Protocol for Clinical Study CP-4-006 ([redacted])

A PHASE 3, OPEN-LABEL, RANDOMIZED, MULTICENTER, 12 MONTHS, EFFICACY AND SAFETY STUDY OF WEEKLY SOMATROGON COMPARED TO DAILY GENOTROPIN® THERAPY IN PRE-PUBERTAL CHILDREN WITH GROWTH HORMONE DEFICIENCY

Open-label Extension (OLE)
Statistical Analysis Plan
(SAP)

Version: **1**

Date: **3 Jan 2024**

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
V1	No separate CP-4-006 (C0311009) OLE protocol. Referring to Section 5.3 study procedure for LT-OLE and sub-section of OLE embedded in each section of the Amendment V5.0 dated 2 May 2018	Original SAP	No

2. INTRODUCTION

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates hepatic production and release of insulin-like growth factor-1(IGF-1) into the systemic circulation. IGF-1 is an important mediator in the promotion of linear growth in children and may play a role in the regulation of metabolism and body composition in adults. These factors are regulated through complex feedback mechanisms involving hGH, IGF-1 binding protein-3 (IGFBP-3) and their complexes.

The majority of currently available hGH products require daily or every other day subcutaneous (SC) or intramuscular (IM) injections to maintain hGH blood levels within the effective therapeutic window. The burden of daily administration and its concomitant side effects (e.g., injection site discomfort, transient edema and arthralgia) cause a reduction in compliance (Rosenfeld and Bakker 2008[2]) and can limit the therapeutic utility of existing formulations.

Somatrogon is a long-acting r-hGH for SC administration. It consists of hGH fused to three copies of the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin; one copy at the N-terminus and two copies (in tandem) at the C-terminus. Somatrogon is the International Nonproprietary Name (INN) of somatrogon and can be used interchangeably with MOD-4023.

The purpose of the current Phase 3 study is to demonstrate that weekly somatrogon administration in pre-pubertal children with growth hormone deficiency (GHD) is clinically non-inferior to daily Genotropin® administration in terms of safety and efficacy after 12 months treatment duration. The study will be conducted in a randomized, open-label, active-controlled, parallel-group design. After completion of an initial 12-month treatment, patients will be eligible to continue treatment with weekly somatrogon in a single arm, long-term

open-label extension (LT-OLE) study for the purpose of collecting additional long-term safety and efficacy information.

As the dose selection is driven by evaluating the annual increment in height velocity (HV), the annual HV data obtained for somatrogon was compared to Genotropin® results in the Phase 2 study for 52 patients (one patient was mis-diagnosed). Based on 12-month auxology data, it is most likely that a minimum somatrogon dose of 0.66 mg/kg/wk will provide an annualized HV comparable to daily hGH at a dose of 34 μg/kg/day.

This SAP provides the detailed methodology for summary and statistical analyses of the OLE data collected in Study CP-4-006 ([redacted]). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

LT-OLE Objective:

To assess the long-term efficacy, safety, and immunogenicity of somatrogon in the LT-OLE period.

2.1.1. Estimand(s)

The estimand of this study uses the treatment policy strategy and estimates the effect for all participants treated regardless of whether an intercurrent event occurs. Each of them includes the following four attributes:

- Population: All patients who entered OLE period and had at least one dose of somatrogon;
- Variable:
  - Annualized height velocity (AHV) at each 12-month interval (cm/year)
  - Height standard deviation score (SDS) and change in height SDS;
  - Change in bone maturation (BM);
  - IGF-1 and IGF-1 SDS levels on day 4 (-1) after somatrogon dosing across study visits;
  - IGFBP-3 levels and IGFBP-3 SDS on day 4 (-1) after somatrogon dosing across study visits;
  - Pubertal status (according to Tanner stages);
  - For males that are 13 years and older: luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone;

- For females that are 12 years and older: LH, FSH and estradiol

- Intercurrent event: All data after an intercurrent event (discontinuation of treatment, discontinuation of study, etc.), if collected, will be included;

- Population-level summary: descriptive summary for absolute values at each visit and/or change from previous interval.

2.1.2. Additional Estimand(s)

Not Applicable.

2.2. Study Design

The study will be divided into two parts: Main Study Period (main study) and OLE Period.

The main study will consist of 12 months, open-label, multi-center, randomized, active controlled, parallel group study comparing efficacy and safety of weekly somatrogon to daily GH, Genotropin®. Both drugs will be injected using a PEN device.

Patients who received somatrogon during the main study will continue in the LT-OLE with the same dose (mg/kg/wk) of somatrogon. Patients who received Genotropin® during the main study will be switched to somatrogon and will begin treatment with a dose of 0.66 mg/kg/wk beginning no less than one day after cessation of Genotropin® treatment.

The key safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) approximately every 6 months. During the entire study (main study and LT-OLE), the dose of somatrogon and Genotropin® will be adjusted every 3 months based on the patient's body weight. Doses may be decreased for safety reasons according to the pre-defined dose-adjustment criteria (which will be based on the severity of adverse events (AEs) or repeated, elevated levels of IGF-1). The dose will be decreased based on two, repeated day 4(-1) post-dose levels of IGF-1 SDS > +2.0. During the LT-OLE, dose reduction for IGF-1 level >+2.0 SDS will be made following consultation with the Global Study Medical Monitor on an individual patient basis.

The LT-OLE will continue until marketing approval.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Efficacy Endpoints

3.1.1. Annualized Height Velocity (cm/year)

AHV at each 12 month is based on the difference between the height (HT) at each 12 month and the height at the previous 12 month.

HT at Month 12 of current year – HT at Month 12 of prior year

$$\text{AHV(cm/year)} = \frac{\text{(Month 12 Visit Date of current year – Month 12 Visit Date of prior year)}}{365.25}$$

The following algorithm will be used in case the reference visit (i.e., previous 12 month visit) is missing:

- If main period Month 12 (OLE Baseline), Visit 16 (OLE Month 12), Visit 20 (OLE Month 24), Visit 24 (OLE Month 36) are not missing, these will serve as reference visits.
- If missing, create anchor visit which is the scheduled visit (non-missing) prior to the missed reference visit, or scheduled or unscheduled visit (non-missing) after the missed reference visit based on the anchor logic described below:
  - A subject showed a missing reference visit at visit 16
  - This subject completed Visit 15 (OLE Month 9; Anchor A) and Visit 17 (OLE Month 15; Anchor B) and did not complete an Unscheduled Visit. One of the scheduled visits (non-missing) will be determined as the Anchor Visit
- Anchor logic:
  - If Anchor B – Anchor A < 6 months (180 days) then Anchor A will be uses as the reference visit.
  - If Anchor B – Anchor A ≥ 6 months (180 days) then Anchor B will be uses as the reference visit.
  - If a reference visit was performed out of window and reported as an unscheduled visit then unscheduled visit will be used as the reference visit, Anchor C.

3.1.2. Change in Height SDS

Height SDS will be calculated as the Z-score using LMS method as:

Z = [((Height / M)^L) – 1] / (S * L),

where L, M, S will be determined from the age and gender standards listed in 2000 CDC Growth Charts (www.cdc.gov/growthcharts) for age 2 to 20, or CDC reference datasets.

Change in height SDS will be calculated as the difference between the height SDS at each scheduled visit in OLE period and the height SDS at the main period baseline.

3.2. Biomarkers

3.2.1. Change in Bone Maturation

Bone maturation will be calculated as bone age (BA) divided by chronological age (CA). BA will be determined by a central reader via X-ray according to the Greulich-Pyle method and reported in years and months. These results will be combined into a decimal value as: years +

months/12. CA will be determined based on the assessment date. A decimal value will be calculated as: age in years + (assessment date – date of birthday + 1) / 365.25.

Change in BM at each visit in the OLE period will be calculated using the formula below:

$$\text{Change in BM} = \frac{\text{BA at post-baseline visit} - \text{BA at baseline}}{\text{CA at post-baseline visit} - \text{CA at baseline}}$$

3.2.2. IGF-1 (ng/mL) and IGF-1-SDS

IGF-1 levels and IGF-1 SDS will be measured and calculated on day 4 (-1) after somatrogon dosing across study visits in OLE at every scheduled visit in OLE period. Change in IGF-1 SDS at each visit will be calculated as the difference between the IGF-1 SDS values in the OLE period and the IGF-1 SDS at the main period baseline.

3.2.3. IGFBP-3 (ng/mL) and IGFBP-3-SDS

IGFBP-3 levels and IGFBP-3-SDS will be measured and calculated on day 4 (-1) after somatrogon dosing across study visits in OLE at every scheduled visit in OLE period. Change in IGFBP-3 SDS at each visit will be calculated as the difference between the IGFBP-3 SDS values in the OLE period and the IGFBP-3 SDS at the main period baseline.

3.3. Other Endpoint(s)

3.3.1. Additional Assessment

The annual assessment will also be conducted according to the protocol schedule, including bone age, pubertal status (Tanner stage as stage I to V), LH, FSH, as well as testosterone for boys 13 years and older or estradiol for girls 12 years and older at every 12 months in the OLE period.

3.4. Baseline Variables

Baseline is defined as the main period baseline for efficacy and biomarker assessment. Except the reference visit for AHV, is defined in Section 3.1 as the values at the previous 12 month in the OLE period.

3.5. Safety Endpoints

3.5.1. Adverse Events

The AE including time of the onset, severity, action/treatment and outcome of the AE resolution, related to somatrogon treatment or not, will be collected at each scheduled visit with the visit window specified in the Schedule of Activities in the protocol.

An AE is considered as a treatment-emergent adverse event (TEAE) if the event started on or after the first dose of somatrogon in the OLE period of the study. The AE reporting period

for this study will be defined as the duration from the first dose of somatrogon in the study until 28 calendar days following the final visit dose. AE with partial dates will be assessed using the available date information to determine treatment-emergent status; AEs with missing onset date/time will be considered as TEAE. AEs with missing resolve date/time will be considered as ongoing.

3.5.2. Laboratory Data

Laboratory data will be collected according to the Schedule of Activities in the protocol, including hematology, chemistry, lipid profile, glucose metabolism, endocrinology and urinalysis lab tests.

3.5.3. Vital Signs

Vital sign data will be collected according to the Schedule of Activities in the protocol, including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature. Any clinically significant (CS) findings will be reported as an AE.

3.5.4. Antibodies

Blood samples for anti-drug antibodies (ADA) will be collected according to the Schedule of Activities in the protocol, including the ADA status (positive, negative, not done or not available) for the following items:

- Anti-human GH (hGH) antibodies
    - neutralizing
    - non-neutralizing
- Anti-somatrogon antibodies
    - neutralizing
    - non-neutralizing

ADA titer will be classified as 0 (i.e., ADA negative), 10, 50, 250, 1250, 6250. Titer values >6250 are reported as 6250.

ADA positivity will be defined as:

- Tested positive after the receipt of drug during the study (either in main period or OLE), if main period baseline was tested negative or titer as 0;
- Post-baseline titer > 4x main period baseline titer, if main period baseline was tested positive.

Otherwise, it will be classified as ADA negative.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

The term "full analysis subset" is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all enrolled patients entered the OLE period. The full analysis set will comprise all treated patients who have received at least one dose of active treatment during the main and OLE phase and who provide any follow-up data. The patients will be grouped by their original randomized treatment in the main period.

The analysis populations for reporting are defined in the following table.

Population	Description
Enrolled	All participants who sign the informed consent document and continued in the OLE period.
Evaluable or Full Analysis Set (FAS)	All participants who continue to the OLE period of the study and take at least one complete dose of somatrogon (or partial dose if adverse events prevent completing dose). Participants will be analyzed overall and according to the randomized study drug that originally received in the main period.
Safety Analysis Set	All participants who continue to the OLE period of the study and take at least 1 complete dose of somatrogon (or partial dose if adverse events prevent completing dose). Participants will be analyzed overall and according to the randomized study drug that originally received in the main period.
Per Protocol Set (PP)	Not applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing in the OLE period for this study.

5.2. General Methods

5.2.1. Analyses for Continuous Endpoints

Descriptive statistics will be provided for continuous variables using number of subjects (N), mean, standard deviation (SD), median, and range.

5.2.2. Analyses for Categorical Endpoints

Frequency and percentage for each category of the variable will be provided as a descriptive summary for each visit.

5.2.3. Analyses for Time-to-Event Endpoints

Not applicable.

5.3. Methods to Manage Missing Data

Missing reference value in calculating primary endpoint of AHV is specified in Section 3.1. The missing data for the post-baseline data of the primary endpoint and all secondary efficacy endpoints will not be imputed and be summarized as observed data.

Missing safety data will be handled according to the Pfizer Clinical Data Interchange Standards Consortium (CDISC) safety rulebook and data standard rules for imputation, including missing dates (when the date is required for a calculation) and missing severity of adverse events.

6. ANALYSES AND SUMMARIES

There are two treatment groups in the OLE, defined as originally randomized to somatrogon and originally randomized to Genotropin® in the main study.

6.1. Efficacy Endpoint

6.1.1. Main Analysis

- Estimand strategy: Treatment policy strategy for AHV every 12 months, as well as for absolute value and change from baseline for each of the efficacy endpoints, including height SDS, IGF-1 and IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS, BM, LH, FSH and testosterone or estradiol.
- Analysis set: FAS (defined in Section 4).
- Analysis methodology: change from baseline to OLE Year 1, Year 2, Year 3, etc., will be descriptively and graphically summarized.
- Intercurrent events: Data after study drug discontinuation will be included.
- Descriptive summary includes N, mean, SD, median, minimum, and maximum for absolute value. It can be presented by treatment group (originally randomized to somatrogon, originally randomized to Genotropin®, and total), by ADA sub-groups including ADA status (positive or negative), ADA titers, and by visit.

6.1.2. Sensitivity/Supplementary Analyses

Not applicable.

6.2. Other Endpoint(s)

6.2.1. Immunogenicity (Antibodies)

Frequency and percentage of anti-somatrogon antibodies in FAS will be reported by year and visit, if adequate data are collected.

6.3. Subset Analyses

There is no planned subset analysis for this study.

6.4. Baseline and Other Summaries and Analyses

Descriptive summary including N, mean, SD, median, minimum, and maximum will be presented for continuous baseline variables. Frequency and percentage will be provided for categorical baseline variables.

6.4.1. Baseline Summaries

The summaries will be provided for demographic data collected at the entry of the OLE period, if data permits.

6.4.2. Study Conduct and Participant Disposition

Frequency counts and percentage will be reported for participant discontinuation due to adverse events and reasons for discontinuation, completion of each OLE year, number of subjects assessed, and number of subjects achieved final height.

Data will be reported in accordance with the Pfizer reporting standards.

6.4.3. Study Treatment Exposure

Frequency counts and percentage will be reported for 6-month intervals for treatment duration in main period and OLE phase. The patient year will be descriptively summarized (median, mean and SD) in main period and OLE.

6.4.4. Concomitant Medications and Nondrug Treatments

The concomitant medication(s) and non-drug treatment(s) in OLE period will be provided in the listings.

6.5. Safety Summaries and Analyses

All the safety data will be summarized descriptively through the appropriate data tabulations in safety population (defined in Section 4) according to Pfizer Safety Rulebook and CDISC standards analyses, to evaluate any potential risk associated with the safety and toleration of administering somatrogon pediatric GHD patients.

6.5.1. Adverse Events

TEAE will be summarized with counts and percentage for safety population (defined in Section 4). The number and percentage of subjects who experienced at least one TEAE as well as the number and percentage of subjects who experienced each specific system organ class (SOC) and preferred term (PT) will be summarized and sorted by descending order of overall incidence.

All AEs will be reported in a data listing.

For analysis purposes, all AEs will be classified to the appropriate MedDRA PT and SOC. For each subject, multiple events that map to the same PT will only be counted once for the PT, and multiple PTs within an SOC will only be counted once for that SOC to assess patient incidence of events by PT and SOC. The count and percentage of patients with each PT and SOC will be summarized for each treatment group. Relationship and severity of AEs will be summarized (count and % of patients, incidence rate based on person-year) for each treatment group. For these summaries, multiple occurrences of an event within a patient will be classified as a single observation with the strongest relationship and maximum severity ratings. In addition, frequency tables of all reported events with each associated relationship and severity will be presented. Serious adverse events (SAEs) will be classified by the investigator and will be summarized by treatment group, PT and SOC, as well as total patients exposed.

In addition to the SOC and PT defined in the live MedDRA version at the final reporting stage, the adverse event of special interest (AESI) will be also summarized using frequency and percentage.

6.5.2. Laboratory Data

Laboratory data will be descriptively summarized by each clinical laboratory panel of hematology, chemistry, lipid profile, glucose metabolism, endocrinology, urinalysis. Shift tables will also be provided for each panel to present the count and percentage shifts from baseline among the categories of low, normal, and high.

6.5.3. Vital Signs

All vital sign data will be listed by participant and visit.

Though vital signs will be collected during each site visit per standard of care, only vital sign collected at the baseline, Month 3, 6, 9 and 12 in each of the OLE year will be summarized descriptively. Absolute values, change from baseline, and percent change from baseline for vital sign data will be summarized using N, mean, SD, median and range.

6.5.4. Physical Examination

Physical examination and neurologic assessment data will be listed only by participant and visit.

7. INTERIM ANALYSES

There is no planned interim analysis in this study.

8. REFERENCES

1. CDC reference standards for 2000 CDC growth charts and SAS programs at the CDC website (http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).

2. Rosenfeld, R. G. and B. Bakker (2008). "Compliance and persistence in pediatric and adult patients receiving growth hormone therapy." Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **14**(2): 143-154

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Not applicable.

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Annual ADA characterization will be performed based on the algorithm below using visit windows as applied to ADPC dataset.

Period	**om**	
Main	Day 2 (main dosing +1)	Day 410
OLE Year 1	Day 2/OLE Baseline (OLE dosing +1)	Day 410 (OLE Month 12)
OLE Year 2	Day 411	Day 774
OLE Year 3	Day 775	Day 1138
OLE Year 4	Day 1139	Day 1502

The following table will provide the adverse events reporting period to a given study period.

Period	**From**	**To**	**AE linking to study period**
Main	On or post first Main dosing date/time (in exposure dataset)	Prior to the first OLE dosing date/time	If the new AE strictly starts between the start and end dates of a given period, it will be counted in that period.
OLE Year 1 (visit13 -16)	On or post first OLE dosing date/time (defined in exposure dataset)	Visit 16 end date; if Visit 16 is missing, then first OLE dosing date + 365	
OLE Year 2 (visit 17-20)	"OLE Year 1 To" date + 1	Visit 20 end date; if Visit 20 is missing, then "OLE Year 2 From" date + 365	
OLE Year 3 (visit 21-24)	"OLE Year 2 To" date + 1	Visit 24 end date; if Visit 24 is missing, then "OLE Year 3 From" date + 365	
OLE Year 4 (visit 25-28)	"OLE Year 3 To" date + 1	Visit 28 end date; if Visit 28 is missing, then "OLE Year 4 From" date + 365	

Appendix 2.2. Endpoint Derivations

Not applicable.

Appendix 2.3. Definition of Protocol Deviations That Relate to Statistical Analyses/Populations

Not applicable.

Appendix 3. Data Set Descriptions

Not applicable.

Appendix 4. Statistical Methodology Details

Not applicable.

Appendix 5. List of Abbreviations

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AHV	Annualized height velocity
BA	Bone age
BM	Bone maturation
CA	Chronological age
CDISC	Clinical Data Interchange Standards Consortium
CDC	Center of Disease Control and Prevention
CS	Clinical significance
CTP	C-terminal peptide
DSMB	Data Safety Monitoring Board
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GHD	Growth hormone deficiency
hGH	Human growth hormone
HT	Height
HV	Height velocity
IGFBP3	Insulin-like growth factor-binding protein-3
IM	Intramuscular
INN	International Nonproprietary Name
LH	Luteinizing hormone
LT-OLE	Long-term open-label extension
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per protocol set
PT	Preferred term
r-hGH	Recombinant human growth hormone

Abbreviation	Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDS	Standard deviation score
SOC	System organ class
TEAE	Treatment-emergent adverse event

Appendix 6. List of Summary Tables

"Total" indicates across ADA status in the summary tables below.

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