STATISTICAL ANALYSIS PLAN
Version 4.0
14 Jun 2019

Protocol: CP-4-006

A Phase 3, Open-Label, Randomized, Multicenter, 12 Months, Efficacy and Safety Study of Weekly MOD-4023 Compared to Daily Genotropin® Therapy in Pre-Pubertal Children with Growth Hormone Deficiency

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1.0	22 Sep 2017	Original final
2.0	10 Apr 2018	Remove IGF-1 normalization Update imputation strategy Add anytime post-baseline to safety shift tables Update ISR strategy
3.0	15 Nov 2018	Update Full Analysis Set definition Add visit windowing
4.0	14 Jun 2019	Add rationale for non-inferiority margin of -1.8 cm/yr Update Full Analysis Set definition Update imputation Include a statement with respect to assessing superiority once primary endpoint of non-inferiority has been met

APPROVALS

Approved:

See electronic signature

PPD

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quantification
BM	Bone Maturation
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eDISH	Evaluation of Drug Induced Serious Hepatotoxicity
GH	Growth Hormone
GHD	Growth Hormone Deficiency
HV	Height Velocity
IGFBP-3	Insulin-like Growth Factor Binding Protein 3
IGF-1	Insulin-like Growth Factor-1
ISR	Injection Site Reaction
LLQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
NCS	Not Clinically Significant
MedDRA	Medical Dictionary for Regulatory Activities
OAT	Observer Assessment Tool
PAT	Participant Assessment Tool
PEN	Single Subject Use, Multi-dose, Disposable Pre-filled Pen
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
QoLISSY	Quality of Life in Short Stature Youth
QTcF	Fredericia's Corrected QT Interval
r-hGH	Recombinant Human Growth Hormone
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
WHO DD	World Health Organization Drug Dictionary

1   PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) details the analyses planned for data collected in study CP-4-006, a Phase 3 study sponsored by OPKO Biologics Ltd., including the definition of the analysis populations, derivation of variables, convention of analysis scope, and statistical methodology for the analyses of efficacy, safety and tolerability of somatrogon (MOD-4023) compared to Genotropin®.

This plan follows the methods described in the protocol and provides more specific details. Any changes to the analysis as described in the protocol will be documented in detail in this plan. Any deviations from this SAP during the actual data analysis will be documented in the clinical study report (CSR).

2 PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to demonstrate that annual (12 month) height velocity (HV) from weekly somatrogon administration is non-inferior to daily Genotropin administration in children with growth hormone deficiency (GHD).

2.1.2 Secondary Objectives

The secondary objectives of the study are to evaluate the safety and tolerability and pre-filled PEN device usability of somatrogon in subjects with GHD, and to characterize other growth parameters (change in height SDS and bone age/maturation), and biochemical markers (insulin-like growth factor-1 [IGF-1] and insulin-like growth factor binding protein-3 [IGFBP-3]), associated with growth hormone therapy.

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary efficacy endpoint is the annual HV in cm/year after 12 months of treatment.

2.2.2 Secondary Endpoints

Secondary auxology efficacy endpoints include:

- Annualized HV after 6 months of treatment
- Change in height standard deviation score (SDS) at 6 and 12 months, compared to baseline
- Change in bone maturation (BM) at the end of 12 months, compared to Screening bone age (calculated as BA/CA)

Secondary biochemical marker endpoints include:

- Absolute IGF-1 on Day 4(-1) after somatrogon dosing across study visits
- IGF-1 SDS 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

2.2.3 Safety Endpoints

The safety endpoints include:

- Incidence of adverse events (AE) and serious adverse events (SAE)
- Incidence of anti-somatrogon antibody formation (including characterization of the antibodies and neutralizing properties)
- Local injection site assessment
- IGF-1 serum levels and SDS
- Parameters of glucose metabolism: blood fasting glucose, fasting insulin level, HbA1c
- Thyroid status

- Lipid parameters
- All other safety hematology, biochemical parameters and urinalysis
- Physical examination
- Vital signs
- Fundoscopy results – if performed (normal/abnormal)
- Electrocardiogram (ECG)

2.2.4   Other endpoints

The other endpoints include:

- Proportion of successful single injections out of total number of single injections using the somatrogon single subject use, multi-dose, disposable pre-filled pen (PEN) in US subjects at Weeks 1, 2, 3, 4, 5, and 6, based on the participant assessment tool (PAT)
- Proportion of successful single injections out of total number of single injections using the somatrogon PEN in US subjects at Week 1, based on the observer assessment tool (OAT)
- Comments on the PAT related to successful or unsuccessful injection attempts
- Comments on the OAT related to successful or unsuccessful injection attempts
- Information gained by inspection of returned devices
- Quality of Life (QoL) core total score as measured by the Quality of Life in Short Stature Youth (QoLISSY) questionnaire at baseline and month 12 at specific countries.

2.3   Study Design

The study is planned as a 12 month, open-label, randomized, active controlled, parallel group study comparing the efficacy and safety of weekly somatrogon to daily growth hormone, Genotropin.

Both treatments will be injected using a PEN device.

After a screening period lasting up to 8 weeks, subjects meeting the eligibility criteria, as approved by global study medical monitor, will be randomized in a 1:1 ratio to somatrogon (investigational treatment, 0.66 mg/kg/week) or growth hormone Genotropin (reference therapy, 0.034 mg/kg/daily which is equivalent to 0.24 mg/kg/week divided equally to 7 injections over a week) for 12 months.

If the subject's screening process is delayed because of a benign illness or unforeseen benign condition (ie, pharyngitis, viral gastrointestinal problems, minor accident or trauma, etc.) or a technical issue that is related to screening procedures (for example, delays with lab results), extra time – equal to the time of subject's unavailability – will be added to the duration of the screening period, but not in excess of an additional 4 weeks (total of 12 weeks screening period).

During the study, somatrogon and Genotropin dose will be adjusted based on the subjects' body weight every three months. The dose may be decreased or maintained for safety reasons according to the pre-defined dose-adjustment criteria (based on the severity of AEs or repeated elevated levels of IGF-1 SDS).

2.4   Study Population

Pre-pubertal boys and girls not yet 12 and 11 years of age, respectively, and diagnosed with GHD.

2.5   Treatment Regimens

2.5.1   *Reference Therapy Dosing Regimen*

Genotropin is a daily growth hormone, which will be used as the reference therapy in this study.

A PEN will be used for daily (evening/bedtime) subcutaneous (SC) administration of Genotropin into the region of the upper arms, buttocks, thighs or abdomen (8 locations). Injection sites should be rotated.

Dose regimen for Genotropin: 0.034 mg/kg/daily (which is equivalent to 0.24 mg/kg/week divided equally into 7 daily injections).

2.5.2   *Investigational Product Dosing Regimen:*

Somatrogon is a long-acting modified recombinant human growth hormone which utilizes C-terminal peptide technology. It will be provided as a solution for injection containing 20 or 50 mg/mL somatrogon in a PEN.

Somatrogon will be administered as a SC injection, preferably in the morning hours once weekly, using the PEN into the upper arms, buttocks, thighs, or abdomen (8 locations).

Injection sites should be rotated, and it is recommended that all 8 injection sites should be used successively, using a different injection site at each subsequent injection.

The starting dose for the weekly administration is 0.66 mg/kg/week.

2.6   Treatment Group Assignments

Subjects will be randomized in a 1:1 ratio to somatrogon (investigational treatment) or daily Genotropin (reference therapy) for 12 months. The randomization will be stratified by:

- Geographical region
    - Western Europe, Israel, Australia, New Zealand, Canada and USA
    - Central and Eastern Europe, Turkey, Greece, Latin America, and Asia except for India and Vietnam
    - India and Vietnam
- Peak growth hormone (GH) levels at screening
    - ≤3 ng/mL
    - >3 ng/mL to ≤7 ng/mL
    - >7 ng/mL to <10 ng/mL
        - Note: The proportion of subjects with peak GH levels >7 ng/mL to <10 ng/mL will be capped at 35-40% of total sample size in the randomization scheme.
- Chronological age
    - >3 years to ≤7 years and 0 days

  o >7 years and 0 days

2.7 Sample Size Determination

The aim of the study is to demonstrate that weekly Somatrogon is non-inferior to daily
Genotropin administration with respect to the primary efficacy endpoint of annual HV in
cm/year after 12 months of treatment.

Non-inferiority will be concluded if the lower bound of the two-sided 95% confidence interval
(CI) for the mean treatment difference (somatrogon – Genotropin) in the primary efficacy
endpoint is >–1.8 cm/year.

The non-inferiority (NI) margin for annual HV for protocol CP-4-006 was set at -1.8 cm/yr and
detailed in the End of Phase 2 (Type B) Briefing Package provided in IND CCI
, submitted on 09 February 2015. This NI was based on the following considerations:

- From historical data, HV response for the first year of daily GH ranged from 10.2 cm/yr,
  SD= 2.5 (Wilton and Gunnarsson, 1988) to 11.4 cm/yr, SD=2.5 (MAcGillivrayMacGillivray
  et al., 1996). Using the standard deviation (SD) of 2.5 from these references, a non-
  inferiorityNI margin of -1.8 cm/yr is well within 1 SD of the expected results, and
  approximately 23% of the reference treatment response distribution would be below this
  value.
- Assuming the HV response for daily GH treatment is 11.5 cm/yr in the first year, a margin of
  -1.8 cm/yr would show that 84% of the growth rate from the reference daily GH treatment
  effect on the approved active control is retained.
- Other studies of long acting GH compared to daily GH have used non-inferiorityNI margins
  of -1.8, to -2.0 cm/yr. , as used in the recent phase 3 Ascendis Pharma heiGHt pivotal trial
  (NCT02781727, https://ascendispharma.gcs-web.com/static-files/692edb83-40e9-449a-866c-
  2368e0898ae9). The use of -1.8 cm/yr is the more conservative value based on the precedent
  set with these other studies.

The following assumptions were made in the sample size calculation:
- two-sided alpha of 0.05
- 80% power
- between-subject standard deviation (SD) of annual growth rate of 2.5 cm/year in all treatment
  groups
- non-inferiority margin of –1.8 cm/year
- true mean treatment difference (somatrogon – Genotropin) in the primary efficacy endpoint
  of –0.8 cm/year.

With these assumptions, 100 subjects per group will provide 80% power for the non-inferiority
test. To allow for an approximate 10% dropout rate, 110 subjects were planned to be
randomized to each treatment group for a total of 220 subjects. The subjects will be enrolled
from approximately 150-180 sites in 30-40 countries.

3 GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following general analysis and reporting conventions will be followed for this study, unless otherwise specified.

All data displays:

- All tables, listings, and figures will have a header showing the sponsor company name, protocol number, page number (X of Y), and display status (i.e., "DRAFT" or "FINAL"), as well as a footer indicating path, file name, listing source, and run date/time.

Summary tables and data listings:

- Unless otherwise specified, data will be summarized by treatment and overall.
- Descriptive statistics for categorical variables will be count and percentage and will be presented in the format 'n (%)'. Unless otherwise specified, the percentage in summary tables will be calculated using number of subjects in the population (header N) for each treatment as denominator.
- Descriptive statistics for continuous variables will be number of observations (n), mean, standard deviation, median, minimum, and maximum.
- All P-values will be reported to 4 decimal places.
- No preliminary rounding will be performed; rounding will only occur after analysis.
- All data collected will be presented in the data listings. Unscheduled assessments or early discontinuation measurements will be presented in the data listings. Unscheduled visits or discontinuation visits may be included in the calculation of summary statistics where applicable.
- Data from subjects excluded from an analysis population will be presented in the data listings but will not be included in the calculation of summary statistics, where applicable.
- Data from each subject will be separated by a blank line. Within a data listing, if a descriptive item appears line after line (eg, repetition of a subject number, date, visit, etc.), only the first occurrence will be displayed (eg, in Listing of Vital Signs, subject number, date and visit will only be displayed on first row when presenting all parameters collected at same visit). Repetition of actual results or outcomes (eg, Adverse Events (AEs), lab results, vital sign values, etc.) will not be collapsed.
- Data listings will be sorted in the order of treatment, subject, and time of assessment, as applicable.
- When change from baseline is calculated, baseline is the last assessment before receiving the first dose of treatment.

Mock tables and data listings will be provided as attachments to this analysis plan. Minor changes to the mocks after formal SAP approval will not necessitate re-approval unless changes to the text of the SAP are required.

All statistical deliverables will be produced, validated, and reviewed for accuracy/consistency.

All analyses will be performed using SAS® version 9.4 or higher.

4 ANALYSIS SETS

The following analysis sets will be used for this study: Safety Analysis Set, Full Analysis Set, and Per Protocol Set.

4.1   Safety Analysis Set

The safety analysis set will include all subjects who have received at least one dose of study treatment. Subjects will be analyzed according to actual treatment received.

4.2   Full Analysis Set

The efficacy analyses will be based on the full analysis set, defined asas subjects who were randomized and have received at least one dose of study medication. Subjects will be analyzed according to randomized treatment group.

4.3   Per Protocol Set

The per protocol (PP) set will consists of all randomized subjects who did not have any major protocol deviations.

The subjects who have any major protocol deviations will be identified before database lock by the clinical team in a blinded review.

5   STUDY SUBJECTS

5.1   Disposition of Subjects

The number of subjects screened and randomized will be summarized.

The number and percentage of subjects in each analysis set, completing the study, prematurely discontinuing the study, and the reason for subject discontinuation, will be summarized.

The number and percentage of subjects in the full analysis set for each randomization strata will be summarized.

The number and percentage of subjects in the full analysis set at each visit (ie, subjects who have data for each visit) will be summarized.

5.2   Protocol Deviations

Protocol deviations will be summarized by deviation classification and category for all randomized subjects.

6   DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics analyses will be performed using the Safety Analysis Set.

6.1   Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize the following variables:

- age
- sex
- ethnicity
- race
- region
- peak GH level group
- age group
- father's height
- mother's height
- target height
- bone age
- HV
- weight
- body mass index

6.2   Medical History

Medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the coded data by the Medical Dictionary for Regulatory Activities (MedDRA®), version 19.1 or higher. The count and percentage of medical condition SOC and PT will be provided for both past and ongoing conditions.

6.3   Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHO DD) Dec 2016 or higher.

If the start date of medication is completely missing in which the day, month, and year are all unknown or only the day is known, then the start date will not be imputed.

For the partial start date of medication these conventions will apply:

- If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to January 1.
- If the year and month are present and the day is missing, set day to 1st day of month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

If the end date of medication is completely missing which the day, month, and year are all unknown or only the day is known, then the end date will not be imputed.

For the partial end date of medication, these conventions will apply:

- If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to December 31.

- If the year and month are present and the day is missing, set day to last day of the month.

6.3.1 Prior Medications

Prior medications will be defined as medications that are utilized prior to first dose of study drug. Medications with missing start date are considered prior.

Prior medications will be summarized by anatomical therapeutic chemical (ATC) level 2 class and PT.

6.3.2 Concomitant Medications

Concomitant medications will be defined as medications that are utilized on or after first dose of study drug. Medications with missing end dates are considered concomitant. Medications with missing start dates and non-missing end dates will be considered concomitant if the end date is on or after first dose.

Concomitant medications will be summarized by ATC level 2 class and PT.

6.3.3 Prohibited Concomitant Medications

Prohibited concomitant medications will be summarized by ATC level 2 class and PT.

7 EXTENT OF INVESTIGATIONAL PRODUCT EXPOSURE

Extent of exposure will be summarized using the Safety Analysis Set.

Descriptive statistics will be reported for duration of treatment. Duration of treatment is defined as:

- Genotropin: last dose date – first dose date + 1
- Somatrogon: last dose date – first dose date + 7

The number and percentage of subjects experiencing a dose reduction due to IGF-1 SDS >2 will be summarized.

7.1   Injection Attempts

In any given week, one (single shot) injection or a multiple number of injections may be required in order to complete the prescribed dose in full. The number of injections is established from counts of: "injection 1"; "injection 2"; "injection 3"; and "injection 4", where the subject answered the successful injection criteria (i.e., non-missing/answered with 'Yes' or 'No').

A successful injection is defined as satisfying the following criteria:

- An answer of "yes" to PAT question 5 "Did the dose window show '0' when you finished your injection?", and "yes" to PAT question 6 "Do you believe that a full dose was injected?"
- An answer of "yes" to OAT questions 1 "…did the user successfully inject into an acceptable injection site without physical assistance?"

OAT and PAT endpoint (USA only) statistical analysis

OAT and PAT results will be summarized by using descriptive statistics.

- The number and percentage of successful injection attempts for PAT will be summarized overall.

For each injection count, intermittent missing observations for the PAT will be imputed as a failure if both the prior and subsequent observations are a failure. Otherwise, intermittent missing observations will be imputed as a success.

- The number and percentage of successful injection attempts for OAT will be summarized overall.
- The number and percentage of successful injection attempts for PAT and OAT will also be summarized by age group, sex, and race.
- The number and percentage of the number of attempts required to achieve a success will be summarized for PAT and OAT.

If the subject engages in multiple injection attempts to achieve a successful injection due to an issue with a pen (e.g. – pen failed to operate; subject was unable to perform a step), only the injection attempt with the first pen is to be included in the calculation of the number of attempts required. The use of a second pen (ie, 'backup' or replacement pen) in place the injection attempt with the first pen is established by a clinical review of free text responses in:

> o PAT question 7 - if any of the following are checked: "preparing the pen"; "prining the pen"; "setting the dose"; "injecting"

    o   OAT question 1 - if "…did the user successfully inject into an acceptable injection site without physical assistance?" is answered "no"

In addition, an overall Successful Injection Rate (SIR) will also be summarized. SIR is defined as the number and percentage of successful injections out of the number of injections required where the subject answered the criteria for delivery success for the PAT assessment at each of the 6 consecutive weekly doses.

Comments on the PAT and OAT related to successful or unsuccessful injection attempts

- Comments on the PAT and OAT related to successful or unsuccessful injection attempts will be listed. Any other written comments will also be listed.

Information gained by inspection of returned devices

- Information gained by inspection of returned devices will be listed.

8 EFFICACY EVALUATION

8.1 Overview of Efficacy Analysis Issues

8.1.1 Handling of Dropouts or Missing Data

For the primary and secondary endpoint analyses performed by ANCOVA, multiple imputation assuming missing not at random using SAS PROC MI will be used to impute missing results. The imputation will be by treatment group. The imputation model will include the randomization stratification factors and baseline height standard deviation score (SDS). For the primary endpoint, annual HV, the imputed value in the somatrogon group will be reduced by 1.8 cm/yr, the non-inferiority margin to avoid imputing to the common mean (Koch 2008).

A total of 100 imputed datasets will be created, and the seed will be set using the database lock date in YYYYMMDD format, and stored in order to be able to replicate the results. An ANCOVA model as described for the primary analysis will be used to calculate the least square means and 95% confidence interval of the treatment difference for each imputed set. These results will then be combined for evaluation with SAS PROC MIANALYZE. The number of imputed datasets may be increased if necessary to achieve adequate numerical precision.

For the somatrogon assay, values below the limit of quantification (BLQ) at the baseline visit will be treated as 0 in statistical analysis of the results.

Handling of missing PAT data is described in Section 7.1.

8.1.2 Multicenter Studies

For select analyses, data will be summarized by the randomization factor of geographical region.

8.1.3 Assessment Time Windows

Scheduled assessments are the preferred source for visit-level data. Visit windows for scheduled assessments are as follows:

Visit	Target Day	Lower Limit	Upper Limit
Month 1	30	2	61
Month 3	92	62	137
Month 6	183	138	228
Month 9	274	229	319
Month 12	365	320	410

If the appropriate scheduled assessment occurs within it's visit window (eg, if a Month 3 assessment occurs in the 62-137 window), it will be used as the assessment of record for that visit, regardless of what other data exists in that window.

If the appropriate scheduled assessment is not performed within the scheduled window for a given visit, the assessment that is closest to the target study day will be selected for analysis.

8.2 Efficacy Variables

8.2.1 Primary Efficay Endpoint

8.2.1.1 Annual HV at 12 Months

Annual HV at 12 months is based on the difference between the heights at 12 months and baseline.

$$Height\ Velocity\left(\frac{cm}{year}\right)$$
$$= \left[\frac{Month\ 12\ Height\ (cm) -\ Baseline\ Height\ (cm)}{Month\ 12\ date - Baseline\ date}\right] * 365.25$$

8.2.2 Secondary Efficacy Endpoints

8.2.2.1 Annualized HV at 6 Months

Annualized HV after 6 months will be calculated based on the difference between the heights at 6 months and baseline.

8.2.2.2 Change in Height SDS at 6 and 12 Months

Height SDS will be determined from the age and gender standards listed in the 2000 CDC Growth Charts (www.cdc.gov/growthcharts).

8.2.2.3 Change in BM at 12 Months

BM is 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 most recent birthday)/365.25

8.2.3 Biochemical Markers

Biochemical markers of interest are IGF-1, IGF-1 SDS, IGFBP-3, and IGFBP-3 SDS. IGF-1 SDS will be determined from the age and gender standards listed in the 2014 JCEM paper by Bidlingmaier et al. (https://www.ncbi.nlm.nih.gov/pubmed/24606072). IGFBP-3 SDS will be determined from the age and gender standards listed in the 2014 JCEM paper by Friedrich et al. (https://www.ncbi.nlm.nih.gov/pubmed/24483154).

8.2.4 QoL Endpoints

The three dimensions (physical, social, and emotional) of the QoLISSY questionnaire will be calculated individually and as a combined core total score based on the QoLISSY scoring manual. This core score is calculated as the sum of the means of these three dimensions and divided by 3. All scores will be transformed from raw scores to 0 to 100 scores.

8.3   Analysis Methods

Analyses will be based on the full analysis set.

Table 8-1 gives an overview of the analysis methods that will be used for each of the efficacy variables.

Table 8-1   Efficacy Variables and Analysis Methods

Efficacy Variables	Method 1	Method 2	Method 3
Annual HV at 12 Months	ANCOVA, 95% CI	Descriptive stats	
Annualized HV at 6 Months	ANCOVA, 95% CI	Descriptive stats	
Change in Height SDS at 6 and 12 Months	ANCOVA, 95% CI	Descriptive stats	
Change in BM at 12 Months		Descriptive stats	Univariate 95% CI
Biochemical Markers		Descriptive stats	
QoL Endpoints		Descriptive stats	

8.3.1   Primary Efficacy Analyses

The aim of the present study is to demonstrate that in terms of the primary efficacy endpoint, Annual Height Velocity at 12 months, weekly somatrogon is non-inferior to daily Genotropin by a non-inferiority margin of 1.8 cm/year.

With μ_M and μ_C representing the mean annual HV at 12 months for the somatrogon and the Genotropin (Control) group, respectively, the following hypotheses will be tested:

Null hypothesis H_0: $\mu_M < \mu_C - 1.8$ cm/year

vs.

Alternate hypothesis H_1: $\mu_M \geq \mu_C - 1.8$ cm/year

Non-inferiority will be concluded if the lower bound of the two-sided 95% CI for the mean treatment difference "somatrogon – Genotropin", in the primary efficacy endpoint is $\geq$-1.8 cm/year.

The CI for the difference of means between the two treatments will be derived from an ANCOVA. The ANCOVA model will include classification terms for treatment, age group, gender, peak GH levels, and region. The model will also include baseline height SDS as a covariate. The determination of non-inferiority will be based on least squares means for the two treatments from the ANCOVA and the 95% CI of the differences between the treatments.

Descriptive statistics will be reported for observed and change from baseline annual HV values at 12 months.

Annual HV values at 12 months will be presented in a scatter plot by treatment.

ANCOVA-based statistics will be reported by age group, gender, and peak GH levels.

Once the primary endpoint of non-inferiority of somatrogon in comparison to Genotropin is met, an assessment of superiority of somatrogon over Genotropin at 12 months will also be performed. Superiority will be achieved if the lower bound of the two-sided 95% CI for the mean HV difference of somatrogon – Genotropin is ≥ 0 cm/year.

8.3.2   Secondary Efficacy Analyses

A similar ANCOVA model as used for the primary endpoint will be used to analyze:

- annualized HV at 6 months
- change in height SDS at 6 months
- change in height SDS at 12 months

Least square mean estimates for the two treatments and the 95% CI of the difference between the treatments will be presented.

Descriptive statistics will also be reported for each of these endpoints.

Descriptive statistics (including univariate 95% CI) will be reported for BM observed and change from baseline at 12 months.

Scatter plots by treatment will be reported for each of the these endpoints.

Descriptive statistics will be reported for HV and height SDS at each visit.

Box plots will be reported for HV and height SDS by visit and treatment.

ANCOVA-based statistics will be reported by the categorical terms used in the ANCOVA model: age group, gender, peak GH levels, and region.

8.3.3   Primary Efficacy Sensitivity Analysis

The ANCOVA-based primary efficacy analysis will be repeated using the PP set.

If the ANCOVA-based primary efficacy analysis supports non-inferiority, the robustness of the result will be assessed using a tipping point approach with the Full Analysis Set. Specifically, a shift parameter will be used to incrementally adjust the imputed values in the somatrogon arm. Values will be shifted downwards in increments of 0.1 cm/year until the analysis no longer supports comparability.

8.3.4   Biochemical Markers Analysis

Descriptive statistics will be reported for observed and change from baseline for all biochemical endpoints at each visit.

The number and percent of subjects who had IGF-1 SDS >2 will be summarized at each visit. The number and percent of subjects who had consecutive IGF-1 SDS >2 assessments anytime post-baseline will be summarized.

8.3.5   QoL Endpoints Analysis

QoLISSY item responses and resulting scores will be presented in a listing. The three dimensions (physical, social, and emotional) of the QoLISSY questionnaire will be calculated individually and as a combined core total score based on the QoLISSY scoring manual. This

core score is calculated as the sum of the means of these three dimensions and divided by 3. All scores will be transformed from raw scores to 0 to 100 scores.

9   SAFETY EVALUATION

9.1   Overview of Safety Analysis Methods

All summaries of safety are to be performed on the Safety Analysis Set unless stated otherwise.

9.2   Adverse Events

All AEs that occurred during this clinical trial will be coded using MedDRA version 19.1 or higher.

A treatment-emergent adverse event (TEAE) is defined as an AE that is starting or worsening at the time of or after study drug administration. Adverse events 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.

All AEs captured in the database will be listed; however, only treatment-emergent AEs (TEAEs) will be summarized.

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.

Within each SOC or PT, subjects experiencing multiple occurrences of the same event will be counted only once.

9.3   Serious Adverse Events and Other Significant Adverse Events

The following subsets of TEAEs will be summarized by SOC and PT:

- SAE
- related to study drug
- leading to study drug withdrawal
- leading to study drug reduction or interruption
- leading to study discontinuation

TEAEs are considered related to study drug if the relationship is one of: "possibly related", "related", or missing.

Separate data listings will be provided for each of the above categories of TEAEs.

TEAEs will also be summarized by maximum severity (mild < moderate < severe) within SOC and PT. Missing AE severity will be considered severe.

TEAEs will also be summarized by strongest relationship (not related < related) within SOC and PT.

Deaths will be presented in a data listing.

9.4   Injection Site Reactions and Pain

Pain scores will be summarized with number of injections as the denominator, where every injection will be counted and summarized. Additionally, pain scores will be summarized with number of overall subjects and subjects with injection site reactions (ISR) as the denominator. Injection site reactions will be also summarized by SOC and PT. For each subject, ISR pain score will be summarized by maximum severity across all SOC and PT. In both summaries, missing values will be considered "hurts worse".

ISR erythema/redness, bruising, induration/swelling and itching will be summarized with number of injections as the denominator, where every injection will be counted and summarized. Additionally, symptoms will be summarized with number of overall subjects and subjects with ISR as the denominator. For each subject and reaction type, symptoms will be summarized by maximum severity across all SOC and PT. In both summaries, missing values will be considered "severe".

9.5   Clinical Laboratory Evaluation

Descriptive statistics will be reported for observed and change from baseline clinical laboratory measurements at each visit. Lab tests will be presented alphabetically within each of the following categories:

- hematology
- chemistry
- lipid profile
- glucose metabolism
- endocrinology
- urinalysis

For each laboratory test, a shift from baseline will be presented by visit. Categories will be 'Low', 'Normal', and 'High'.

For each laboratory test, box plots will be created by visit and treatment group.

The number and percentage of subjects with increases in any of the following will be summarized at each visit and anytime post-baseline:

- ALT >2xULN, >3xULN, <5xULN
- AST >2xULN, >3xULN, <5xULN
- Bilirubin >3xULN and ALT >2xULN
- Bilirubin >3xULN and AST >2xULN

Two eDISH (evaluation of Drug Induced Serious Hepatotoxicity) scatter plots will be produced: maximum bilirubin vs. maximum ALT and maximum bilirubin vs. maximum AST.

9.6   Vital Signs, Physical Findings, and Other Observations Related to Safety

9.6.1   *Vital Signs*

Descriptive statistics will be reported for observed and change from baseline vital sign measurements at each visit. The vital signs data will include:

- systolic blood pressure (mmHg)
- diastolic blood pressure (mmHg)
- heart rate (beats/min)
- respiratory rate (breaths/min)
- temperature (degree C)

9.6.2   *Physical Examinations*

Physical examination findings will be reported as medical history at screening and as adverse events after screening. As such, there will be no physical examination summaries.

9.6.3   *Other Safety Measures*

9.6.3.1   *Electrocardiograms (ECG, 12-lead)*

Descriptive statistics will be reported for observed and change from baseline ECG measurements at each visit. The ECG data will include:

- heart rate (beats/min)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- RR interval (msec)
- QTc interval (msec)
- Fredericia's corrected QT interval (QTcF)
    - calculated as QT interval/Cubic root of (60/heart rate)

The interpretation for each ECG will be categorized as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). The number and percentage of subjects in each category will be presented by visit.

A shift from baseline table will be presented by visit and anytime post-baseline.

9.6.3.2   *Fundoscopy*

The number and percentage of subjects who had fundoscopy done will be summarized. The number and percentage of subjects experiencing intracranial hypertension will be summarized.

9.6.3.3   *Immunogenicity*

The number and percentage of subjects with the presence of each of the following will be summarized at each visit:

- anti-recombinant human GH (r-hGH) antibodies
  - neutralizing
  - non-neutralizing
- anti-somatrogon antibodies
  - neutralizing
  - non-neutralizing

Descriptive statistics will be reported for anti-r-hGH and anti-somatrogon antibody titers at each visit.

The number and percentage of subjects who tested positive for anti-rhGH antibodies and anti-somatrogon antibodies at any point in time during the study will be reported for both neutralizing and non-neutralizing antibodies.

9.6.3.4 Pregnancy

Urine pregnancy assessment will be performed in female subjects after first menstrual cycle (menarche).

10 PHARMACOKINETIC EVALUATION

Pharmacokinetic analyses will be described and summarized in a separate report that will serve as a supplement to the final CSR.

11 INTERIM ANALYSES AND DATA MONITORING

11.1   Interim Analysis

Not applicable.

11.2   Data Monitoring

The primary responsibility of the independent and external DSMB is to provide guidance to the Sponsor regarding the safe conduct of the study based on their periodic review of safety data. The DSMB will review study safety summaries. Efficacy data on individual subjects will be available to assist safety reviews. The DSMB's membership, full scope of responsibilities, operating procedures, access to data, and reporting and record keeping requirements will be established by Sponsor and/or its representative, and will be described in a DSMB charter.

12 CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

There are no changes to the analyses planned in the protocol.

13 REFERENCES

Keizer RJ, Jansen RS, Rosing H, et al. Incorporation of concentration data below the limit of quantification in population pharmacokinetic analyses. Pharmacology Research & Perspectives. 2015;3(2):e00131. doi:10.1002/prp2.131.

Wilton P, Gunnarsson R. Clinical experience with Genoptropin in growth hormone deficient children. Acta Paediatr Scand Suppl. 1988;343:95-101.

MacGillivray MH, et al. Outcome of a four-year randomized study of daily versus three times weekly somatropin treatment in prepubertal naïve growth hormone-deficient children. Genentech Study Group. J Clin Endocrinol Metab. 1996 May;81(5):1806-9.

Koch GC, Comments on 'Current issues in non-inferiority trials' by Thomas R Fleming. 2008. Statistics in Medicine 27(3):333-42.

14 LIST OF PLANNED TABLES

Shells of planned tables are found in Attachment A of the Statistical Analysis Plan.

15 LIST OF PLANNED FIGURES

Shells of planned figures are found in Attachment A of the Statistical Analysis Plan.

16 LIST OF PLANNED DATA LISTINGS

Shells of planned listings are found in Attachment A of the Statistical Analysis Plan.

17 APPENDICES

17.1   Schedule of Events

The screening period, Visit 1, can take place over an 8 to 12 week period. Randomization will take place prior to or on Visit 2 (Day 1/Baseline), which is on day of first dosing. Visit 4 (Month 1/Week 4 [±1 week]), Visit 5 (Month 3/Week 13 [±1week]), Visit 6 (Month 6/Week 26 [±1week]), Visit 7 (Month 9/Week 39 [±1week]), and Visit 8 (Month 12/Week 52 [±1week]) will be conducted on Day 4 (-1 day) post dose to obtain IGF-1 measurements expected to reflect average levels throughout the week.

For somatrogon subjects only, collection of immunogenicity and PK sample will be conducted at Visit 3 (Day 10 [+4] days post first dose) and on the dosing day for Visit 6a (Month 6/Week 26 [±3 weeks]) and Visit 8a (Month 12/Week 52 [±1week]), with the dose to be administered after sampling. These visits can be done at the subject's house or at the clinic, based on local regulations and nurse availability. If home visit is conducted, a questionnaire will be completed to collect information on AE, local tolerability and concomitant medications. For Genotropin subjects, no samples will be collected, and these visits will be conducted via phone interview to the same information on AE, local tolerability and concomitant medications.

Visit 6b (Month 6/Week 26 [±3 weeks]) will be conducted at 7 to 12 hours post-dose for somatrogon subjects for ECG evaluation. Visit 6a and 6b might be combined on the same day with the blood samples collected in the morning, dose, and then return 7-12 hours post dosing for ECG assessment.

Genotropin subjects will have an ECG assessment at Visit 6 with no time limitation.

Figure 16-1: Schedule of Events - Part 1 of 4

Study Procedure	Screening		Treatment										
Study Day	[a]-56 to -1		1/Baseline	10 (+4)									
Study Week (± in week/s)					4 (±1)	13 (±1)	26 (±1)	26 (±3)	26 (±3)	39 (±1)	52 (±1)	52 (±1)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12
Study Visit	1		2	3	4	5	6	6a [b]	6b	7	8	8a [b]
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographic & medical history including parent's height	X											
Auxology measurements [c]	X		X			X	X			X	X	
Physical examination and vital signs	X		X		X	X	X			X	X	
ECG			X pre-dose				X [d]		X [e]			
Pubertal status (Tanner stages)	X		X			X	X			X	X	
Bone age (Greulich-Pyle method using central bone age reader)	X		X [f]								X	
Karyotype assessment (girls only)	X											
Fundoscopy			ONLY if there are signs or symptoms indicative of benign intracranial hypertension									
Randomization		X										

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[a] For the screening period, additional 4 weeks might be added due to technicalities or Patient's benign illness.

[b] Dosing day (assessments will be conducted pre-dose). This visit is applicable only for patients in MOD 4023 arm.

[c] Actual height (mean of 3 consecutive measurements per patient per visit) measured on a calibrated wall mounted stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items

[d] Genotropin patients

[e] ECG will be conducted at 7-12 hours post-dose (MOD-4023 arm only). Patients will be requested to inject MOD-4023 during the day/night at their convenience and come to the clinic at the requested time point for ECG.

[f] Bone age will be done at Visit 2 only in cases where historical bone scans (<6 months prior to screening) were used to fulfill entry criteria. When performed, bone age scans will be completed prior to dosing.

Figure 16-2: Schedule of Events - Part 2 of 4

Study Procedure	Screening		Treatment										
Study Day	[a]-56 to -1		1/Baseline	10 (+4)									
Study Week (± in week/s)					4 (±1)	13 (±1)	26 (±1)	26 (±3)	26 (±3)	39 (±1)	52 (±1)	52 (±1)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12
Study Visit	1		2	3	4	5	6	6a [b]	6b	7	8	8a [b]
Verification of eligibility [g]		X										
Dispense study drug			X		X	X	X			X		
Individual dose adjustment						X	X			X		
Training on drug administration			X									
Drug administration at clinic			X					X				X
OAT completion at clinic			X									
PAT [h]			X									
PAT return					X	X						
Diary Card return					X	X	X			X	X	
QoL questionnaire completion (specific countries)			X								X	
Injection site reactions			X	X [i]	X	X	X	X [i]	X	X	X	X [i]
Adverse events			X	X [i]	X	X	X	X [i]		X	X	X [i]
Prior & concomitant medications	X		X	X [i]	X	X	X	X [i]		X	X	X [i]
MOD-4023 IMP return					X	X	X			X	X	
MRI [j] or CT (if required) post GH stimulation	X											
Laboratory Assessments												

[g] Once all data is available, the investigator will complete an Eligibility Verification Request Form and will forward it to the Medical Monitor for review. Each patient will be enrolled after a written confirmation from the Medical Monitor **prior** to randomization visit.

[h] PAT will be evaluated during the first 6 full dose administrations (at the site for Visit 2 (for training) and at home for next 5 full dose administrations.

[i] For MOD-4023 arm: assessment will be conducted at the clinic or at the patient's house (according to local regulations), for Genotropin arm: by phone interview.

[j] MRI which was conducted no more than 6 months prior to ICF signature data will be acceptable as well.

Figure 16-3: Schedule of Events - Part 3 of 4

Study Procedure	Screening	Treatment									
Study Day	[a]-56 to -1	1/Baseline	10 (+4)								
Study Week (± in week/s)				4 (±1)	13 (±1)	26 (±1)	26 (±3)	26 (±3)	39 (±1)	52 (±1)	52 (±1)
Study Month	-2	0	0.5	1	3	6	6	6	9	12	12
Study Visit	1	2	3	4	5	6	6a [b]	6b	7	8	8a [b]
Hematology [k], Biochemistry [l], & Urinalysis [m]	X	X		X	X	X			X	X	
GH stimulation (provocation) test [n]	X										
Morning cortisol (up to 8am ±1am)	X										
ACTH or CRH stimulation test [o]	X										
SHOX (short stature homeobox) gene evaluation	X										
IGF-I, IGF-I SDS, IGFBP-3, and IGFBP-3 SDS	X	X		X	X	X			X	X	
MOD-4023 serum levels [p]		X	X	X	X	X	X	X	X	X	X
Endocrinology (TSH, fT4)	X	X			X	X			X	X	
Glucose metabolism [q]	X	X			X	X			X	X	
Lipid profile [r]		X			X	X			X	X	
Antibodies to r-hGH (Genotropin arm)		X			X	X			X	X	

[k] Hematology: Red Blood Cell Count; Hemoglobin (HGB); Hematocrit (HCT); Mean Cell Hemoglobin (MCH); Mean Cell Hemoglobin Concentration (MCHC); Mean Corpuscular Volume (MCV); White Blood Cell (WBC) Count and Differential; Platelet Count, PT/INR, PTT (if indicated only).

[l] Biochemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LFT, LDH, CPK, alkaline phosphatase; fasting glucose, fasting insulin, HbA1C; sodium, potassium, calcium, phosphate; BUN, creatinine.

[m] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein.

[n] Two different GH stimulation (provocation) tests (insulin tolerance test, with serum cortisol response to hypoglycemia if insulin stimulation test is chosen OR arginine test/clonidine test/glucagon test (with or without propranolol)/L-dopa plus propranolol.

[o] ACTH or CRH stimulation test will be conducted if morning corticol is below 190 nmol/L (7 µg/dL), and only if the patient was not previously assessed for the hypothalamus-pituitary-adrenal axis. Insulin Tolerance test with serum cortisol response to hypoglycemia is adequate for assessment of adrenal insufficiency and no ACTH stimulation test is required if such results are available.

[p] For MOD-4023 arm only.

[q] Glucose metabolism: fasting glucose and fasting insulin; HbA1c.

[r] Lipid profile: overnight fasting total cholesterol, LDL cholesterol and triglycerides, HDL and FFA; Lp(a) once every three months.

Figure 16-4: Schedule of Events - Part 4 of 4

Study Procedure	Screening		Treatment										
Study Day	[a]-56 to -1		1/Baseline	10 (+4)									
Study Week (± in week/s)					4 (±1)	13 (±1)	26 (±1)	26 (±3)	26 (±3)	39 (±1)	52 (±1)	52 (±1)
Study Month	-2		0	0.5	1	3	6	6	6	9	12	12
Study Visit	1		2	3	4	5	6	6a [b]	6b	7	8	8a [b]
Antibodies to r-hGH (all patients)	X											
Antibodies to MOD-4023 [p]			X	X				X				X

18 ATTACHMENTS

Attachment A – Shells for Planned Tables, Figures, and Listings

Signature Page for CP-4-006_SAP v4.0 Final v2.0

Approval	PPD Clinical 17-Jun-2019 16:45:10 GMT+0000

Approval	PPD Statistics 17-Jun-2019 18:40:22 GMT+0000

Approval	PPD QA & Regulatory 18-Jun-2019 10:15:40 GMT+0000

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