STATISTICAL ANALYSIS PLAN
Version 3.0
19 May 2020

Protocol: CP-4-009

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

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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
1.0	2018-03-27	Initial version
2.0	2020-04-08	4.2 Full Analysis Set Full Analysis Set definition was updated. 5.1 Disposition of Subjects Summary of the number of subjects prematurely discontinuing treatment was removed. 6.1 Demographics and Baseline Characteristics Bone maturation was added. Height Velocity was changed to Height SDS. 8.1.1 Handling of Dropouts or Missing Data Handling of missing data for the primary analysis was changed to multiple imputation (MI) from carrying the last non-missing height value forward (LHCF) on the assumption of missing not at random (MNAR). 8.1.3 Assessment Time Windows Unscheduled assessments within the visit window were not selected for analysis. 8.3 Analysis Methods 95% CIs were added in Table 8-1. 8.3.1 Primary Efficacy Analyses Descriptive statistics of observed annual HV values at 12 months by ADA status was added. 8.3.2 Secondary Efficacy Analyses Univariate 95% CI was included in descriptive statistics for BM observed and change from baseline at 12 months. 8.3.3 Primary Efficacy Sensitivity Analysis The tipping point approach was removed.

The similar analysis to the ANCOVA-based primary efficacy analysis, but using the different missing imputation method, were added.

The similar analysis to the ANCOVA-based primary efficacy analysis, but including different covariates, were added.

8.3.4 Biochemical Markers Analysis

Descriptive statistics of CCI by ADA status was added.

9.2 Adverse Events

Summary of TEAEs by SOC and PT and by ADA status was added.

9.3 Serious Adverse Events and Other Significant Adverse Events

Summary of TEAEs by subject was added.

Summary of severe TEAEs was added.

Summary of TEAEs resulting in death was removed.

Summaries of TEAEs of special interests were added.

9.4 Injection Site Reactions and Pain

Summary of ISR by ADA status was added.

Summaries of pain scores, ISR erythema/redness, bruising, and induration/swelling with number of injections as the denominator, where every injection are counted and summarized were removed.

Summaries of pain scores, ISR erythema/redness, bruising, and induration/swelling with number of subjects with ISR as the denominator were added.

9.6.3.5 Hypersensitivity

Summary of Hypersensitivity by ADA status was added.

CCI

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Changes described in the Protocol CP-4-009 Administrative Change Letter #2 to Version 9.0 of the Protocol were shown.

		Discrepancies eliminated and typographical errors corrected.
3.0	2020-05-19	6.1 Demographics and Baseline Characteristics Handlings of peak GH was specified for continuous variable. 8.3.3 Primary Efficacy Sensitivity Analysis Condition was added for the 3rd sensitivity analysis.

APPROVALS

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BA	Bone Age
BLQ	Below the Limit of Quantification
BM	Bone Maturation
CA	Chronological Age
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
hGH	Human Growth Hormone
HV	Height Velocity
CCI	[redacted]
IGF-1	Insulin-like Growth Factor-1
ISR	Injection Site Reaction
NCS	Not Clinically Significant
MedDRA	Medical Dictionary for Regulatory Activities
PEN	Single subject use, multi-dose, disposable pre-filled pen
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QTcF	Fredericia's Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

LIST OF ABBREVIATIONS (continued)

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-4-009, a phase III study sponsored by OPKO Health Inc., 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 comparable 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 of Somatrogon in subjects with GHD, and to characterize other growth parameters (change in height standard deviation score (SDS) and bone age (BA)/maturation), and biochemical markers (insulin-like growth factor-1 (IGF-1) CCI [redacted], associated with growth hormone (GH) 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 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/chronological age (CA))

Secondary biochemical marker endpoints include:

CCI [redacted]

- IGF-1 SDS on day 4(-1) after Somatrogon dosing across study visits

CCI [redacted]

2.2.3 Safety Endpoints

The safety endpoints include:

- Incidence of adverse events (AE)
- Serious adverse events (SAE) and adverse events leading to discontinuation of treatment
- 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 and biochemical parameters
- Physical examination
- Fundoscopy (normal/abnormal)
- Vital signs
- Electrocardiogram (ECG)

2.3 Study Design

The study will consist of a 12 month, open-label, randomized, active controlled, parallel group study comparing the efficacy and safety of weekly Somatrogon to daily GH, Genotropin.

Both drugs will be injected using a single subject use, multi-dose, disposable pre-filled pen (PEN) device.

After a screening period lasting up to 4 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): weekly subcutaneous (SC) injections for 12 months; initially over the first 6 weeks, Somatrogon will be administered in 3 stepwise escalating doses (0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week) each for 2 weeks sequentially. For the remaining 46 weeks, patients will continue to receive Somatrogon at a dose of 0.66 mg/kg/week

- Genotropin (reference therapy): daily SC injections for 12 months; 0.025 mg/kg/daily which is equivalent to 0.175 mg/kg/week divided equally to 7 injections over a week

If the subject's screening process is delayed because of a benign illness or unforeseen benign condition (i.e. 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 one additional week (total of 5 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 11 and 10 years of age, respectively, and diagnosed with GHD.

2.5 Treatment Regimens

2.5.1 Reference Therapy Dosing Regimen

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

A PEN (5.3 mg or 12 mg) will be used for daily (evening/bedtime) 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: 0.025 mg/kg/daily (which is equivalent to 0.175 mg/kg/week divided equally into 7 daily injections).

2.5.2 Investigational Product Dosing Regimen:

Somatrogon is a long-acting modified recombinant human GH 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 using the PEN into the upper arms, buttocks, thighs, or abdomen (8 locations).

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

Initially over the first 6 weeks, Somatrogon will be administered in 3 stepwise escalating doses (0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week) each for 2 weeks sequentially. For the remaining 46 weeks, patients will continue to receive Somatrogon at a dose of 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 not be stratified.

2.7 Sample Size Determination

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

Comparability will be concluded if the mean treatment difference (Somatrogon – Genotropin) for the primary efficacy endpoint is ≥ –1.8 cm/year.

The following assumptions were made in the sample size calculation:

- between-subject standard deviation (SD) of annual growth rate of 2.5 cm/year in all treatment groups
- comparability 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, 20 subjects per group will provide approximately 88% probability that the observed difference between Somatrogon and Genotropin will be greater than -1.8 cm/year.

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 protocol number, page number (X of Y), as well as a footer indicating SDTM creation date, source data, output file name with path, and generation 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, SD, median, minimum, and maximum.
- Minimum and maximum will be reported to the same level of precision as the original data. Mean and median will be reported to 1 more decimal than the original data. SD will be reported to 2 more decimals than the original data.
- Analysis of covariance (ANCOVA) estimates and confidence intervals (CI) will be reported to 1 more decimal than the original data. Standard errors will be reported to 2 more decimal places than the original data. 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 but will not be included in the calculation of summary statistics presented by visit.
- 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 (e.g., repetition of a subject number, date, visit, etc.), only the first occurrence will be displayed (e.g., 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 (e.g., 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.

Minor changes to the mocks after formal SAP approval will not necessitate re-approval unless changes to the text of the SAP are required.

SAP amendment will be made in accordance with OPKO Health Inc. standard operating procedure (DM.003).

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

4. ANALYSIS SETS

Three 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 full analysis set will include all subjects who were randomized and have received at least one dose of study treatment, and will be the primary efficacy analysis set. 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 study discontinuation, will be summarized.

The number and percentage of subjects in the full analysis set at each visit (i.e., 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
- race
- father's height
- mother's height
- target height
- bone age
- bone maturation
- height SDS
- weight
- body mass index
- peak GH*

For continuous variable, the peak GH is calculated based on GH test. GHRP-2 if performed will be ignored. If there are two GH tests performed, higher value in the 2 different tests was used as baseline peak GH value.

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 past events and for 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,

- 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,

- 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 dose reduction due to IGF-1 SDS > 2 will be summarized.

8. EFFICACY EVALUATION

8.1 Overview of Efficacy Analysis Issues

8.1.1 Handling of Dropouts or Missing Data

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.

For the height-related primary and secondary endpoints of HV and height SDS, 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 be the same as the primary analysis model. 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[1]).

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.

8.1.2 Multicenter Studies

Study center will not be utilized during analysis.

8.1.3 Assessment Time Windows

Scheduled assessments are the preferred source for visit-level data.

8.2 Efficacy Variables

8.2.1 Primary Efficacy 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.

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

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

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 national survey in year 2000 (Ministry of Health, Labor and Welfare's Infant and Children's Growth Survey Report (0 to 6 years old) and the Ministry of Education, Culture, Sports, Science and Health Statistics Report (6 to 17 years old) in 2000 (http://jspe.umin.jp/medical/taikaku.html).

8.2.2.3 Change in BM at 12 Months

BM is calculated as BA divided by CA. BA will be determined by a central reader via X-ray according to Tanner-Whitehouse 2 Method[2] 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 CCI IGF-1 SDS, CCI IGF-1 SDS will be determined from the age and gender standards listed in the article by Isojima T. *et al.*[3].

8.3 Analysis Methods

Analyses will be based on the full analysis set.

[2] Murata M. Japanese specific BA standard on the TW2. Clin Pediatr Endocrinol 1993; (Suppl 3):35-41
[3] Standardized central curves and reference intervals of serum insulin-like growth factor-I (IGF-I) levels in a normal Japanese population using the LMS method. Endocrine Journal 2012, 59 (9), 771-780

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	

8.3.1 Primary Efficacy Analyses

The aim of the present study is to demonstrate that in terms of the primary efficacy endpoint, Annual HV at 12 months, weekly Somatrogon is comparable to daily Genotropin.

Comparability will be concluded if the mean treatment difference "Somatrogon – Genotropin" in the primary efficacy endpoint is ≥ -1.8 cm/year.

The difference of means between the two treatments will be derived from an ANCOVA. The ANCOVA model will include classification terms for treatment and gender. The model will also include baseline peak GH value and height SDS as covariates. The determination of comparability will be based on least squares means for the two treatments from the ANCOVA and the difference between the treatments.

Descriptive statistics will be reported for observed annual HV values at 12 months. In addition, descriptive statistics will be reported for observed annual HV values at 12 months by ADA status.

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

ANCOVA-based statistics will be reported by the categorical term used in the ANCOVA model: gender.

8.3.2 Secondary Efficacy Analyses

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

- 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 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 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 term used in the ANCOVA model: gender.

8.3.3 Primary Efficacy Sensitivity Analysis

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

The similar analysis to the ANCOVA-based primary efficacy analysis, but using the different missing imputation method, will be repeated using the FAS. The method will be carrying the last non-missing height value forward and using this value to derive HV. Unscheduled and early discontinuation measurements will be carried forward.

The similar analysis to the ANCOVA-based primary efficacy analysis, but including different covariates, will be repeated using the FAS. The model will include classification terms for treatment, Peak GH level (low vs high, based on: ≤3 ng/mL or >3 to ≤6 ng/mL; or if GHRP-2 provocation test is used, ≤10 ng/mL or >10 to ≤16 ng/mL, if there are adequate number of subjects in each of the classification levels) and chronological age (3-7 years old or above 7 years old). The model will also include height SDS as continuous variable.

8.3.4 Biochemical Markers Analysis

Descriptive statistics will be reported for observed and change from baseline for all biochemical endpoints at each visit. In addition, descriptive statistics will be reported for CCI by ADA status.

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.

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. AEs 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 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 SOC and PT will be summarized and sorted by descending order of overall incidence. In addition, the number and percentage of subjects who experienced each specific SOC and PT will be summarized by ADA status.

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

TEAEs will be summarized by relationships (all causalities and treatment related). TEAEs are considered related to study drug if the relationship is one of: "possibly related", "related", or missing.

9.3 Serious Adverse Events and Other Significant Adverse Events

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

- SAE
- severe AE
- leading to study drug withdrawal
- leading to study drug reduction or interruption
- leading to study discontinuation

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 maximum severity (mild < moderate < severe) and strongest relationship (not related < related) within SOC and PT.

TEAEs of special interest will also be summarized by event type and PT. The event type will be described in the safety narrative plan.

Deaths will be presented in a data listing.

9.4 Injection Site Reactions and Pain

Injection site reactions (ISR) will be summarized by SOC and PT. In addition, ISR will be summarized by SOC and PT by ADA status.

Pain scores will be summarized with number of overall subjects and subjects with ISR as the denominator. For each subject, ISR pain score will be summarized by maximum severity. In both summaries, missing values will be considered "hurts worse".

ISR erythema/redness, bruising, and induration/swelling 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. 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 at each 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 either 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 or AST > 2xULN)

Two evaluation of Drug Induced Serious Hepatotoxicity (eDISH) 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 AEs 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.

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 Growth Hormone (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.

9.6.3.4 Pregnancy

The population under study consists of pre-pubertal children. As such, no pregnancy assessments will be performed. In case of pregnancy, study treatment will be terminated, and study procedures will be performed as scheduled.

9.6.3.5 Hypersensitivity

Hypersensitivity will be summarized by ADA status.

10. CCI

CCI

11. INTERIM ANALYSES AND DATA MONITORING

11.1 Data Monitoring

An independent and external data safety monitoring board (DSMB) will be established. The primary responsibility of the DSMB will be 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

According to the Protocol CP-4-009 Administrative Change Letter #2 to Version 9.0 of the Protocol, the following analyses were not conducted.

8.4.3 Secondary PK/PD Endpoints
Biochemical endpoints:
IGF-BP3 SDS

8.6 EFFICACY ANALYSIS
Secondary Analysis:
For the secondary endpoints that are measured over time, MMRM analysis with similar factors as the ANCOVA model (in the primary endpoint) will be used to estimate the time specific results. This MMRM approach is not intended to test for statistical significance of factors. These analyses are considered to be supportive efficacy analyses.

In addition, the following strikethrough and underlined parts were changed.

8.2.1 Full Analysis Set
The Full Analysis Set will include all ~~randomized~~ patients <u>who were randomized and have received at least one dose of study treatment</u>.

8.3 HANDLING OF MISSING DATA
Multiple Imputation (using SAS PROC MI) assuming data missing <u>not</u> at random will be used to impute missing observations in the primary efficacy analysis. Sensitivity analyses will be performed to evaluate the effect of missing data.

8.6 EFFICACY ANALYSIS
Primary Efficacy Analysis:
The goal of the primary efficacy analysis is to estimate the mean treatment difference between weekly MOD-4023 and daily Genotropin® with respect to the primary efficacy endpoint (HV after 12 months of treatment). Least square means and 95% CI for HV at 12 months will be calculated from an ANCOVA model, with treatment, gender, as factors (class variables); and peak hGH value during stimulation test, and baseline ~~HV~~<u>Height SDS</u> as covariates.

13. APPENDICES

13.1 Schedule of Events

The screening period, Visit 1, can take place over a 4 to 5 week period. Randomization will take place prior to or on Visit 2 (Day 1/Baseline), which is on day of first dosing. Visits 3, 4, and 5 will differ between the 2 treatment arms due to the 6-week dose escalation and PK/PD sampling in the MOD-4023 treatment arm. Visits 6 to 9 (every 3 months) will be similar for both treatment arms (except where noted).

Figure 13-1: Schedule of Events - Part 1 of 5

APPENDIX A: SCHEDULE OF ACTIVITIES – MOD-4023 TREATMENT ARM –VISITS 1 – 5.1

Study Procedure	Screening	Baseline	Treatment Period - Dose escalation phase (6 weeks)					
Study Month	-1 to Day -1	0	0.5		1		1.5	
Study Week	-4[a] to Day -1	1	2		4		6	
Study Visit	1	2	3	3.1	4	4.1	5	5.1
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographic & medical history including parent's height	X							
MRI (if required) post GH stimulation[b]	X							
BMI and BMI SDS	X							
Auxology measurements[c]	X[d]	X						
Weight measurement						X		
Physical examination and vital signs	X	X		X		X		X
ECG		X pre-dose						
Pubertal status (according to Tanner stages)	X	X						
BA (TW2 using central bone age reader)	X[e]	X[f]						
Fundoscopy			ONLY if there are signs or symptoms indicative of benign intracranial hypertension					
Verification of eligibility[g]	X							
Randomization		X[g]						
Training on drug administration, injection site reactions, patient diary completion, and dosing review		X		X		X		
Drug administration at clinic		X						
Dispense study drug and patient diary		X				X		
Patient diary, study drug return & accountability						X		
Local tolerability (Injection site reactions)		X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X
Prior & concomitant medications	X	X	X	X	X	X	X	X

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] MRI to be performed upon investigator judgment. In addition, MRI which was conducted within 6 month prior to ICF signature date will be acceptable
[c] Actual height (mean of 3 consecutive measurements) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.
[d] Including Patient's Height SDS and HV SDS
[e] For Screening visit, historical BA assessment might be accepted if they were done no more than 6 months prior to the ICF signature date. If the patient will be eligible, the BA should be repeated at Visit 2, before the dosing. The Visit 2 scan will be the baseline scan for these patients.
[f] BA assessment should be performed at Visit 2 only if not performed at screening.
[g] Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

Figure 13-2: Schedule of Events - Part 2 of 5

Study Procedure	Screening	Baseline	Treatment Period - Dose escalation phase (6 weeks)					
Study Month	-1 to Day -1	0	0.5		1		1.5	
Study Week	-4[a] to Day -1	1	2		4		6	
Study Visit	1	2	3	3.1	4	4.1	5	5.1
Laboratory Assessments								
Hematology[b], Biochemistry[c], & Urinalysis[d]	X	X				X		
Thyroid Assessment (TSH, FT4)	X	X						
Glucose metabolism[e]	X	X						
Lipid profile[f]	X	X						
GH stimulation (provocation) test[g]	X							
Morning cortisol (up to 8am ±1hr)[h]	X							
ACTH or CRH stimulation test[i]	X							
CCI IGF-1 SDS[j]	X	X	X	X	X	X	X	X
CCI		X	X	X	X	X	X	X
MOD-4023 serum levels		X	X	X	X	X	X	X
Antibodies to hGH	X							
Antibodies to MOD-4023		X pre-dose				X		
Blood volume (mL)[l]	8-42	9-12	6	6	6	12	6	6

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] Hematology: RBC; HGB; HCT; MCH; MCHC; MCV; WBC, Count and Differential; Platelet Count
[c] Biochemistry: total protein, albumin, total bilirubin; ALT AST, GGT, LDH, CPK, alkaline phosphatase; glucose; sodium, potassium, calcium, phosphate; BUN, creatinine;
[d] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein
[e] Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel) and insulin; HbA1c
[f] Lipid profile: morning fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
[g] 2 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 /L-dopa/ GHRP-2). Prior local laboratory results, will be accepted subject to pre-approval by Sponsor medical monitor and if the tests were conducted as specified in the protocol.
[h] Morning cortisol assessment will be subject to the investigator judgment.
[i] ACTH or CRH stimulation test will be conducted if morning cortisol 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 or CRH stimulation test is required if such results are available
[j] Frequency of sampling from Visits 3 – 5.1 as per assigned sub-block
[k] Frequency of sampling from Visits 3 – 5.1 as per assigned sub-block
[l] The total blood volume to be collected during screening (maximum 5 weeks) is shown. The maximum blood volume per day differs according to the selection of assessments. Based on the pediatric clinical guidance, blood sampling must be performed so the required minimum blood volume is obtained, and such GH stimulation tests and other assessments are taken on different days.

Figure 13-3: Schedule of Events - Part 3 of 5

APPENDIX B: SCHEDULE OF ACTIVITIES – MOD-4023 TREATMENT ARM (VISITS 6 - 10)

Study Procedure	Active treatment period				EOT		EOS
Study Month	3	6		9	12		13
Study Week	13 (±1Weeks)	26 (±3Weeks)		39 (±1Weeks)	52 (±3Weeks)		56 (+1week)
Study Visit	6[a]	7[b]	7.1[c]	8[d]	9[e]	9.1[f]	10
Auxology measurements[g]	X		X	X		X	
Physical examination and vital signs	X		X	X		X	
ECG			X				
Pubertal status (according to Tanner stages)	X		X	X		X	
BA (TW2 method using central bone age reader)						X	
Fundoscopy	ONLY if there are signs or symptoms indicative of benign intracranial hypertension						
Individual dose adjustment	X		X	X			
Dispense study drug and patient diary	X		X	X			
Patient diary, study drug return & accountability	X		X	X		X	
Local tolerability (Injection site reactions)	X		X	X		X	
AEs	X	X pre-dose	X	X	X pre-dose	X	
Prior & concomitant medications	X	X pre-dose	X	X	X pre-dose	X	
Phone interview per Appendix I							X
Laboratory Assessments							
Hematology[h], Biochemistry[i], & Urinalysis[j]	X		X	X		X	
IGF-1 and IGF-1 SDS	X		X	X		X	
MOD-4023 serum levels	X	X pre-dose	X	X	X pre-dose	X	
Thyroid Assessment: (TSH, FT4)	X		X	X		X	
Glucose metabolism[k]			X			X	
Lipid profile[l]			X			X	
Antibodies to MOD-4023	X	X pre-dose		X	X pre-dose		
Blood volume (mL)[m]	9	6	10	9	6	10	0

[a] Visit will be conducted 4 days (-1) post dose (Day 3 or 4 post-injection).
[b] Blood Sampling, AE and concomitant medication will be conducted on dosing day (predose/Visit 7)
[c] Visits 7 and 9 post-dose assessments will be conducted 4 days (-1) after that week's injection.
[d] Visit will be conducted 4 days (-1) post dose (Day 3 or 4 post-injection).
[e] Blood Sampling, AE and concomitant medication will be conducted on dosing day (predose/Visit 9)
[f] Visit will be conducted 4 days (-1) post dose (Day 3 or 4 post-injection).
[g] Actual height (mean of 3 consecutive measurements) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items
[h] Hematology: RBC; HGB; HCT; MCH; MCHC; MCV; WBC, Count and Differential; Platelet Count
[i] Biochemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; glucose; sodium, potassium, calcium, phosphate; BUN, creatinine;
[j] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein
[k] Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel) and insulin; HbA1c
[l] Lipid profile: morning fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
[m] Based on the pediatric clinical guidance, blood sampling must be performed so the required minimum blood volume is obtained, and such GH stimulation tests and other tests are taken on different days.

Figure 13-4: Schedule of Events - Part 4 of 5

APPENDIX C: SCHEDULE OF ACTIVITIES – GENOTROPIN® TREATMENT ARM

Study Procedure	Screening	Baseline	Active treatment period									EOT	EOS
Study Month	-1 to Day -1	0	0.5		1		1.5		3	6	9	12	13
Study Week	-4[a] to Day -1	1	2		4 (±1)		6		13 (±1w)	26 (±1w)	39 (±1w)	52 (±1w)	56 (+1w)
Study Visit	1	2	3[b]	3.1	4	4.1	5	5.1	6	7	8	9	10
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographic & medical history including parent's height	X												
MRI (if required) post GH stimulation[c]	X												
BMI and BMI SDS	X												
Auxology measurements[d]	X[e]	X							X	X	X	X	
Physical examination and vital signs	X	X			X				X	X	X	X	
ECG		X pre-dose								X			
Pubertal status (according to Tanner stages)	X	X							X	X	X	X	
BA (TW2 method using central bone age reader)	X[f]	X[g]										X	
Fundoscopy					ONLY if there are signs or symptoms indicative of benign intracranial hypertension								
Verification of eligibility[h]	X												
Randomization		X[h]											
Training on drug administration, injection site reactions, diary completion, and dosing review		X											
Drug administration at clinic		X											
Individual dose adjustment									X	X	X		

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] No clinic Visit 3 for Genotropin® arm only phone interview
[c] MRI to be performed upon investigator judgment. In addition, MRI which was conducted within 6 month prior to ICF signature date will be acceptable
[d] Actual height (mean of 3 consecutive measurements) measured on a calibrated stadiometer. Body weight, ideally fasted in the morning, without shoes and having removed all outwear and heavy pocket items.
[e] Including Patient's Height SDS and Height Velocity (HV) SDS
[f] At screening visit, historical BA assessment might be accepted if they were done no more than 6 months prior to the ICF signature date. If the patient will be eligible, the BA should be repeated at Visit 2, before the dosing. The Visit 2 scan will be the baseline scan for these patients.
[g] BA assessment should be performed at Visit 2 only if not performed at screening.
[h] Randomization must be performed prior to Baseline Visit and only after the medical monitor approval of the patient eligibility. Randomization must occur within the screening period. The Baseline Visit (Visit 2/Day 1) is to occur within 2 weeks (or 10 working days) after randomization.

Figure 13-5: Schedule of Events - Part 5 of 5

Study Procedure	Screening	Baseline	Active treatment period									EOT	EOS
Study Month	-1 to Day -1	0	0.5		1		1.5		3	6	9	12	13
Study Week	-4[a] to Day -1	1	2		4 (±1)		6		13 (±1w)	26 (±1w)	39 (±1w)	52 (±1w)	56 (+1w)
Study Visit	1	2	3[b]	3.1	4	4.1	5	5.1	6	7	8	9	10
Dispense study drug and patient diary		X			X				X	X	X		
Patient diary, study drug return & accountability					X				X	X	X	X	
Local tolerability (Injection site reactions)		X			X				X	X	X	X	
AEs		X			X				X	X	X	X	
Prior & concomitant medications	X	X			X				X	X	X	X	
Phone interview per Appendix I			X				X						X
Laboratory Assessments													
Hematology[c], Biochemistry[d], & Urinalysis[e]	X	X			X				X	X	X	X	
GH stimulation (provocation) test[f]	X												
Morning cortisol (up to 8am ±1hr)[g]	X												
ACTH or CRH stimulation test[h]	X												
IGF-1 and IGF-1 SDS	X	X			X				X	X	X	X	
Thyroid Assessment: (TSH, FT4)	X	X							X	X	X	X	
Glucose metabolism[i]	X	X								X		X	
Lipid profile[j]	X	X								X		X	
Antibodies to hGH	X	X pre dose							X	X	X	X	
Blood volume (mL)[k]	8-42	9-12	0		7		0		9	9	9	9	0

[a] If the patient's screening process is delayed because of a benign illness or unforeseen benign condition or a technical issue that is related to screening procedures extra time equal to the time of patient's unavailability will be added to the duration of the Screening period, but not in excess of an additional weeks 1 (total of 5 weeks Screening period).
[b] No clinic Visit 3 for Genotropin® arm only phone interview
[c] Hematology: RBC; HGB; HCT; MCH; MCHC; MCV; WBC, Count and Differential; Platelet Count
[d] Biochemistry: total protein, albumin, total bilirubin; ALT, AST, GGT, LDH, CPK, alkaline phosphatase; glucose; sodium, potassium, calcium, phosphate; BUN, creatinine;
[e] Urinalysis: pH, glucose, ketones, erythrocytes, leukocytes, protein
[f] 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 /L-dopa
[g] Morning cortisol assessment will be subject to the investigator judgment.
[h] ACTH or CRH stimulation test will be conducted if morning cortisol 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 or CRH stimulation test is required if such results are available
[i] Glucose metabolism: morning fasting glucose (will be tested as part of biochemistry panel) and insulin; HbA1c
[j] Lipid profile: morning fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
[k] Based on the pediatric clinical guidance, blood sampling must be performed so the required minimum blood volume is obtained, and such GH stimulation tests and other tests are taken on different days.