-004.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives

The primary objective of this analysis is to evaluate the safety of somatrogon in extended treatment after the Periods I and II, including the transition to PEN to the EOS.

3.1.2 Secondary Objectives

The secondary objective is to evaluate the growth outcome of somatrogon in long term treatment beyond the initial 12 months of the primary study, including the transition to PEN to the EOS.

3.2 Endpoints

3.2.1 Safety Endpoints

1. Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation
2. Incidence of anti-somatrogon antibody formation (including characterization of the antibodies and neutralizing properties)
3. Local injection site assessment
4. IGF-1 levels and IGF-1 SDS
5. IGF binding protein-3 (IGFBP-3) levels
6. Parameters of glucose metabolism: blood glucose, fasting insulin level, glycosylated hemoglobin A1c (HbA1c).
7. Thyroid status (free thyroxine [FT4], triiodothyronine [T3], and thyroid stimulating hormone [TSH])
8. Lipid parameters
9. Cortisol levels
10. All other hematology and biochemical parameters
11. Physical examination
12. Vital signs
13. Electrocardiogram (ECG) parameters

3.2.2 Growth Outcomes

1. Annualized HV (cm/year)
2. Change in HT SDS
3. Annual bone maturation (BM)

4 STUDY DESIGN

CP-4-004 is an open label, randomized, multi-center study with yearly extension until marketing approval. The main study (Periods I and II) consisted of three dose levels (0.25 mg/kg, 0.48 mg/kg, and 0.66 mg/kg) of the investigational drug somatrogon administered weekly, and one active control, daily rhGH therapy (Genotropin®).

After the 12 months study (main study, including Period I and II), all patients continued with open label treatment, to be continued until marketing approval. There are three defined extension periods:

- Period III: OLE of 12 months duration with continuous dosing with the original three assigned dose levels of somatrogon (0.25, 0.48 and 0.66 mg/kg/week). Patients who were originally assigned to daily Genotropin were randomly re-assigned to one of the three dose levels.
- Period IV: Long-term OLE, where all patients were transitioned to 0.66 mg/kg/week. This was originally planned to follow the 12 months in Period III. However, due to timing of regulatory approval in different regions, the transition to 0.66 mg/kg/week varied, and did not start at the beginning of 3rd year for all patients.
- Period V: Long-term OLE with PEN device and formulation. The transition to PEN takes placed based on regulatory approval and patient scheduling, so the study month of transition will vary and not be at a specific study month.

Some patients may have an interval of [redacted] without treatment between periods. Patients may also have dose adjustment per the dose adjustment paradigm as specified in the protocol. Patients with adjusted doses will be kept in the main treatment dose groups as defined, and not be analyzed as additional dose groups.

4.1 Sample Size and Statistical Power Consideration

All patients who completed 12 months of treatment in the main study (Periods I and II) were eligible to enroll into the OLE (Periods III, IV, etc.). Fifty-three (53) patients completed Period II and started the OLE. There are no formal power considerations nor hypothesis tests for the OLE data.

4.2 Treatment Assignment and Randomization

Patients who were randomized to somatrogon in the main study (Periods I and II) continued with the same dose (mg/kg) of somatrogon they received in the main study. Patients who received the active control during the main study (Periods I and II) were randomized to one of the three somatrogon doses (0.25 mg/kg, 0.48 mg/kg, and 0.66 mg/kg) at the start of Period III. Patients were then transitioned to 0.66 mg/kg in Period IV, and finally to PEN for Period V. In addition, individual dose modification may be made based on the assessment of the growth progress and overall safety per pre-determined rules within the protocol.

4.3 Study Flow Chart OLE (Periods III, IV, V)

Period III (starting 2nd year of treatment, i.e. first year OLE)

OLE	Day 1 and Month 1 OLE [1] Visits 1-2	Every 3 months OLE visit	Every 6 months OLE visit	Every 12 months
Previous and concomitant medication	X	X		
Actual HT	X	X		
Body weight	X	X		
Physical examination	X	X		
Vital signs	X	X		
Injection site reaction (local tolerability)	X	X		
ECG				X
Pubertal status (Tanner)				X
BA (Greulich-Pyle)				X
Routine safety biochemistry/ hematology and urinalysis	X	X		
IGF-I and IGFBP-3	X	X		
Somatrogon serum levels	X	X		
Anti-somatrogon antibodies			X	
Thyroid status (FT4, T3, TSH)	X	X		
Cortisol levels	X	X		
Fasting glucose, fasting insulin	X	X		
HbA1c	X	X		
Lipid panel	X	X[2]		
Lipoprotein				X
AE assessment	X	X		
Fundoscopy[2]				X[2]
Somatrogon administration	X			
Training for study medication administration	X			
Dispense study medication	X	X		
Dispense patient diary	X	X		
Return and accountability of study medication	X	X		
Return and review of patient diary	X	X		

[1] Only patients who received Genotropin in the main study and switched to somatorogon will attend these 2 visits- applicable only for first year of extension
[2] Earlier if there are clinical signs of intracranial hypertension

Periods IV (Treatment with 0.66 mg/kg)

OLE	Every 3 months OLE visit - day 4 (-1) post dose	Every 6 months OLE visit – day 4 (-1) post dose	Every 12 months OLE and EOS when marketing approval received - on dosing day
Auxology measurements: Actual HT measured on a calibrated stadiometer and body weight measurement	X		
Adjustment of dose for weight	X		
AEs	X		
Local tolerability	X		
Concomitant medication	X		
Dispensing of drug	X		
IGF-1, IGFBP-3 and somatrogon serum levels		X	
Anti-somatrogon antibodies			X
Physical examination			X
Vital signs			X
Parameters of glucose metabolism (fasting glucose, fasting insulin and HbA1c)			X
Other hormonal levels (TSH, FT4, T3, cortisol)			X
Parameters of lipid metabolism			X
Routine safety laboratory (biochemistry, hematology and urinalysis)			X
Pubertal status			X
ECG			X
BA			X
Lutinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone.[3]			X
LH, FSH and estradiol[4]			X

[3] For male patients that are on the age 13 years old and above
[4] For female patients that are at the age of 12 years old and above

Period V LT-OLE PEN – First 12 Months

OLE PEN	Every 3 months OLE visit - day 4 (-1) post dose	Every 6 months OLE visit – day 4 (-1) post dose	Every 12 months OLE and EOS when marketing approval received - on dosing day/ from second year, visits are done on day 4 (-1) post dose
Auxology measurements: Actual HT measured on a calibrated stadiometer and body weight measurement	X		
Adjustment of dose for weight	X		
AEs	X		
Local tolerability	X		
Concomitant medication	X		
Dispensing of drug	X		
Return of used drugs	X		
IGF-1, IGFBP-3	X		
Somatrogon serum levels	X	X -from second year	X
Anti-somatrogon antibodies	X	X -from second year	
Physical examination	X		
Vital signs	X		
Glucose metabolism (fasting glucose, fasting insulin and HbA1c)	X[5]	X – from second year	
Other hormonal levels (TSH, FT4, T3, cortisol)	X[5]	X – from second year	
Parameters of lipid metabolism	X[5]	X – from second year	
Routine safety laboratory (biochemistry, hematology and urinalysis)	X[5]	X – from second year	
Urine pregnancy test	X		
Pubertal status	X		
ECG around Tmax (7-12 hours post dose)[7]			X
BA			X
LH, FSH and testosterone.[3]			X
LH, FSH and estradiol[4]			X

[5] Data collected every 3 months with the exception of month 9.
[3] For male patients that are on the age 13 years old and above
[4] For female patients that are at the age of 12 years old and above

Long-Term OLE PEN (LT-OLE-PEN) Period V From 2nd Year Until Marketing Approval

	LT OLE PEN visits by Month over each year the study is running			
	Month 3 visit (±2 week)	**Month 6 visit (±2 week)**	**Month 9 visit (±2 week)**	**Month 12 (±2 week)[5]**
Assessments	**day 4 (-1) post dose**	**day 4 (-1) post dose**	**day 4 (-1) post dose**	**day 4 (-1) post dose**
Auxology measurements: actual height measured on calibrated stadiometer	X	X	X	X
Body weight measurement	X	X	X	X
Adjustment of dose for weight	X	X	X	X
AEs	X	X	X	X
Local tolerability	X	X	X	X
Concomitant medication	X	X	X	X
Dispensing of drug	X	X	X	X
Return of used drugs	X	X	X	X
Fundoscopy - If required	X	X	X	X
IGF-I, IGFBP-3	X	**X**	X	X
MOD- 4023 serum levels		**X**		X
Anti-MOD-4023 antibodies		X		X
Physical examination	X	X	X	X
Vital signs	X	X	X	X
Glucose metabolism (fasting glucose & insulin, HbA1c)		X		X
Other hormonal levels (TSH, free T4, cortisol)		X		X
Parameters of lipid metabolism		X		X
Routine safety laboratory (biochemistry, hematology and urinalysis)		X		X
Urine pregnancy test[6]	X	X	X	X
Pubertal status[7]	X	X	X	X
ECG				X
Bone age				X
LH, FSH and Testosterone[8]				X

[5] In case ET/EOS visit is conducted all assessment should be done as one with no split.
[6] For females of child bearing potential. In case urine pregnancy test is positive, please refer to section **Error! Reference source not found.** in the protocol.
[7] In case the patient becomes pubertal, childbearing potential and refraining from sexual activity will be discussed with the patient.
[8] For male patients that are at the age of 13 years and above.

	LT OLE PEN visits by Month over each year the study is running			
	Month 3 visit (±2 week)	**Month 6 visit (±2 week)**	**Month 9 visit (±2 week)**	**Month 12 (±2 week)[5]**
LH, FSH and Estradiol[9]				X
Provide patient diary and return of completed diaries	X	X	X	X[10]

[9] For female patients that are at the age of 12 years and above.
[10] Dispensing patient diary is not applicable for termination visit, only return of completed diaries.

5 ANALYSIS POPULATIONS (ANALYSIS SETS)

Since this is an OLE with patients from the primary study, all patients will be included in a single Full Analysis Set for reporting.

6 CONVENTION FOR REPORTING TREATMENT PERIODS

Periods III and IV: The protocol defines Period III as a 12 month period when patients are in three specific dose groups, and Period IV as starting on 0.66 mg/kg/week after 12 months in Period III. Because of the differences in timing of transition to the 0.66 mg/kg/week dose, all data from Periods III and IV will be presented in 12 month intervals, starting with the first dose of treatment at the start of Period III. The dose at the beginning of each 12 month period will be used to classify the patient to a dose group for disposition purposes. For the first 12 months, the results will be reported by the assigned dose group. After the initial year on OLE, all patient results will be summarized in a single treatment group, regardless of assigned dose level, or any individual patient dose adjustments.

For patients with gaps of [redacted] in treatment, the re-start of treatment will be the start of the new 12 month interval, regardless of the elapsed days. Safety data collected during the period without treatment will be included in the previous 12 month interval.

Period V: This period will contain data from patients on PEN treatment. Baseline data for this period will be the data collected at the visit for the first PEN dose, prior to the first PEN dose.

The cumulative change in HT SDS from the start of treatment in Period I will also be summarized. For these summaries, the original dosing assignment will be used, and the reporting periods will be at each of the scheduled Month 12 visit of the period. Gaps in treatment will be included, so that the elapsed time may be longer than 12 months.

7 STATISTICAL ANALYSIS METHODS

7.1 Statistical Methods

This is an open label long-term extension study. No formal hypothesis testing will be performed. Descriptive statistics will include mean, median, standard deviation, minimum, maximum, range, count and confidence intervals to present the results. All output will be created with SAS version 9.4 or higher.

7.2 Interim Analysis

Not applicable.

7.3 Adjustment for Clinical Center

The analysis will not be stratified by study site.

7.4 Data Handling and Missing Data

Because of the observational nature of this study, missing data in general will not be imputed, except for:

1. specific items associated with AEs as specified in Section 9.1;

2. missing day or month will be imputed to the 1st of each if needed for calculations, unless this imputation contradicts a previous date (such as between start and stop dates). In this case, the imputed date will be last day or month, or be missing and presented as "ongoing."

Unscheduled assessments or multiple results within a specified visit window will be listed, but not used in the visit summary. The assessment closest to the scheduled visit date will be used.

Early termination assessments will be assigned to the appropriate annual interval based on treatment month within a period.

7.5 Issues of Laboratory Data

If there were two or more evaluable results in a given visit, the latest test result will be used for analysis. If the evaluable result was indicated by <nn, half of the value (= nn/2) will be used for the summary. If the evaluable result was >nn, the value (= nn) will be used for the summary.

8 DEMOGRAPHICS, BASELINE CHARACTERISTICS AND STUDY SUMMARY

8.1 Patient Disposition

The number and percentage of patients entering and completing each 12 month period will be summarized by the dose level at the beginning of each period. A listing will be provided to show the reason for discontinuation and time of discontinuation for each patient.

Protocol deviations will be listed and summarized within each period, but will not be used to define patient groups.

8.2 Demographics

The demographics (age, gender, race) will be summarized using descriptive statistics at the start of Period III, and for each 12 month reporting period.

Age will be the age at the start of each reporting period, calculated from the date of day 1 of each period and the date of birth. If the date of birth is not available, then the age will be calculated from the elapsed months added to the age reported at the beginning of Period 1 of the study.

8.3 Weight, Height and BMI

Patient weight, HT, body mass index (BMI), HT SDS, IGF-1 SDS, BA, and HV will summarized at the start of OLE. Patient weight, HT and BMI will be summarized for each 12 month period. The patient's reported HT for each visit is the average of the three consecutive measurements made by study personnel. See Section 10.1 for details on HT outcomes.

8.4 Medical History

The medical history data collected in the main study will be summarized for the patients in the OLE by System Organ Class (SOC) and preferred terms based on the coded data by the Medical Dictionary for Drug Regulatory Activities (MedDRA). The count and percentage of ongoing medical condition per preferred terms will also be provided.

9 ANALYSIS OF SAFETY ENDPOINTS

9.1 Adverse Events

AEs will be coded using MedDRA v20.1. TEAEs for each 12 month period will be defined as those that start in each 12 month period and separately for Period V on PEN, which will be cumulative. The denominator used for calculation of AE rates will be the number of patients at the beginning of each period or year. For patients who have gaps in treatment, the events that start in the gap will be included in the prior treatment period. In addition, a summary of AEs for the entire extension period will be provided.

The results will be presented:

- by order of the frequency of AEs by the MedDRA preferred term (PT)
- by severity of AEs
- by the relationship of AEs to the study drug
- and all SAEs

Patient incidence of AEs of special interest will also be summarized overall and by SOC through the entire extension period. The AEs of special interest are:

Adverse Event of Special Interest	MedDRA v20.1 Definition Criteria
Glucose metabolism impairment	Hyperglycaemia/new onset diabetes mellitus (standardized medDRA queries [SMQ]) Full Scope
Thyroid function impairment	Thyroid dysfunction (SMQ) Full Scope
Intracranial hypertension	Increased intracranial pressure disorders (high level term [HLT] - All Paths)
Neoplasias	Malignancy (SMQ) Full Scope
Intracranial aneurysm	Central nervous system aneurysms and dissections (HLT - All Paths)
Immunogenicity (including positive anti-drug antibody and allergic reactions) and Hypersensitivity	Laboratory result parameter: Anti somatrogon antibody or Neutralizing Antibody present, Anaphylactic reaction (SMQ) Narrow Scope, Angioedema (SMQ) Narrow Scope, Hypersensitivity (SMQ) Narrow Scope
Injection site reactions (including lipoatrophy/skin dystrophy)	Injection site reactions (HLT - All Paths) and select PTs (Lack of injection site rotation, Lipoatrophy, Skin hypertrophy, and Skin dystrophy) and PTs containing 'Administration site'
Epiphysiolysis	PT Epiphysiolysis
Haemangioma of skin	PT Haemangioma of skin
Oedema	Oedema NEC (HLT - All paths) and Total fluid volume increased (HLT - All Paths)
Scoliosis	PT Scoliosis
Acute and chronic pancreatitis	Acute and chronic pancreatitis (HLT - All Paths)
Increased Protein kinase	PT Blood creatine phosphokinase increased

Adverse Event of Special Interest	MedDRA v20.1 Definition Criteria
Adrenal cortical hypofunctions	Adrenal cortical hypofunctions (HLT - All Paths)
Myalgia	PT of Myalgia
Myositis	PT of Myositis
Arthralgia	PT of Arthralgia

A listing of TEAEs that lead to withdrawal from the study will also be provided.

Missing values will be treated as missing except for causality, intensity, and outcome of an AE, at which occurrence a "worst case" approach will be taken in the analysis. Thus, if causality is missing the AE will be regarded as related to the investigational medicinal product (IMP), if the intensity is missing the intensity of the AE will be regarded as severe, and if the outcome is missing and the stop date is not provided the outcome is regarded as "ongoing." If the classification of SAE (seriousness) is missing, all efforts should be made prior to database lock to make sure that this information is available.

9.2 Antibodies

Anti-somatrogon antibody (ADA), anti-somatrogon neutralizing antibody, and anti-hGH neutralizing antibody will be tested at month six and month 12 in Period III and then every six months thereafter. The results of the antibody testing will be summarized for each test at each of the OLE and PEN time points tested. The titer and specificity (anti-hGH and CTP) of confirmed ADA will be summarized. The anti-somatrogon and anti-hGH neutralizing antibody status (positive or negative) are only assessed when a patient is confirmed positive for ADA, so any sample that has not shown somatrogon specificity will be considered negative for NAb. The numeric values for titer will be summarized by median, min and max.

Overall incidence of TEAEs and injection site reactions will also be summarized by ADA status.

HV, HT SDS, and peak IGF-1 SDS will be summarized for each reporting period by ADA status.

ADA status will be assigned on a rolling or dynamic basis. A patient is only considered ADA positive at the beginning of the year in which they test positive and for the remainder of the study.

9.3 Injection Site Reactions and Pain

Incidence of injection site reaction (ISR) AEs will be summarized by SOC and PT, including pain, redness, bruising, swelling, or itching at the injection site. Summaries will be provided for each 12 month period, and during Period V on PEN.

The [redacted] pain scores will be summarized with number of overall patients at the beginning of each year as the denominator. For each patient, ISR pain score will be summarized by maximum severity for each period. Missing values will be considered "hurts worse."

ISR erythema/redness, bruising, induration/swelling, itching, and tenderness scores will be summarized with number of overall patients at the beginning of each year as the denominator.

For each patient and reaction type, symptoms will be summarized by maximum severity. Missing values will be considered "severe."

9.4 IGF-1 and IGF-1 SDS

IGF-1 will be listed for each patient, but not summarized. IGF-1 SDS will be listed, and summarized at each visit. In addition, the number and proportion of patients with IGF-1 SDS > 2 will be summarized. The denominator will be the number of patients with results at each visit. For the summaries of each 12 month period with multiple visits, each patient will be counted once, and will be counted as having IGF-1 SDS >2 if any results within that summarized interval is >2. IGF-1 SDS will also be summarized by ADA status.

9.5 IGFBP-3

IGFBP-3 levels will be provided in a listing.

9.6 Laboratory Test Results

Clinical laboratory measurements will be summarized with descriptive statistics at each visit. Changes within each 12 month period will use the first visit of the 12 month period as the baseline. For Period V the baseline will be the first visit with PEN injection. If data from the first visit of each period are not available, the last previous visit data will be used. Summary of abnormal results (reported as low, high, clinically significant) will be provided for each 12 month period, with the number of patients at the beginning of each period for the denominator.

The following laboratory results will be presented:

- Glucose Metabolism, Endocrinology, and Lipid Metabolism:

Glucose Metabolism	**Endocrinology**	**Lipid Metabolism**
Fasting blood Glucose	FT4	Cholesterol
Fasting Insulin	T3	High density lipoprotein (HDL)
HbA1c	Thyrotropin (= TSH)	Low density lipoprotein (LDL) Cholesterol
	Cortisol, Free	Lipoprotein-A
	Females >=12 y.o.: FSH, LH and estradiol	Triglycerides
	Male >=13 y.o.: FSH, LH and testosterone	

- Chemistry, Hematology, and Urinalysis:

Clinical Chemistry	Hematology	Urinalysis
Albumin	Differential Blood Count of Leukocytes	Bilirubin
Alkaline phosphatase	Erythrocyte Count	Glucose
Calcium	Hematocrit	Ketones
Chloride	Hemoglobin	Leukocyte Esterase
Creatinine	Leukocytes	Nitrite
Gamma-glutamyl Transferase (GGT)	Mean Corpuscular Hemoglobin (MCH)	pH
Lactate Dehydrogenase (LDH)	Mean Corpuscular Hemoglobin Concentration (MCHC)	Protein
Phosphate	Mean Corpuscular Volume (MCV)	Specific Gravity
Potassium	Platelet Count	Urinalysis Blood
Serum Glutamic Oxaloacetic Transaminase (SGOT)		Urobilinogen
Serum Glutamic Pyruvic Transaminase (SGPT)		
Serum Iron and Transferrin		
Sodium		
Total Bilirubin		
Total Proteins		
Urea (blood urea nitrogen)		
Uric Acid		

The increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin will be examined for liver function. The count and percentage of the increases will be tabulated for each visit including baseline. The increases of ALT and AST will be examined in three categories, i.e. >2 × upper limit of normal (ULN), >3 × ULN, and >5 × ULN, and that of total bilirubin combined with ALT or AST increases will be examined in 1 category, total bilirubin >3 × ULN and ALT or AST >2 × ULN.

9.7 Physical Examinations

Physical examination data (every three months in Period III and every 12 months in the later period) will be tabulated by frequency count and percentage for each organ system category by visit.

9.8 Vital Signs

The vital signs (systolic / diastolic blood pressure in seated position, respiratory rate, pulse rate, and body temperature) will be summarized at each visit. The change from the beginning of OLE, and the change within each year for continuous parameters will be presented.

9.9 ECG

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, RR intervals, $QTc\text{-}_{Bazett}$ interval) will be listed. The clinical assessments: Normal / Abnormal – same as screening / Abnormal – new, clinically not significant / Abnormal – new, clinically significant or aggravated, collected at the end of each OLE and PEN year will be summarized as proportion of patients with each assessment, with the number of patients at the beginning of the period as the denominator.

9.10 Magnetic Resonance Imaging (MRI)

MRI results will be listed for each visit.

9.11 Fundoscopy

The fundoscopy examination is done at the end of the first year of the OLE period and performed if there is any clinical sign of intracranial hypertension. The number and percentage of patients who have fundoscopy done in each 12 month period, and the number and percentage of patients who have signs of intracranial hypertension in each period will be presented.

9.12 Concomitant Medications

Medications will be coded and presented using World Health Organization (WHO) Drug Dictionary version September 2017, Anatomical Therapeutic Chemical Code (ATC) level 2, as well as, the primary term. The medications used within each 12 month period will be summarized by ATC level 2. For PEN treatment in Period V, the medications will be separately summarized.

9.13 Extent of Exposure

The total duration of treatment (in months) for each patient will be calculated as:

1. The total duration since first treatment in this study (since the first dose of Period I)
    a. For patients initially randomized to Genotropin, the total duration of exposure to somatrogon will be calculated from the date for first treatment with somatrogon.
2. The total duration in each assigned dose level and on PEN.
3. The overall exposure will be calculated as Last dose – First dose + 7 days (to account for the once weekly dose exposure). To convert to months, the total daily exposure will be divided by 30.147.

Because of potential gaps in treatment between periods, the total duration may not represent continuous exposure. A listing of the patients with gaps in treatment will be provided showing the time period without treatment.

The number and proportion of patients who have the dose adjusted due to IGF-1 SDS >2 or other reasons will be summarized by reason for each 12 month period, with the denominator as the number of patients who started each period. The listings will show the dose at which the IGF-1 SDS excursion occurred.

10 GROWTH OUTCOMES

10.1 Annualized HV

Descriptive statistics or HT will be presented. Annualized HV between two time intervals X and Y will be calculated as:

$$Height\ Velocity\ \left(\frac{cm}{year}\right) = \left[\frac{Month\ X\ Height\ (cm) - \ Reference\ Month\ Y\ Height\ (cm)}{Month\ X\ date - Reference\ Month\ Y\ date}\right] * 365.25$$

HV will be calculated for the following intervals:

1. Periods III and IV
   a. 12 month intervals, with the first 12 months starting with the first injection of Period III. Gaps in treatment will not alter that calculation of these 12 month intervals.
   b. Last 6 and 12 month interval, using the last measure in Period IV with the measures at 6 and 12 months prior to the last measure as the reference.
2. Period V (PEN)
   a. Intervals of 6 and 12 months from the start of the PEN injection as the reference for the first year.
   b. After the first year of PEN, HV at the end of each year uses the measure at the Month 12 visit in each year with the measure at the Month 12 visit of the prior year as the reference. In cases where there is a gap in treatment between years, the measure at the restart of treatment (if available) will be used as the reference.

HV will also be presented for each treatment year, including Periods I and II, by the original treatment group assignment.

For patients who discontinue from the study between these specific defined visits for the calculations, their last HT measurement and date will be used for the annualized HV in the interval of interest.

Annualized HV by year, annualized HV on PEN treatment, change in HT SDS by year and change in HT SDS on PEN treatment will be summarized by ADA status.

10.2 Achievement of Final Adult Height

The number (and proportion) of patients who achieve adult height will be summarized by age. The denominator for proportion for this summary will be the total of patients in the study, so that patients who discontinue from the study are simply considered not to have achieved adult height. A Kaplan-Meier curve will be used to display the proportion of patients achieving adult height by age. For the Kaplan-Meier curve, discontinued patients will be censored, and removed from the denominator. Achievement of final adult height is defined as the HT when annualized HV < 1 cm/year over at least six-month period.

10.3 Change in Height SDS

HT SDS will be summarized with descriptive statistics at the end of OLE years 1 - 4 and for each year on PEN. HT SDS will also be presented for each treatment year, including Period I and II, by the original treatment group assignment and total. In addition, HT SDS will be summarized by ADA status. Descriptive statistics will be used to characterize the change in HT SDS. The change in HT SDS will be calculated from baseline of Period I, as well as each 12 month period.

In addition, the cumulative change in HT SDS from the baseline at Period I will be calculated for each of the scheduled Month 12 visit of each year, using the original treatment groups assignment and total.

10.4 Bone Maturation

BM will be evaluated as the BA divided by the chronological age (CA).

BM = BA/CA

BA is reported as year and months, and will be converted to a decimal value as years + months/12.

CA will be calculated as (date of BA assessment – Birth date)/365.25.

BM will be calculated at 12 month intervals. The change in BM will be calculated as the change in BA/change in CA for each of the intervals defined for the calculation of HV, when the BA assessment is available. Descriptive statistics will be used to characterize the change in BM.

10.5 Pubertal Status

The pubertal status will be reported at the end of each year of the OLE and PEN periods.

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