Non-Interventional Study Protocol

A6281314

Genotropin

Special Investigation

– SGA long-term follow-up investigation –

Statistical Analysis Plan

Version: 2.0

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Date: 27-OCT-2016

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1. REVISIONS FROM PREVIOUS VERSION

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0/29-JUN-2015/PPD	Original version
2.0/27-OCT-2016/PPD	5.2 Efficacy Analysis Set The eligible criteria set was added. 8.2.1 Patient Summary The case when the summary analysis results in the eligible criteria set were required was added. 8.2.2 Patient Characteristics and Treatment History The case when the summary analysis results in the eligible criteria set were required was added. New summary requirements were added to the "Treatment status of Genotropin." 8.2.4 Efficacy Analysis The case when the summary analysis results in the eligible criteria set were required was added. 8.2.4.1 Change in Height The preparation of a new graph was added. 8.2.4.2 Change in Height SDS The preparation of a new graph was added.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the special investigation (SGA long-term follow-up investigation) of Genotropin (hereinafter referred to as Genotropin). The texts drawn from the protocol are described using ***italics*** in this plan.

2.1. Study Design

Study Subjects

The indication for Genotropin in this investigation is as follows.

<Indication>

SGA (small-for-gestational age) dwarfism without epiphyseal closure.

Patient with the above disease who meet the following conditions will be enrolled in this investigation. In addition, the data in patients receiving Genotropin prior to the contract conclusion will also be included in this investigation.

1. *Patients receiving Genotropin and consenting in writing to take part in this investigation.*

2. *Newly enrolled patients who meet the following enrollment criteria.*

3. *Patients who have already been enrolled in "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure."*

<Enrollment criteria>

Patients who meet all of the following criteria

1. *Patients whose height and weight at birth are both below the 10^{th} percentile for patients of the same gestational age, and at the same time, either body weight or height is less than -2 SD compared to patients of the same gestational age. Neonates whose body height at birth were immeasurable and thus were not measured will be evaluated with birth weight.*

2. *Eligibility for the treatment*

    1. *Patients must be not younger than 3 years.*

    2. *The current body height must be less than -2.5 SD of the standard height.*

    3. *A pre-treatment height velocity within 1 year prior to the commencement of treatment must be less than 0 SD.*

3. *Patients whose poor physical growth after birth is attributable to disease other than intrauterine growth retardation cannot be enrolled in this investigation. Also patients who are currently receiving treatment that is known to cause poor physical growth cannot take part in this investigation.*

Assessment period

Assessment period for newly-enrolled patients

The fiscal assessment period of the year in which patient is enrolled will be defined as a period starting with the commencement of Genotropin therapy (which may be tracked back) and ending with the fiscal end. The fiscal assessment period of each subsequent year will be defined as the corresponding annual fiscal period.

Assessment period for ongoing subjects

For patients transferring from "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure," the initial fiscal assessment period will be defined as a period starting on the day following the final assessment of data recorded in the last booklet for "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure" and ending with the fiscal end of the applicable year. The fiscal assessment period of each subsequent year will be defined as the corresponding annual fiscal period.

For ongoing subjects, data collected during the "Genotropin Special Investigation - Investigation of Genotropin long-term use in patients with SGA dwarfism without epiphyseal closure" are included in the analysis set.

Height follow-up period

Patients completing or discontinuing Genotropin therapy will be followed up to document body heights from the completion or discontinuation of Genotropin therapy to the completion of investigation or until reaching adult height (final assessment). The follow-up period for each booklet will correspond to each fiscal year.

Target sample size

The target number of subjects from which data will be collected is approximately400.

2.2. Objective

This investigation is intended to evaluate the long-term efficacy and safety of Genotropin in children with SGA dwarfism without epiphyseal closure. Responses of patients to Genotropin in relation to clinical conditions of patients, dose schedule, past history of growth hormone treatment, and other relevant factors will be investigated.

3. INTERIM AND FINAL ANALYSES

This investigation will perform interim analysis to consider the extension of the investigation period. Of the statistical analysis items specified in this plan, only those considered necessary will be analyzed at interim analysis. All the statistical analysis items specified in this plan will be analyzed at the final analysis.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Since this is not a confirmatory investigation, statistical testing will be considered to be exploratory. The *p* value of test results will be evaluated as a descriptive statistic and no significance level will be specified, although ex-post threshold values may be set for screening.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as the full analysis set that is as close to all the patients who received Genotropin as possible. Specifically, the safety analysis set is defined as a set of enrolled or reported patients from which those who meet any of the following conditions are excluded.

a. Patients who violated the contract or for whom a defect was found in the contract (mentioned as "contract violation" and "defective contract" in the report).

b. Patients who violated the enrollment criteria (mentioned as "enrollment violation" in the report).

c. Patients for whom the dose of the product to be investigated has not been reported at all (mentioned as "no visit after the first prescription day" or "no dosing" in the report).

d. Patients for whom no adverse event information has been reported at all (mentioned as "no adverse event information").

The details of the criteria are according to the "Patient Enrollment Criteria to Analysis Sets and Guidance for Handling Data in Drug Use Survey."

5.2. Efficacy Analysis Set

The efficacy analysis set is defined as a set of patients excluded those who meet the following condition from the safety analysis set.

a. Patients who have not reported efficacy evaluation at all (mentioned as "No efficacy information" in the report).

Additionally, an eligible criteria set will be established to more specifically evaluate the efficacy of Genotropin from the viewpoint of the proper use of the product. The eligible patient set is defined as a set of patients excluded those who meet any of the following conditions from the efficacy analysis set.

a. Patients aged less than 3 years old at the start of Genotropin.

b. Patients whose height at the start of Genotropin is -2.5 SD or higher of the standard height.

c. Patients for whom the height velocity in 1 year before the start of Genotropin is 0 SD or higher of the standard height velocity.

d. Patients for whom the epiphyseal line is already closed at the start of Genotropin (bone age of 17 years or older for males and 15 years or older for females).

5.3. Other Analysis Sets

Set of patients who reached adult height (near final height).

The set of patients who reached adult height (near final height) is defined as a set of patients in the efficacy analysis set for whom adult height (near final height) was measured. Adult height (near final height) is defined as height after the time point that any of the following conditions is met.

a. Annual height velocity of less than 2 cm after the maximum growth by puberty.[1]

b. Bone age of 17 years or older for males and 15 years or older for females.[1]

c. Reason for discontinuation in patient's profile of "reaching adult height (near final height)" or "epiphyseal closure".

Set of patients who did not reach adult height (near final height).

The set of patients who did not reach adult height (near final height) is defined as a set of patients in the efficacy analysis set who meet all the following conditions at the discontinuation of treatment and for whom height was measured at least once on Day 91 after the discontinuation of treatment or later.

a. No puberty.

b. Annual height velocity of 2 cm or higher after the maximum growth by puberty.

c. Bone age of less than 17 years for males and less than 15 years for females.

d. Reason for discontinuation in patient's profile of "reaching the standard height," "growth rate," "preference of patient/parent(s)," "non-compliance," "discontinuation of public funding," "change in diagnosis," "poor clinical response," "adverse event," "laboratory abnormal," or "others".

5.4. Subsets

The following patient characteristics will be analyzed for efficacy by subsets.

- Age [less than 5 years, 5 years or older and less than 7 years, 7 years or older].
- Mother's birth history [the first childbirth / multipara].
- Presence/absence of GHD family history.
- Twin/multiplets.
- Fetus week number [less than 33 weeks, 33 weeks or older and less than 37 weeks, 37 weeks or older].

- Silver-Russell syndrome [yes, no].
- Period from the first date of treatment with growth hormone products including Genotropin to the pubescence [less than 2 years, 2 years or longer].

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse drug reaction: Adverse events related to Genotropin, as judged by the physician or company.
- Adverse event: Adverse events, all-causality.
- Laboratory tes.t

6.2. Efficacy Endpoints

- Height.
- Height SDS: (height - standard height for chronological age/gender[2]) / standard deviation.
- Height velocity: 365.25 × (height - height of 1 year before) / (date of height measurement - date of height measurement of 1 year before) (height of 1 year before: Height of the previous year as used according to "Appendix A1.3 Definition of timing for visit 3").
- Height velocity SDS: (height velocity - mean height velocity for chronological age/gender[3]) / standard deviation.

CCI [redacted]

6.3. Other Endpoints

Not applicable.

6.4. Covariates

There are no identified or potential covariates from the clinical study or other data on the safety or efficacy of Genotropin.

7. HANDLING OF MISSING VALUES

Any missing data on the seriousness, measures taken, and outcome of adverse events will be handled as "unknown" in summarizing data.

Measured values outside the acceptable range (Appendix 1) at each evaluation time point of the efficacy endpoints and clinical laboratory parameters will be handled as missing and missing data will not be imputed.

The procedure to handle uncleaned data is described below.

- Items with missing data: Missing data will be handled as missing ("unknown" for the category of classification variables) for both tabulation and listing.
- Items with inconsistent data: Inconsistent data will be handled as missing for both tabulation and listing. In this regard, however, a data handling list will be prepared separately.
- No signature: Descriptions in the report form without signature of the contract physician (or with signatures of other physicians than the contract physician) will be handled as missing for both tabulation and listing. No date or inconsistent date in the signature date section (eg, date of signature before or after the start date of treatment) will be considered to indicate that there is no signature on the report form.

8. STATISTICAL METHODS AND ANALYSIS

8.1. Statistical Methods

8.1.1. Analysis of Continuous Data

Summary statistics (number of patients, mean, standard deviation, median, maximum value, and minimum value) will be calculated. Additionally, the first and third quartile points will be calculated as summary statistics for the efficacy endpoints.

8.1.2. Analysis of Categorical Data

The frequency of each category (eg, number of patients) and its proportion will be calculated.

8.1.3. Analysis of Binary Data

Frequency and its proportion will be calculated. A two-sided 95% confidence interval (exact method) will be calculated in calculating the confidence interval of proportion.

8.2. Statistical Analysis

8.2.1. Patient's Profile

- **Patient disposition**

The number of enrolled patients, patients who completed the investigation, patients in the safety analysis set, and patients in the efficacy analysis set will be summarized in enrolled patients. Additionally, the number of patients for whom the report form was not collected,

patients excluded from the safety analysis set, and patients excluded from the efficacy analysis set and number of patients by reasons for exclusion will be summarized.

- **List of discontinuations/dropouts**

The number and proportion of patients who discontinued the investigation by the time point of completed height follow-up (less than 1 year, 1 year or longer and less than 2 years, 2 years or longer and less than 3 years, --- and N years or longer and less than N + 1 years) will be summarized for the safety analysis set, efficacy analysis set, and eligible criteria set. Then, the number and proportion of patients will be summarized by the reason for discontinuation.

- **List of patients excluded**

The list of patients excluded from the safety analysis set, efficacy analysis set, and eligible criteria set will be prepared with the reason for exclusion.

8.2.2. Patient Characteristics and Treatment History

- **Patient characteristics**

The following patient characteristics will be summarized according to 8.1 for the safety analysis set, efficacy analysis set, and eligible criteria set.

- Gender [male, female].
- Age (continuous variable) [less than 5 years, 5 years or older and less than 7 years, and 7 years or older].
- Height of father (continuous variable).
- Height of mother (continuous variable).
- Mother’s birth history [the first childbirth/multipara].
- Presence/absence of GHD family history.
- Twin/multiplets.
- Childbirth procedures [normal, breech presentation, Caesarean section, multiple selection].
- Fetus week number [less than 33 weeks, 33 weeks or older and less than 37 weeks, 37 weeks or older].
- Apgar score (1 minute) (continuous variable).
- Apgar score (5 minutes) (continuous variable).

- Apgar score (10 minutes) (continuous variable).
- Birth height (continuous variable).
- Birth weight (continuous variable) [less than 1000 g, 1000 g or higher and less than 2500 g, and 2500 g or higher].
- Birth head circumference (continuous variable).
- IGF-I (continuous variable).
- IGF-I SDS (continuous variable).
- Height (continuous variable).
- Height SDS (continuous variable) [less than -2.5 SD, -2.5 SD or higher].
- Height velocity (continuous variable): 365.25 × (height at start of treatment - Height at 1 year before start of treatment) / (Height measurement date at start of treatment - Height measurement date at 1 year before start of treatment).
- Height velocity SDS (continuous variable) [less than 0 SD, 0 SD or higher).
- Body weight (continuous variable).
- Body weight SDS (continuous variable).
- BMI (continuous variable).
- BMI SDS (continuous variable).
- Head circumference (continuous variable).
- Bone age (male) [less than 17 years, 17 years or older].
- Bone age (female) [less than 15 years, 15 years or older].

The following number and proportion of patients will be summarized by system organ class (SOC) and preferred term (PT) in the safety analysis set.

- Details of past histories.
- Details of concurrent disease.

The following number and proportion of patients will be summarized in the safety analysis set, efficacy analysis set, and eligible criteria set.

- Details of concomitant medications.

- Details of non-drug concomitant therapies.
- Details of pretreatment drugs.

- **Treatment status of Genotropin**

The following treatment status of Genotropin will be summarized in the safety analysis set.

- Dose at start (continuous variable) [less than 0.23 mg/kg/week, 0.23 mg/kg/week or higher and less than 0.35 mg/kg/week, 0.35 mg/kg/week or higher and less than 0.47 mg/kg/week, 0.47 mg/kg/week or higher]: Dose per week/kg body weight described at the starting date of the first treatment.
- Duration of treatment (continuous variable) [less than 1 year, 1 year or longer and less than 2 years, 2 years or longer and less than 3 years,---, N years or longer and less than N + 1 year]: (ending date of the last treatment - starting date of the first treatment + 1) /365.25.

The Duration of treatment is defined as the period from the first treatment day to the day of the last treatment confirmed in this investigation, including washout period.

To confirm the dose modification, the dose per week/kg, change in the dose from the start of Genotropin, and change in the dose from the previous year will be summarized at the start of Genotropin and once a year thereafter. The body weight value measured on the earliest date in each period will be used to calculate the dose per week/kg. The dose per week/kg will be considered as missing when there is no body weight measurement during the period.

8.2.3. Safety Analysis

8.2.3.1. Adverse Drug Reactions

- **All adverse drug reactions**

The number and proportion of patients who developed an adverse drug reaction will be summarized by SOC and PT.

- **Serious adverse drug reactions**

The number and proportion of patients who developed a serious adverse drug reaction will be summarized by SOC and PT.

- **Details on adverse drug reaction**

The number and proportion of patients who developed an adverse drug reaction will be summarized by SOC and PT for each of the following items.

- Seriousness [serious, non-serious].
- Known/unknown [known, unknown].

- Measures taken [permanently discontinued, temporarily discontinued, dose reduced, dose increased, no dose change].

- Outcome [not recovered, recovered with sequelae, resolving, disappeared/resolved, unknown].

When the same patient experiences the same adverse drug reaction (with the same PT) more than once, the adverse drug reaction will be handled as follows in summarizing the number of patients with the adverse drug reaction.

- Seriousness: The adverse drug reaction will be handled as serious when it develops as both serious and non-serious events.

- Known/unknown: The adverse drug reaction will be handled as unknown when it develops as both known and unknown events.

- Number of days before onset: The number of days before the adverse drug reaction developed for the first time.

- Measures taken: When more than one measure has been taken, one of them will be employed with the order of preference of permanently discontinued, temporarily discontinued, dose reduced, and others (no measure/dose increased).

- Outcome: The outcome of the event that developed last will be used.

- **Timing for development of adverse drug reaction**

The number of patients who develop an adverse drug reaction for the first time in less than 1 year after the start of treatment will be summarized by SOC and PT for patients who receive Genotropin for less than 1 year. Similarly, the number of patients who develop an adverse drug reaction for the first time during the period of 1 year or longer and less than 2 years after the start of treatment will be summarized by SOC and PT for patients who receive Genotropin for 1 year or longer and less than 2 years. The same will be repeated to summarize it for the period of 2 years or longer and less than 3 years and so on (N years or longer and less than N + 1 years).

The number of patients will be summarized cumulatively. For example, patients for whom the duration of treatment is 2 years or longer and less than 3 years will be included in patients for whom the duration of treatment is less than 1 year and those for whom the duration of treatment is 1 year or longer and less than 2 years.

- **Development status of adverse drug reaction by inclusion in safety analysis set**

A list of adverse drug reactions in patients excluded from the safety analysis set will be prepared for the patients for whom the report form is collected. Furthermore, the number of patients who develop an adverse drug reaction will be summarized by SOC and PT.

8.2.3.2. Adverse Event

- **All adverse events**

The number and proportion of patients who develop an adverse event will be summarized by SOC and PT.

- **Adverse events by seriousness**

The number and proportion of patients who developed serious adverse events will be summarized by SOC and PT. The number and proportion of patients who develop a non-serious adverse event will be summarized in the same manner.

8.2.3.3. Other Endpoints

- **Laboratory test parameters**

The summary statistics of measured values of HbA1c at each evaluation point and change from the start of Genotropin will be calculated. The 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.3 Definition of timing for visit 3.

8.2.3.4. CCI

[redacted]

8.2.4. Efficacy Analysis

8.2.4.1. Change in Height

The summary statistics of measured values of height at each age will be calculated for the efficacy analysis set and eligible criteria set. The evaluation points are according to Appendix A1.1 Definition of timing for visit 1. The change in height will be plotted with a solid line for individual male and female patients separately, with age on the horizontal axis and height on the vertical axis. On the plot, the plots of the standard height and standard height ±1 SD, ±2 SD, -2.5 SD, and -3 SD will be superimposed using a dotted line as a reference line for male and female patients, separately. The start of treatment will be indicated as ▲, pubescence as ●, and reaching adult height (near final height) as ▼. They will be plotted with a different dotted line from that used for the reference line after the completion/discontinuation of treatment.

The same calculation will be performed to prepare plots in the same manner for the set of patients who reached adult height (near final height) and set of patients not reached.

Additionally, a plot will be prepared with the change in the dose per week/kg after the start of Genotropin on the horizontal axis and change in height after the start of Genotropin on the vertical axis. The evaluation points of the change are according to Appendix A1.3 Definition of timing for visit 3. Furthermore, a plot will be prepared with the change in the dose per

week/kg from the previous year on the horizontal axis and the change in height from the previous year on the vertical axis.

8.2.4.2. Change in Height SDS

The summary statistics of measured values of height SDS at each age will be calculated for the efficacy analysis set and eligible criteria set. The evaluation points are according to Appendix A1.1 Definition of timing for visit 1. The change in height SDS will be plotted with a solid line for individual male and female patients separately, with age on the horizontal axis and height SDS on the vertical axis. The start of treatment will be indicated as ▲, pubescence as ●, and reaching adult height (near final height) as ▼. They will be plotted with a dotted line after the completion/discontinuation of treatment.

The same calculation will be performed to prepare plots in the same manner for the set of patients who reached adult height (near final height) and set of patients not reached.

The summary statistics of measured values of height SDS at each evaluation point and change from the start of Genotropin will be calculated for a set of patients who reached adult height (near final height). The 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.2 Definition of timing for visit 2. The change in height SDS will be plotted with a solid line for individual male and female patients separately, with evaluation points on the horizontal axis and height SDS on the vertical axis. The start of treatment will be indicated as ▲, pubescence as ●, and reaching adult height (near final height) as ▼. They will be plotted with a dotted line after the completion/discontinuation of treatment.

The summary statistics of measured values of height SDS at each evaluation point and changes from the start of Genotropin will be calculated in the efficacy analysis set and eligible criteria set. The 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.3 Definition of timing for visit 3. The change in height SDS will be plotted with a solid line for individual male and female patients separately, with evaluation points on the horizontal axis and height SDS on the vertical axis. The start of treatment will be indicated as ▲, pubescence as ●, and reaching adult height (near final height) as ▼. They will be plotted with a dotted line after the completion/discontinuation of treatment.

The same calculation will be performed to prepare plots in the same manner for the set of patients not reached adult height (near final height).

Additionally, a plot will be prepared with the change in the dose per week/kg after the start of Genotropin on the horizontal axis and change in height SDS after the start of Genotropin on the vertical axis. The evaluation points of the change are according to Appendix A1.3 Definition of timing for visit 3. Furthermore, a plot will be prepared with the change in the dose per week/kg from the previous year on the horizontal axis and the change in height SDS from the previous year on the vertical axis.

8.2.4.3. Change in Height Velocity

The summary statistics of measured values of height velocity at each evaluation point and change from the start of Genotropin will be calculated for the efficacy analysis set and eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.3 Definition of timing for visit 3. The change in height velocity will be plotted with a solid line for individual male and female patients separately, with evaluation points on the horizontal axis and height velocity on the vertical axis. The start of treatment will be indicated as ▲, pubescence as ●, and reaching adult height (near final height) as ▼. They will be plotted with a dotted line after the completion/discontinuation of treatment.

The same calculation will be performed to prepare plots in the same manner for the set of patients not reached adult height (near final height).

8.2.4.4. Change in Height Velocity SDS

The summary statistics of measured values of height velocity at each evaluation point and changes from the start of Genotropin will be calculated in the efficacy analysis set and eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.3 Definition of timing for visit 3. The change in height velocity SDS will be plotted with a solid line for individual male and female patients separately, with evaluation points on the horizontal axis and height velocity SDS on the vertical axis. The start of treatment will be indicated as ▲, pubescence as ●, and reaching adult height (near final height) as ▼. They will be plotted with a dotted line after the completion/discontinuation of treatment.

The same calculation will be performed to prepare plots in the same manner for the set of patients not reached adult height (near final height).

8.2.4.5. Change in Body Weight SDS

The summary statistics of measured values of body weight SDS at each age will be calculated for the efficacy analysis set and eligible criteria set. The evaluation points are according to Appendix A1.1 Definition of timing for visit 1.

The same calculation will be performed for the set of patients who reached adult height (near final height) and set of patients not reached.

The summary statistics of measured values of body weight SDS at each evaluation point and change from the start of Genotropin will be calculated for a set of patients who reached adult height (near final height) in the eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.2 Definition of timing for visit 2.

The summary statistics of measured values of body weight SDS at each evaluation point and changes from the start of Genotropin will be calculated in the eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.3 Definition of timing for visit 3.

The same calculation will be performed for the set of patients not reached adult height (near final height) in the eligible criteria set.

8.2.4.6. Change in BMI SDS

The summary statistics of measured values of BMI SDS at each age will be calculated in the efficacy analysis set and eligible criteria set. The evaluation points are according to Appendix A1.1 Definition of timing for visit 1.

The same calculation will be performed for the set of patients who reached adult height (near final height) and set of patients not reached.

The summary statistics of measured values of BMI SDS at each evaluation point and change from the start of Genotropin will be calculated for a set of patients who reached adult height (near final height) in the eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.2 Definition of timing for visit 2.

The summary statistics of measured values of BMI SDS at each evaluation point and change from the start of Genotropin will be calculated in the eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.3 Definition of timing for visit 3.

The same calculation will be performed for the set of patients not reached adult height (near final height) in the eligible criteria set.

8.2.4.7. Change in IGF-I SDS

The summary statistics of measured values of IGF-I SDS at each age will be calculated in the efficacy analysis set and eligible criteria set. The evaluation points are according to Appendix A1.1 Definition of timing for visit 1.

The same calculation will be performed for the set of patients who reached adult height (near final height) and set of patients not reached.

The summary statistics of measured values of IGF-I SDS at each evaluation point and change from the start of Genotropin will be calculated for a set of patients who reached adult height (near final height) in the eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.2 Definition of timing for visit 2.

The summary statistics of measured values of IGF-I SDS at each evaluation point and change from the start of Genotropin will be calculated in the eligible criteria set. Further, the 95% confidence interval of the mean of the change will be calculated. The evaluation points are according to Appendix A1.3 Definition of timing for visit 3.

The same calculation will be performed for the set of patients not reached adult height (near final height) in the eligible criteria set.

8.2.4.8. Subset Analysis

A subset analysis of the change in height SDS will be performed by the factors specified in 5.4.

8.2.4.9. CCI [redacted]

[redacted]

9. LISTS

The following lists will be prepared.

- Patient list.
- List of patients with adverse events.
- List of patients with adverse drug reactions.
- List of patients with adverse drug reactions excluded from safety analysis set.
- List of patients with serious adverse drug reactions.
- List of patients with serious adverse events.
- List of laboratory test parameters.

10. REFERENCES

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2. Materials Prepared with Data from 2000 Ministry of Health, Labour, and Welfare Infant Physical Growth Survey Report and 2000 Ministry of Education, Culture, Sports, Science, and Technology School Health Statistics Survey Report (supervised by: Kenji Fujieda/authors: Katsuhiko Tachibana, Noriko Kato, and Zenya Ito).

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11. APPENDIXES

11.1. Appendix 1: Details of Data Extraction

A1.1 DEFINITION OF TIMING FOR VISIT 1

Timing for visit	Endpoint	Definition [allowable range]
3 years	Height Height SDS Body weight SDS BMI SDS IGF-I SDS	3 years and 0 month to 3 years and 11 months
4 years	Height Height SDS Body weight SDS BMI SDS IGF-I SDS	4 years and 0 month to 4 years and 11 months
N years	Height Height SDS Body weight SDS BMI SDS IGF-I SDS	N years and 0 month to N years and 11 months

The measured value on the latest date will be used when the same patient receives more than one measurement during the same visit.

A1.2 DEFINITION OF TIMING FOR VISIT 2

Timing for visit	Endpoint	Definition [allowable range]
Start of Genotropin therapy	Height SDS Body weight SDS BMI SDS IGF-I SDS	90 days before the first date of treatment (the start date of treatment) to the start date of treatment for this investigation
Pubescence	Height SDS Body weight SDS BMI SDS IGF-I SDS	The date evaluated as the pubescence +90 days
At reaching adult height (near final height)	Height SDS Body weight SDS BMI SDS IGF-I SDS	The date evaluated to reach adult height (near final height) +90 days

The measured value on the earliest date will be used when the same patient receives more than one measurement during the same visit.
In this regard, all the data measured after reaching adult height (near final height) will be used if plots are prepared.

A1.3 DEFINITION OF TIMING FOR VISIT 3

Timing for visit	Endpoint	Definition [allowable range]
Start of Genotropin therapy	Laboratory test parameters Height SDS Height velocity Height velocity SDS Body weight SDS BMI SDS IGF-I SDS	90 days before the first date of treatment (the start date of treatment) to the start date of treatment for this investigation
1 year later	Laboratory test parameters Height SDS Height velocity Height velocity SDS Body weight SDS BMI SDS IGF-I SDS	365 ±90 days after the start of treatment
2 years later	Laboratory test parameters Height SDS Height velocity Height velocity SDS Body weight SDS BMI SDS IGF-I SDS	730 ±90 days after the start of treatment
N years later	Laboratory test parameters Height SDS Height velocity Height velocity SDS Body weight SDS BMI SDS IGF-I SDS	365 × N ±90 days after the start of treatment
Completion of Genotropin therapy	Laboratory test parameters Height SDS Height velocity Height velocity SDS Body weight SDS BMI SDS IGF-I SDS	Final date of treatment for this investigation (completion date of treatment) ±90 days

Timing for visit	Endpoint	Definition [allowable range]
Completion of height follow-up	Height SDS Height velocity Height velocity SDS Body weight SDS BMI SDS	Completion date of height follow-up ±90 days

The measured value on the earliest date will be used when the same patient receives more than one measurement during the same visit.
In this regard, all the data measured after the completion of height follow-up will be used if plots are prepared.