**Official Title:** Long-term Phase IV Multicentre Study on the Safety and Efficacy of Omnitrope® (rhGH) in Short Children Born Small for Gestational Age (SGA)

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Sandoz Biopharmaceuticals Clinical Development

EP2000 (INN: somatropin), Omnitrope

EP00-401

# Long-term phase IV multicenter study on the safety and efficacy of Omnitrope (rhGH) in short children born small for gestational age (SGA)

# Statistical Analysis Plan (SAP)

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I herewith approve the statistical analysis - Final analysis for EMA Report.

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## Document History – Changes compared to previous version of the SAP.

| Date | Version | Title | Purpose of the SAP / Main Changes |
|---|---|---|---|
| 25-Nov-2009 | 1.0 | Statistical Analysis Plan for Protocol Number: EP00-401 | Initial version |
| 27-Jul-2011 | 1.0 | Statistical Analysis Plan for Interim Analysis | Specific SAP version used for the 1 year interim analysis<br>Outputs limited to data collected during the first year of treatment |
| 19-Jan-2012 | 1.0 | Further statistical Methods for Interim Analysis | Document specifying further programming details for 1 year interim analysis |
| 13-Feb-2012 | 1.0 | Statistical Analysis Plan for Interim Analysis – SAP Amendment | Amendment to specific SAP version used for the 1 year interim analysis |
| 10-Oct-2013 | 2.1 | Statistical Analysis Plan for 2 Years Interim Analysis | Specific SAP version used for the 2 years interim analysis<br>Outputs limited to data collected during the first two years of treatment |
| 18-Apr-2017 | 1.0 | Statistical Analysis Plan – Interim Analysis 2017 | Specific SAP version prepared for a third interim analysis planned for 2017.<br>All data available at database cut-off to be analysed. This interim analysis was not performed. |
| 11-May-2017 | 2.0 | Statistical Analysis Plan – Interim Analysis 2017<br>(Note: The interim analysis 2017 was not peformed.) | Updated version of the specific SAP version prepared for a third interim analysis planned for 2017 based on discussions during the DRM meeting. This interim analysis was not performed. |
| 31-May-2021 | 4.0 | Statistical Analysis Plan | SAP version for the final analysis including all data available.<br>Main changes:<br>Removal of per protocol set according to Protocol Amendment 04 dated 24-Aug-2017<br>Updated Type 2 diabetes mellitus definition to 2016 revised WHO criteria which includes $HbA_{1C}$. Definitions for IGT and IFG added. |
| 26-Apr-2022 | 5.0 | Statistical Analysis Plan | SAP version for the final analysis including all data available.<br>Main changes:<br>Subgroup analysis of an overweight population added.<br>Additional tables and figures added. |

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## List of abbreviations

| | |
|---|---|
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| [redacted] | [redacted] |
| CA | Chronological age |
| CRF | Case report form |
| FAS | Full analysis set |
| FPG | Fasting plasma glucose |
| HA | Height age |
| $HbA_{1C}$ | Glycated hemoglobin test |
| HCP | Host Cell Protein |
| HOMA | Homeostasis model assessment |
| HV | Height velocity |
| HV SDS | Height velocity standard deviation score |
| IFG | Impaired fasting glucose |
| IGT | Impaired glucose tolerance |
| OGTT | Oral glucose tolerance test |
| Q1 | First quartile |
| Q3 | Third quartile |
| QUICKI | Quantitative insulin sensitivity check index |
| rhGH | Recombinant human growth hormone |
| SAE | Serious adverse event |
| SAF | Safety set |
| SD | Standard deviation |
| SGA | Small for gestational age |

# 1 Introduction

This study is performed as part of the Marketing Authorization Holder's post-authorization Risk Management Plan in order to investigate the long-term safety, in particular the diabetogenic potential and immunogenicity of Omnitrope treatmentin short children born small for gestational age (SGA).

This study is designed as an open phase IV, prospective, non-comparative, multicenter trial. Omnitrope treatment will continue until final height is reached. Treatment should be discontinued after the first year of treatment if the height velocity standard deviation score (HV SDS) is below +1. Treatment should be discontinued if height velocity is below 2 cm/year [redacted]

# 2 Statistical and analytical plans

Data will be analyzed by [redacted] according to this statistical analysis plan.

## 2.1 Study documents and general considerations

This document describes the procedures and conventions to be used for the final analysis of all patients who were included into study EP00-401 and is based on study protocol V6.0, dated 07-Feb-2020, incorporating amendment no. 05.

Raw data listings, summary tables, graphs and statistical tests will be generated by means of the program SAS 9.4 and SAS/STAT Version 14.3.

The following descriptive statistical parameters will be shown in summary tables

- Continuous variables: n (valid cases), n (missing data), mean, standard deviation (SD), min, 1st quartile (Q1), median, 3rd quartile (Q3), max
- Categorical variables: Count and percentage of category. Percentages are routinely based on the total category count excluding the missing category if not otherwise mentioned. Percentages showing a rate relative to the total number of patients in this group are given in special tables (e.g. Adverse Event (AE) tables). Footnotes will specify the percent basis.

For continuous variables, if not otherwise specified, mean, median and standard deviation values will be reported to one decimal place greater than the data were collected. Minimum and maximum values will be reported with the same precision, as they were collected.

Generally, percentages will be displayed in the format xx.d, i.e. one decimal place will be shown; if the calculated percentage is 100, no decimal is required (i.e. 100% and not 100.0%). If the count is zero no percentage needs to be shown.

## 2.2 Study objectives

The primary objective of this study is to evaluate the long-term effect of growth hormone treatment on the development of diabetes in short children born SGA during the treatment.

The secondary objectives of this study are:

- to report the incidence of anti-recombinant human growth hormone (rhGH) antibodies during Omnitrope treatment
- to evaluate the efficacy (with respect to changes in height parameters) of Omnitrope treatment in short children born SGA
- to evaluate IGF-1 and IGFBP-3 levels during treatment
- to evaluate incidence and severity of adverse events

## 2.3 Endpoints

### 2.3.1 Primary endpoint

The development of diabetes is the primary endpoint of the study and is evaluated on the basis of the carbohydrate metabolism (fasting plasma glucose (FPG), oral glucose tolerance test (OGTT)) and $HbA_{1C}$.

### 2.3.2 Secondary endpoints

The development of anti-rhGH antibodies is a secondary endpoint.

The efficacy endpoints of this study are the height and the standardized height (SDS), the height velocity (HV) and the HV SDS assessed at screening, every 3 months during the first two years of GH treatment and annually thereafter until final height is reached (end of treatment).

Additionally efficacy endpoints of this study are the development of the hGH-induced serum parameters IGF-1 and IGFBP-3 assessed by a central laboratory at screening, after 3, 6, 9, 12 months and then biannually during treatment.

Additional criteria for assessing safety will consist of monitoring and recording all (serious) adverse events, vital signs and body weight, physical condition, hematology, blood chemistry, thyroid function tests, lipids and urinalysis. Fundoscopy will be performed if intracranial hypertension is suspected.

## 2.4 Statistical methods planned in the protocol

Analyses planned are described in section 10 of the protocol.

Safety and efficacy endpoints will be summarized descriptively. For all efficacy endpoints mean difference between the baseline visit and all later visits and respective 95% confidence will be provided.

## 2.5 Determination of sample size

There was no formal sample size calculation for this study which is intended to exploratorily investigate the long-term effect of the treatment with respect to the development of diabetes. No such incidences are currently available to allow for a rigorous sample size estimation. Results obtained in this study will be compared to data published in the literature.

[redacted]

Patients dropping out before completing 1 year of treatment will be replaced.

[redacted]

## 2.6 Definitions of analysis sets

The **safety analysis set** (SAF) comprises all patients who have received at least one dose of study medication and had at least one post-baseline safety assessment. All safety analyses will be based for the SAF.

The **full analysis set** (FAS) follows the intent-to-treat principle and consists of all patients who received at least one dose of study medication.. All baseline and efficacy analyses will be summarized for the FAS.

## 2.7 Subgroup analyses

Since the study population consists of patients treated with Omnitrope 5 mg/ml powder for the first twelve months and with Omnitrope 5 mg/1.5 ml solution for injection thereafter as well as of patients treated continuously with Omnitrope 5 mg/1.5 ml mg/ml solution for injection, a corresponding subgroup analysis will be performed.

Moreover, a subgroup analysis will also be done for an overweight population with international cut-off points for BMI for overweight by sex and age as defined by the percentile that passes through BMI of 25 at age 18.

Further subgroup investigations concerning efficacy endpoints will be carried out with regard to sex, completers and total.

# 3 Changes to planned analyses

The assessment of laboratory findings related to diabetes mellitus is no longer based on WHO definition of 2006, but on the version published in 2016.

The protocol planned to analyze treatment compliance based on the percentage of medication used compared to the amount prescribed for each visit and the frequency of non-compliant patients (daily dose range 80% or >120%). This approach was changed currently the number of non-compliant patients will be assessed based on the investigator's assessment that is collected on dose change page in the CRF.

Analysis for anti-HCP was added.

# 4 Statistical analyses

## 4.1 General considerations

### Baseline visit

In principal, Visit V01 (start) is regarded as baseline visit. For some patients only a screening visit, but no baseline visit was performed. For these patients screening visit will be used as baseline visits.

### Alignment of final visits

A final visit should be performed for all patients terminating study drug. These visits will be analyzed together with the regularly performed study visits. A final visit will be assigned to the appropriate study visit as follows:

In a first step the respective limit between two visit used for assignment, will be assessed as follows: limit = (Day on which VX [= Visit X] should have been performed - Day on which VX-1 should have been performed)/2. The respective limit was rounded if necessary. Days on which a visit should have been performed according to protocol will be assessed as follows (excluding V0 and V1): Month given in the protocol *(365.25/12) (i.e. V2 = Day 92, V3 = Day 183, V4 = 274 ...).

In a second step final visits performed between VX-1 and the limit (included) will be assigned to VX-1, final visits performed after the limit and prior to VX will be assigned to VX.

For example: A final visit performed between V3 and V4, will be assigned to V3, if performed at or before Day 229 (= (Day 274 + Day 183)/2 = 228.5 => rounded to 229). If performed after Day 229 and at or before V4, the final visit will be assigned to V4.

If due to the assignment of final visits to regular visits two assessments are available for one visit, the assessment nearest to the day on which the visit had to be performed will be used.

If the final visit was performed on the same day as a regular visit, the regular visit will be used for analysis.

### Retest of fasting blood glucose

Retest values for fasting blood glucose will be listed only.

## 4.2 Disposition of patients and protocol deviations

Information regarding patient enrolment and patient disposition over time will be summarized in a table, listing the participating sites and providing the following variables: site code, number of patients enrolled at screening and number of patients at subsequent visits. Further, a table providing number of patients screened, and number and percentage in each analysis set will be provided.

Protocol deviations were collected based on the PD specification and were classified during the DDRM by the reponsible team members. Based on these a summary table and listing of all important protocol deviations will be provided, sorted by site code and patient number. In

addition to site code and patient number, this listing includes: a description of the deviation, the deviation code, and a variable indicating whether the patient discontinued study treatment prematurely. If a patient was withdrawn from the study, date and reason for withdrawal are given.

A listing of all patients who discontinued the study will be provided, sorted by site code and patient number. In addition to site code and patient number, this listing includes date and primary reason for study discontinuation as well as information on last study drug intake. Additionally, number and percentage of patients having completed the study as planned, discontinuing the study prematurely as well as the primary reason for discontinuation will be summarized.

## 4.3 Demographics and baseline characteristics

### 4.3.1 Demographics

Demographic data of patients are collected at the screening visit (month 0).

Demographic information will be summarized for age, height, height SDS, height velocity (HV), HV SDS, weight, BMI, BMI SDS, sex, and ethnic origin. Separate summaries of age, sex and ethnic origin will be produced, stratified by initial treatment (powder/solution). Further ethnic origin will be stratified by sex.

Separate tables by country and by age group will be prepared for FAS.

#### Parents' height

Parents' height data will be stratified by sex and initial treatment.

#### Patient birth history

Birth weight, birth length, birth weight SDS, birth length SDS and gestational age will be summarized for the whole group of patients and stratified by sex and initial treatment. Assessment of birth weight and length SDS is described in the Project Specific Procedure – Calculation of Auxological data v3.0 dated 4-July-2011.

### 4.3.2 Medical history

Medical history will be recorded at the screening visit and will be coded according to Novartis MedDRA, Version 24.1 or later.

Medical history data will be summarized, providing the proportions resolved, intermittent, and ongoing illnesses by MedDRA system organ class and preferred term for the FAS. Further, all data on medical histories will be listed sorted by site code, patient number, and date of diagnosis.

### 4.3.3 Baseline values of height measurements

Values for height parameters measured/derived at start of treatment will be summarized for all patients. The summary table will display descriptive statistics for the body height, height SDS, midparental adjusted height SDS, HV, HV SDS and for the time period (in days) between date of visit and historical height measurement used to calculate height velocity at start of treatment.

Midparental adjusted height SDS is defined as H SDS of the patient minus midparental height SDS. The midparental H SDS is defined as 0.5*(H SDS of the mother + H SDS of the father).

### 4.3.4 Pubertal status

Pubertal status is determined at each visit.

Pubertal status will be summarized for the whole group of patients as well as for the two sexes separately. In these tables, numbers and proportions of Tanner stages will be reported by visit. The tables will be produced for the FAS.

### 4.3.5 Prior and concomitant medication

Concomitant medication is documented at each visit from start of treatment onwards.

Medication will be coded to the preferred term using the Novartis WHO drug dictionary version Novartis WHO DDE 17.3-28.08.2018; all possible ATC codes will also be applied.

Prior medication is defined as all medication stopped prior to first intake of study medication. All other medication is considered as concomitant medication.

If stop date of medication is given partial only, the last day of months or 31 December will be assumed. If neither a stop date is given nor ongoing was ticked, the respective medication was regarded as concomitant medication.

Prior and concomitant medication data will be summarized separately by Anatomical Therapeutic Chemical (ATC) term (level 2) and preferred term, providing the proportion of patients to whom medication was administered. This summary will be prepared for the FAS.

## 4.4 Treatment regimen, compliance and exposure to drug

The patient's exposure to study drug will be calculated from the date of first dose to the date of last study drug administration for patients that prematurely discontinued or completed the study, and presented in years as a decimal.

If date of last study drug administration is missing completely or only a year is given and the patient has discontinued or completed the study, then the date the patient discontinued or completed the study shall be used instead. If date of last study drug administration was given only partial (i.e. month and year given), the first date of the month will be assumed as last administration date. Study drug exposure in days will be converted to study drug in years as follows:

- Exposure (years) = Exposure (days)/365.25.

The patient's exposure to study drug will also be summarized by site for FAS.

The total daily dose administered per kg body weight will be summarized by visit to assess the appropriateness of the applied dose for FAS.

A summary table providing the number and percentage of patients with any study drug dose change documented by reason for dose change overall and by number of times the respective reason was documented per patient will be provided. As for some patients dose change records

were documented when the patient returned to the recommended dose, all records with a daily dose of 0.035 mg/kg will be excluded from the summary tables.

## 4.5 Analysis of the primary endpoint

### Definitions according to the World Health Organization (WHO):

According to the 2016 revised WHO criteria (WHO, 2016), the diagnosis of diabetes mellitus, impaired glucose tolerance (IGT) and impaired fasting plasma glucose (IFG) on laboratory results is defined by the following criteria:

### Diabetes mellitus (DM):

FPG ≥ 126 mg/dl (≥7.0 mmol/l)

**or**

2-h plasma glucose ≥ 200 mg/dl (≥11.1 mmol/l) during OGTT

**or**

$HbA_{1C}$ ≥ 6.5%

### Impaired Glucose Tolerance (IGT):

FPG < 126 mg/dl (<7.0 mmol/l)

**and**

2-h plasma glucose between 140 – 200 mg/dl (≥7.8 and <11.1 mmol/l)

### Impaired Fasting Glucose (IFG):

FPG 110 - 125 mg/dl (6.1 - 6.9 mmol/l)

**and**

2-h plasma glucose < 140 mg/dl (<7.8 mmol/l)

The identification of diabetes mellitus on laboratory results had to be in accordance to the documentation of diabetes mellitus as an AE.

## 4.6 Analysis of secondary endpoints

### 4.6.1 Efficacy evaluation

Data regarding efficacy endpoints will be summarized by visit. Time trends of means will be presented graphically for the secondary endpoints.

For all endpoints, 95% confidence intervals will be calculated for the mean difference between the baseline visit and all later visits, respectively.

Summary tables, plots, and confidence intervals will be presented by visit for the FAS analysis set as well as by sex and the two Omnitrope formulations (i.e. initially treatment). All summary table stratified by initially treatment will be limited to the visit during the first year of treatment. Plots presenting parameters in SDS will not be presented by sex. No plots by initially treatment will be presented. In summary tables presenting data that is also presented graphically confidence limit for means will be added.

All efficacy analyses will be done by completers (who reached the final height) and total.

### Body height and derived parameters

Patients' body height is determined at each visit. The three other primary endpoints are calculated using the recorded height measurements. HV will be calculated in cm/year as the difference between two height measurements divided by the time interval (in days) between these two measurements and multiplied by 365.25. Patients' body height at start of treatment serves as baseline value for calculating HV at month 3, 6, 9 and 12. From the 15-months-visit onwards, the baseline value for HV calculation will be patients' body height at the visit dating back 12 month in the past, e.g., height after 3 months will serve as baseline value to determine HV at 15-months-visit, height after 6 months will serve as baseline to determine HV at 18-months-visit, and so on ("moving 12-months HV basis").

HV and HV SDS for the baseline visit are calculated using historical height data. All corresponding values are recorded in the CRF. The historical reference values to assess the height velocity at screening (V0) and baseline (V1) will be assessed as follows: The historical value, which was assessed next to day 365 prior to height assessment at baseline, will be selected. If there are two values, one assessed x days prior to day 365 and one assessed x days after day 365, the one assessed longer ago will be selected. Derived height velocity values will be rounded to two digits. If for any historical height assessments, the assessment date was given partial only, the 15th of the respective month will be used. If in the final data negative HV values are assessed, this will be set to 0 for analysis.

Height and height velocity will also be expressed in SDS. SDS reflects the deviation of a measured value from the mean value of normally growing children of the same sex and chronological age, expressed in units of the standard deviation of normally growing children of the same sex and chronological age.

In general, the SDS values for H and HV will be calculated according to the formula SDS=(X1-X2)/SD, where X1 is the measured value, X2 the mean value for the relevant chronological age and sex, and SD the standard deviation for the relevant sex and age. Standardization of patients' height will be performed according to the protocol using national reference ranges of body height (Appendix B). If respective national references for height are provided as median and 3$^{rd}$ percentiles SDS values will be calculated according to the following formula: SDS = (X1-X3)/ (0.5*(X3 – X4), where X1 means the measured value, X3 the median value for the relevant chronological age and sex, and X4 the 3$^{rd}$ percentile for the relevant chronological age and sex applying the respective national references. Resulting SDS values will be rounded to two digits.

To derive reference values for age groups in between the age groups reported in literature, the original tables were extended by linear interpolation between the reported values for mean and standard deviation. Standardization of a patient's HV between two successive visits will be based not on the patient's chronological age at the time of the second of the two visits, but on the mean of the chronological ages at the two visits. Means and standard deviations of normally growing children will be taken from tables provided by Prader (1989). To derive reference values for age groups in between the age groups reported by Prader (1989), the original tables

were extended by linear interpolation between the reported values for mean and standard deviation (Appendix A). To derive references values for patients older than the provided age groups the reference for the maximal age will be used (for H and HV).

In order to derive individual HV SDS values, two methods of HV standardization will be used. The two alternative methods used for standardization:

- cross sectional = HV $SDS_{CS}$,
- peak centered, HV $SDS_{PC}$,

differ only regarding the reference tables used to look up values for means and standard deviations (reference values) for the standardization.

### HV $SDS_{CS}$

Individual values for HV $SDS_{CS}$ are calculated using reference values from Table 1 (for boys) or Table 2 (for girls), both given in Appendix D. Each of these tables was derived by tables provided by Prader (1989). For a description of the performed combinations and extensions please refer to the foot note below the attached tables. The abbreviation "CS" in HV $SDS_{CS}$ stands for "cross sectional", meaning that tabled reference values for specific age groups directly correspond to means and standard deviations for HV as observed in the referenced longitudinal study. Averages and variability are estimated for each age group from raw data, not taking into account any information regarding the individual onset or peak of pubertal growth spurt.

### HV $SDS_{PC}$

Individual values for HV $SDS_{PC}$ are calculated using reference values from the tables given in Appendix D. These HV references were obtained for each sex at the end of the referenced longitudinal study, aligning individual velocity curves on mean age of peak height velocity. The abbreviation "PC" in HV $SDS_{PC}$ stands for "peak centered".

Mean time-trends of these four efficacy endpoints will be illustrated graphically.

All four endpoints will be summarized by visit overall and stratified by sex and initially treatment.. In addition, 95% confidence intervals will be calculated for the mean difference between the baseline visit and all later visits, respectively.

#### 4.6.1.1 IGF-1 and IGFBP-3 serum levels

Blood samples for the determination of IGF-1 and IGFBP-3 serum levels will be drawn at baseline, at 3, 6, 9, 12, 18, and 24 months, then every 6 months during treatment, and at the end of treatment. Serum levels as well as ratios of IGF-1 and IGFBP-3 will be assessed by a central laboratory.

Data regarding secondary efficacy parameters will be summarized by visit overall and stratified by sex and initially treatment. In summary tables by visit overall confidence limit for means will be provided. Time trends of means will be presented graphically for all patients only by sex. In addition, 95% confidence intervals will be calculated for the mean difference between the baseline visit and all later visits, respectively. Relative changes from baseline of IGF-1 and IGFBP-3 will be summarized by visit.

Shift tables for changes in the reference range classification will be provided for IGF-1 and IGFBP-3. Shift tables will be prepared for the two formulations separately. In these tables baseline data will be presented in rows and data from the visits at 6, 12, 18, and 24 months will be cross-tabulated in columns. The categories "low"(< lower limit of normal), "normal", "high" (>upper limit of normal) and "missing" will be used in the shift tables. Shifts between categories will be displayed using absolute counts.

IGF-1, IGFBP-3 and ratio will be expressed in SDS. SDS reflects the deviation of a measured value from the mean value of healthy children of the same sex and chronological age, expressed in units of the standard deviation of unexposed children of the same sex and chronological age.

Standardization of patients' IGF-1, IGFBP-3 and ratio will be performed according to Elmlinger (2004). SDS values will be assessed according to the following formulas: SDS = (X1-X2)/((X2-X3)/2) if X1 < X2 and SDS = (X1-X2)/((X4-X2)/2) if X1 ≥ X2, where X1 means the measured value, X2 the mean value for the relevant chronological age and sex, X3 the –2 SD value for the relevant chronological age and sex, and X4 the +2 SD value for the relevant chronological age and sex according to Elmlinger (2004).

Mean, -2 SD, and +2 SD values given by Elmlinger (2004) are provided for age intervals. These values were used as references for patients with an age equal to the mid of this age interval. For patients with an age between two mids of age intervals, mean, -2 SD, and +2 SD values will be interpolated.

SDS values of secondary efficacy parameters will be summarized by visit overall and stratified by sex and initially treatment. In summary tables by visit overall confidence limit for means will be provided. Time trends of means will be presented graphically for all patients only. In addition, 95% confidence intervals will be calculated for the mean difference between the baseline visit and all later visits, respectively.

#### 4.6.1.2 Additional efficacy endpoints

In addition to the endpoints described in 0 and 4.6.1.1, [redacted] height age will be derived in the analysis.

[redacted]

For the determination of height age (HA), body height recordings from the baseline and then yearly during treatment period will be compared to mean heights given in the extended reference tables for height (Appendix A). HA will be derived by taking that age from the reference table for which the observed height is the same as the average height in normally growing children.

[redacted]

To assign one height age value to a given height using the respective reference table, the following rule was applied: If the height assessment was between two height assessments in the reference table, the lower age is used, if the height assessment was lower or equal to half of the distance. Otherwise the upper age will be used (i.e. if higher than half of the distance between lower and upper height).

[redacted], HA and CA will be summarized by visit overall and stratified by sex and initially treatment. In addition 95% confidence intervals will be calculated for the mean difference between baseline visit and all later visits, respectively.

The progresses in CA, [redacted] and HA will be compared by deriving the means of the following ratios: [redacted]/ΔCA, ΔHA/ΔCA and ΔHA/[redacted]. To derive individual ratios corresponding to changes ΔCA, [redacted] and ΔHA will be calculated as the difference in CA, [redacted] and HA between the baseline visit and the annual visits under treatment. Calculated ratios will be summarized by visit overall and stratified by sex and initial treatment. Performing one-sample t-tests, it will be evaluated whether mean ratios differ significantly from the theoretical value of 1.0.

### 4.6.2 Safety evaluation

All tables, figures and listings in this section will be presented for the SAF analysis set.

#### 4.6.2.1 Adverse events

Adverse events (AEs) are to be recorded during the whole study period.

AEs are coded according to Novartis MedDRA, Version 24.1.

The AE data will be listed, sorted by site code, patient number, and preferred term. This list will include: adverse event, MedDRA system organ class, MedDRA preferred term, start date, stop date, intensity, outcome, relationship to study drug, action taken, and a variable indicating whether an AE was considered a serious adverse event (SAE).

AEs starting prior to start of treatment will not be included in the summary tables, but listed only.

A general summary table of AEs will contain the total number of AEs, the total number of SAEs, and separate descriptions of the splits for the variables relationship to study drug, action taken,

outcome and intensity. Outcome is categorized according to the CRF as “resolved” (i.e. resolved completely or resolved with sequelae), “ongoing”, “fatal” or “unknown”.

The incidence of an AE is defined as the number of patients who experience that event, divided by the number of patients in the SAF population. With AE incidence, each event will be counted only once for a given patient. More specifically, if a patient reports the same event more than once, as determined by preferred term and system organ class, that patient will be counted only once for the incidence of the AE. For example, when a patient reported three instances of headache, this patient counts only once towards the total incidence of headache. Incidence of events within a system organ class is defined similarly. Whenever incidence is cross-tabulated with intensity in the summary tables, the incidence of an AE will be calculated for each level of intensity, i.e., the number of patients who experience that AE on a certain level of intensity.

Incidence tables will provide information about rates of AEs per patient-year, calculated as {(number of patients who experience that event) / (years of exposure)}. Additional tables will enable a direct comparison of formulation specific rates of events per patient year.

The occurrence of an AE is defined as the total number of times the event occurs in the SAF population. With AE occurrence, a patient may contribute more than once to the total occurrence count. More specifically, if a patient reports a particular event, as determined by preferred term and system organ class (and having removed duplicate reporting of the same event, as described above) more than once, each event will count once towards the total event occurrence. Using the above example, headache would be counted three times for the patient who reported three separate occurrences of headache.

Occurrence tables will provide information about rates of AEs per patient-year, calculated as {(number of events) / (years of exposure)}. Additional tables will enable a direct comparison of formulation specific rates of events per patient year.

The incidence and occurrence of each AE will be reported by MedDRA system organ class and preferred term, cross-tabulated with the intensity, action taken, and outcome. Additionally, total incidence and occurrence will be provided for each system organ class.

The whole set of AE summary tables will be produced for all AEs and separately for adverse drug reactions (ADR), serious AEs and serious ADRs. Adverse events will be considered as adverse drug reactions if a causal relationship to the study drug is suspected by the investigator.

For the Final CSR and registry purposes a summary of non-serious AEs by SOC, PT and intensity is required in addition.

AEs of special interest are defined as intracranial haemorrhage and intracranial aneurysm and possible drug interaction with sex steroids, corticosteroids, anticonvulsants and cyclosporine.

#### 4.6.2.2 Carbohydrate metabolism

Fasting plasma glucose, insulin levels and glycosylated hemoglobin ($HbA_{1C}$) are measured at baseline (start of treatment), at 6 and 12 months, then annually during GH treatment, and at the end of treatment. An OGTT is performed at the same time points.

The OGTT is a provocation test to examine the efficiency of the body to metabolize glucose. The OGTT provides information on latent diabetes states.

Insulin resistance will be estimated using both the homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI)

$$\text{HOMA} = \frac{\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mg/dl)}}{405*}$$

*use constant 22.5 instead of 405 if glucose concentration is reported in mmol/L

$$\text{QUICKI} = \frac{1}{\log \text{fasting insulin } (\mu\text{U/ml}) + \log \text{fasting glucose (mg/dl)}}$$

Carbohydrate metabolism data will be listed per parameter and will include: visit, sample date, parameter result, reference range, outside reference range indicator, clinical significance and a column containing comments.

Carbohydrate metabolism data as well as HOMA and QUICKI scores will be summarized by parameters and visit for the SAF for absolute values, and absolute and relative changes from baseline.

Shift tables for changes in the reference range classification as compared to baseline will be prepared for fasting plasma glucose, fasting insulin levels and $HbA_{1C}$. The categories "low", "normal", "high" and "Missing" will be used in the shift tables. Shifts between categories will be displayed using absolute counts. Percentages will be provided per baseline category (without considering missings) for each post-baseline category, and based on all non-missing patients for total line/column.

In addition number and percentage of patients with DM and without DM finding will be presented. Patients fulfilling any criteria for DM given in section 4.5 will be regarded as patients with DM, patients not fulfilling any criteria on at least one visit will be considered as patients without DM finding.

Implausible insulin or glucose values will be excluded, i.e. Glucose values below 0.1 mmol/L and insulin values below 0.1 pmol/L will not be used for the calculation of HOMA and QUICKI.

#### 4.6.2.3 Vital signs

Vital signs are collected at all visits.

The vital signs data include: date of examination, systolic blood pressure, diastolic blood pressure and pulse rate.

These data will be summarized by parameters and visit.

#### 4.6.2.4 Physical examination

A thorough physical examination is performed at all visits.
The frequency of normal and abnormal evaluations and parameters not evaluated will be summarized for each physical examination system by visit. Shift table for normal / abnormal findings will be presented by body system for each visit versus baseline. The specification for other body systems will be reviewed by the sponsor. If this review identified that the entry does not belong to an other body system but to a body system already given in the CRF, the entry will be considered for the existing body system.

Weight, BMI and BMI SDS will be summarized by visit for the SAF. For details regarding BMI SDS calculation see Appendix C.

#### 4.6.2.5 Conversion factors for laboratory parameters

In order to harmonize laboratory results by using the same units, some laboratory results will be converted. Corresponding conversion factors will be displayed in a table.

All glucose values will be converted to values given in mmol/l (if possible). To omit problems in assessment of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) caused by this conversion all the converted glucose values will be rounded to one digit before assessing IGT and IFG.

If albumin is given in %, the respective values will be converted to g/l using total protein values.

#### 4.6.2.6 Hematology

Hematology data are collected at baseline (start of treatment), at 6 and 12 months, then annually during GH treatment, and at the end of treatment.

Hematology data include: visit, sample date, parameter result, reference range, outside reference range indicator, clinical significance and a column containing comments. The parameters included in the hematology data are: hemoglobin, hematocrit, white blood cell count (total and differential) (WBC), red blood cell count (RBC), platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), erythrocyte sedimentation rate (ESR).

Hematology data will be summarized by parameters and visit.

#### 4.6.2.7 Blood chemistry

Blood chemistry data are measured at baseline (start of treatment), at 6 and 12 months, then annually during GH treatment, and at the end of treatment.

Blood chemistry data include: visit, sample date, parameter result, reference range, outside reference range indicator, clinical significance and a column containing comments. The blood chemistry parameters are creatinine, urea, aspartate aminotransferase (SGOT/AST), alanine aminotransferase (SGPT/ALT), gamma-glutamyltransferase (gamma-GT), alkaline phosphatase, total bilirubin, albumin, total protein, HDL, LDL, sodium, potassium, chloride, uric acid, total cholesterol, triglycerides, calcium, phosphorus.

Blood chemistry will be summarized by parameters and visit for the SAF. Thyroid panel

Thyroid panel data are will be measured at baseline (start of treatment), at 6 and 12 months, then annually during GH treatment, and at the end of treatment.

Thyroid panel data include: visit, sample date, parameter result, reference range, outside reference range indicator, clinical significance and a column containing comments. The thyroid panel parameters are free thyroxine (fT4) and thyroid stimulating hormone (TSH).

Thyroid panel data will be summarized by parameters and visit.

Shift tables for changes in the reference range classification as compared to baseline will be provided for each parameter. The categories "low", "normal", "high" and "Missing" will be used in the shift tables. Shifts between categories will be displayed using absolute counts. Percentages will be provided per baseline category (without considering missings) for each post-baseline category, and based on all non-missing patients for total line/column.

#### 4.6.2.8 Urinalysis

Urinalysis data are collected at baseline (start of treatment), at 6 and 12 months, then annually during GH treatment, and at the end of treatment.

The urinalysis data include: visit, sample date, parameter result, clinical significance and a column containing comments. The parameters included in the urinalysis data are pH, glucose, ketones, bilirubin, protein.

Ph values will be summarized by visit.

All remaining urinalysis parameters will be presented as shift tables comparing baseline to post-baseline values. The categories "+", "++", "+++", “++++” and "Missing" will be used in the shift tables. Shifts between categories will be displayed using absolute counts. Percentages will be provided per baseline category (without considering missings) for each post-baseline category, and based on all non-missing patients for total line/column.

### 4.6.3 Immunogenicity

All patients with a positive ADA result at any time during the study will be listed individually.

Tests for anti-rhGH antibodies were performed at baseline, at 3, 6, 9, 12 18 and 24 months, then annually during Omnitrope treatment and the end of treatment. As per protocol amendment 3, the anti HCP testing should be stopped after the amendment became effective in the respective country. Therefore, all HCP results since V01 will be presented up to the Visits occurred until the amendment 3 became effective. Number and percentage of patients with positive test for anti-hGH antibodies and anti-HCP antibodies will be provided by visit and overall (for anti-HCP antibodies).

In addition summary tables and figures for H SDS and HV SDS will be presented for patients with and without positive anti-rhGH antibody test.

## 4.7 Handling of missing data in the analyses

IGF-1 and IGFBP-3 serum levels which are found to be below the level of detection will be imputed as one-half of the lower limit of detection for the corresponding analysis.

If for any laboratory parameter (hematology, blood chemistry, thyroid) a < or > sign is documented, this sign will be listed only. For calculation of summary tables, the respective value without sign will be used. If it is not possible to assess, whether the laboratory value is lower, inside, or higher the normal range, although laboratory value and normal range are given (e.g. lower range > upper range; < and > signs used), the respective value will be assessed as missing in the shift table.

To enable calculation of time differences, partial dates will be completed: missing day is set to the 15th and missing month set to June, if no remaining dates are available.

For safety or other efficacy parameters, missing values will not be imputed.

## 4.8 Analyses during an ongoing study

According to the protocol three interim analyses were planned at the following time points:

- Q4/2011 with data of patients who completed 1 year of treatment
- Q4/2012 with data of patients who completed 2 years of treatment
- Q4/2020 with data of patients who finished treatment

The first two interim analyses were performed as planned including data on 278 treated patients. In the first interim analysis all information regarding the first year of treatment was included that was available on 19-Oct-2011; in the second interim analysis all information regarding the first two years of treatment were summarized based on data cut-off 20-Mar-2013. The third interim analysis was anticipated for Q4 2020 (with data of patients who finished treatment) and to be submitted as per the current RMP version 11 by 2021. However, Sandoz reached out to EMA in Aug-2021 with submitting PAM to provide the study status and ask for final report submission in 2022 EMEA/H/C/000607/MEA/010.3).

This SAP describes the analyses planned for the final analysis that will be performed when all patients have discontinued/completed the study.

# 5 Tables, listings and figures

## 5.1 Demographic Tables including shells

**TABLE 14.1-1 ANALYSIS SETS**

| | Study Population (N=XXX) | |
|---|---|---|
| | n | % |
| Patients eligible for treatment | XXX | |
| Full Analysis Set | XXX | (XXX%) |
| Safety Analysis Set | XXX | (XX.X%) |

Percentages are based on all patients in Full Analysis Set.

**TABLE 14.1-2 PATIENT ENROLMENT**

| | Number of patients* | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Site code | SCR | V01 M0 | V02 M3 | V03 M6 | V04 M9 | V05 M12 | V06 M15 | V07 M18 | V08 M21 | V09 M24 | V10 M30 | V11 M36 | … |
| XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX |
| XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX |
| … | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX |
| Total | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX |

* for whom the respective visit was documented or the final visit was assigned to the respective visit

Note: One patient had only V01 performed, received study medication and was lost to follow-up thereafter. This patient was excluded from the SAF since no information with respect to safety is available.

## TABLE 14.1-3 SUMMARY OF REASONS FOR STUDY DISCONTINUATION (FAS)

| | Number of patients (%)<br>(N=XXX) |
|---|---|
| Study terminated | XXX (XX.X%) |
| Study discontinuations due to | |
| Withdrawal of informed consent | XXX (XX.X%) |
| Treatment failure | XXX (XX.X%) |
| Lost to follow-up | XXX (XX.X%) |
| Other | XXX (XX.X%) |
| Adverse event | XXX (XX.X%) |
| … | |
| Total | XXX (XX.X%) |

Note for programmer:
Sort reasons by frequency.

## TABLE 14.1-4 SUMMARY OF PATIENTS EXPOSURE TO STUDY DRUG (FAS)

| | Exposure to study drug [years] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Missing | Mean | SD | Min | Q1 | Median | Q3 | Max |
| Total | XXX | XXX | XX.X | XX.X | XX | XX.X | XX.X | XX.X | XX.X |
| Site code | | | | | | | | | |
| XXX | XXX | XXX | XX.X | XX.X | XX | XX.X | XX.X | XX.X | XX.X |
| XXX | XXX | XXX | XX.X | XX.X | XX | XX.X | XX.X | XX.X | XX.X |
| … | XXX | XXX | XX.X | XX.X | XX | XX.X | XX.X | XX.X | XX.X |

## TABLE 14.1-5 SUMMARY OF TOTAL DAILY DOSE ADMINISTERED PER KG BODY WEIGHT (FAS)

| | Total daily dose administered [mg/kg] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Missing** | **Mean** | **SD** | **Min** | **Q1** | **Median** | **Q3** | **Max** |
| Visit | | | | | | | | | |
| XXX | XXX | XXX | XX.X | XX.X | XX | XX.X | XX.X | XX.X | XX.X |
| XXX | XXX | XXX | XX.X | XX.X | XX | XX.X | XX.X | XX.X | XX.X |
| ... | XXX | XXX | XX.X | XX.X | XX | XX.X | XX.X | XX.X | XX.X |

## TABLE 14.1-6 SUMMARY OF REASONS FOR DOSE CHANGES (FAS)

| | Number of patients (%) (N=XXX) |
|---|---|
| **Overall** | |
| Any dose change documented | XXX (XX.X%) |
| Reason for dose change | |
| Patient is unable to tolerate the protocol-specified dosing scheme | XXX (XX.X%) |
| Reason documented 1 time | XXX (XX.X%) |
| Reason documented 2 times | XXX (XX.X%) |
| … | XXX (XX.X%) |
| Dose interruption | XXX (XX.X%) |
| Reason documented 1 time | XXX (XX.X%) |
| Reason documented 2 times | XXX (XX.X%) |
| … | XXX (XX.X%) |
| IGF-1/IGFBP-3 ratio exceeds +2SD | XXX (XX.X%) |
| Reason documented 1 time | XXX (XX.X%) |
| Reason documented 2 times | XXX (XX.X%) |
| … | XXX (XX.X%) |
| Non-compliance | XXX (XX.X%) |
| Reason documented 1 time | XXX (XX.X%) |
| Reason documented 2 times | XXX (XX.X%) |
| … | XXX (XX.X%) |
| Other | XXX (XX.X%) |
| Reason documented 1 time | XXX (XX.X%) |
| Reason documented 2 times | XXX (XX.X%) |
| … | XXX (XX.X%) |
| … | XXX (XX.X%) |

Note for programmer:
Classification of other variable will be provided by the sponsor.

## TABLE 14.1-7 SUMMARY OF SEX AND ETHNIC ORIGIN (FAS)

| Characteristic | Number of patients (%) |
|---|---|
| Sex | |
| Male | XXX (XX.X%) |
| Female | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Initial treatment | |
| Solution | XXX (XX.X%) |
| Powder | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Sex by initial treatment | |
| Solution | |
| Male | XXX (XX.X%) |
| Female | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Powder | |
| Male | XXX (XX.X%) |
| Female | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Ethnic origin | |
| Caucasian | XXX (XX.X%) |
| Oriental | XXX (XX.X%) |
| Other | XXX (XX.X%) |
| Black | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Ethnic origin by initial treatment | |
| Solution | |
| Caucasian | XXX (XX.X%) |
| Oriental | XXX (XX.X%) |
| Other | XXX (XX.X%) |
| Black | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Powder | |
| Caucasian | XXX (XX.X%) |
| Black | XXX (XX.X%) |
| Oriental | XXX (XX.X%) |
| Other | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Ethnic origin by sex | |
| Male | |
| Caucasian | XXX (XX.X%) |
| Oriental | XXX (XX.X%) |
| Black | XXX (XX.X%) |

| Characteristic | Number of patients (%) |
|---|---|
| Other | XXX (XX.X%) |
| Total | XXX (XX.X%) |
| Female | |
| Caucasian | XXX (XX.X%) |
| Other | XXX (XX.X%) |
| Black | XXX (XX.X%) |
| Oriental | XXX (XX.X%) |
| Total | XXX (XX.X%) |

## TABLE 14.1-8 SUMMARY OF DEMOGRAPHIC CHARACTERISTICS (FAS)

| Characteristic | | Total | Female | Male |
|---|---|---|---|---|
| Age at screening (years)* | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| Age at screening (years)* for patients with initial powder treatment | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| Age at screening (years)* for patients with initial solution treatment | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| Height SDS at screening | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| Height at screening (cm) | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |

| Characteristic | | Total | Female | Male |
|---|---|---|---|---|
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| Height velocity SDS at screening | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| Height velocity at screening (cm/yr) | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| Weight at screening (kg) | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |
| BMI at screening | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |

| Characteristic | | Total | Female | Male |
|---|---|---|---|---|
| | Max | X.X | X.X | X.X |
| BMI SDS at screening | N | XXX | XXX | XXX |
| | Mean | X.XX | X.XX | X.XX |
| | Std | X.XX | X.XX | X.XX |
| | Min | X.X | X.X | X.X |
| | Q1 | X.XX | X.XX | X.XX |
| | Median | X.XX | X.XX | X.XX |
| | Q3 | X.XX | X.XX | X.XX |
| | Max | X.X | X.X | X.X |

* calculated in whole years from visit date when demography data was collected

## TABLE 14.1-9 SUMMARY OF PUBERTAL STATUS (FAS)

| | | | | | Number of patients (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sex** | **Visit** | **Total** | **Missing** | **N** | **Tanner I** | **Tanner II** | **Tanner III** | **Tanner IV** | **Tanner V** |
| Male | SCR | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) |
| | V01 | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) |
| | … | | | | | | | | |
| Female | SCR | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) |
| | V01 | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) |
| | … | | | | | | | | |
| Total | SCR | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) |
| | V01 | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) |
| | … | | | | | | | | |

## TABLE 14.1-10 SUMMARY OF PATIENTS BIRTH HISTORY (FAS)

| | | N | Missing | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| Birth Weight (g) | Males | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Birth Length (cm) | Males | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Gestational Age (weeks) | Males | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Birth Weight SDS | Males | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Birth Length SDS | Males | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |

**TABLE 14.1-11 SUMMARY OF PARENTS HEIGHT (FAS)**

| | | N | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|
| Father's height (cm) | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Mother's height (cm) | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |

## TABLE 14.1-12 SUMMARY OF BASELINE VALUES OF HEIGHT MEASUREMENTS (FAS)

| | | N | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|
| Height (cm) | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Height SDS | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Height Velocity (cm/yr) | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Height Velocity SDS | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Time since historical measurement (days) | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| Midparental adjusted Height SDS | Males | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Females | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Powder | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Solution | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |
| | Total | XX | XXX.X | XX.X | XXX.X | XXX.X | XXX.X | XXX.X | XXX.X |

## TABLE 14.1-13 SUMMARY OF MEDICAL HISTORY (FAS)

| Novartis MedDRA version<br>System Organ Class<br>Preferred Term | Number of patients (%) with resolved illness (N=XXX) | Number of patients (%) with intermittent illness (N=XXX) | Number of patients (%) with ongoing illness (N=XXX) |
|---|---|---|---|
| Total | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) |
| Infections and infestations | | | |
| Total | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) |
| Pneumonia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) |
| Varicella | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) |
| Bronchitis | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) |
| …. | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) |

Note for programmer:
Sort by overall frequency.

## TABLE 14.1-14 SUMMARY OF CONCOMITANT MEDICATIONS BY ATC TERM (FAS)

## TABLE 14.1-15 SUMMARY OF PRIOR MEDICATIONS BY ATC TERM (FAS)

| Concomitant Medication<br>ATC Code Level 2<br>Preferred Term | Number of patients (%) to whom medication was administered (N=XXX) |
|---|---|
| TOTAL | XX (XX.X%) |
| ANTIBACTERIALS FOR SYSTEMIC USE | XX (XX.X%) |
| Cefuroxime Axetil | XX (XX.X%) |
| Clarithromycin | XX (XX.X%) |
| Amoxicillin W/Clavulanate Potassium | XX (XX.X%) |
| Amoxicillin | XX (XX.X%) |
| Azithromycin | XX (XX.X%) |
| Bactrim | XX (XX.X%) |
| Amoxi-Clavulanico | XX (XX.X%) |
| …. | XX (XX.X%) |

Note for programmer:
Sort by overall frequency.

## TABLE 14.1-16 SUMMARY OF PROTOCOL DEVIATION (FAS)

| Category<br>Protocol deviation | All Patients (N=XXX)<br>n(%) |
|---|---|
| Any protocol deviation | XX (XX.X%) |
| Protocol deviation regarding | |
| Inclusion/exclusion criteria | XX (XX.X%) |
| INCL 1 not met: …. | XX (XX.X%) |
| … | |
| Withdrawal criteria met, but patient not discontinued | XX (XX.X%) |
| Failure to perform key procedures | XX (XX.X%) |
| Missing visit | XX (XX.X%) |
| Deviations from protocol specified window | XX (XX.X%) |
| Key asssessments not performed: other lab parameters | XX (XX.X%) |
| … | |
| Trial treatment deviation | XX (XX.X%) |
| Prohibited concomitant medication | XX (XX.X%) |
| GCP-related deviation | XX (XX.X%) |
| Re-consent ICF missing | XX (XX.X%) |
| Re-consent ICF not appropriately obtained | XX (XX.X%) |
| … | |

Note for programmer: Provide only available categories. s available. Sort by descending frequency.
Use Sandoz main category and PD description (based on PD ID) according to PD specification for categories.

**Table 14.1-17 Actual number of patients enrolled in the study by age category (Full Analysis set)**

| Age (years) | Number of patients (%) (N=XXX) |
|---|---|
| 0-<4y | XX (XX.X%) |
| 4y- <12y | XX (XX.X%) |
| 12y-<18y | XX (XX.X%) |
| >=18y | XX (XX.X%) |

**Table 14.1-18 Actual number of patients enrolled in the study by country (Full Analysis set)**

| Country | Number of patients (%) (N=XXX) |
|---|---|
| Germany | XX (XX.X%) |
| Italy | XX (XX.X%) |
| ..... | XX (XX.X%) |

## 5.2 Efficacy and other non-safety Tables including shells

**TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS)**

| Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|
| V01 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| V03 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| V05 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| … | | | | | | | | | |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit. Please add confidence interval for means here.

**TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)**

| Visit | by | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| V01 | Males | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| | Females | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| V02 | Males | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| | Females | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| .. | Males | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| | Females | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

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Programming note: Please add confidence interval for means here.

**TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)**

| Visit | by | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| V01 | Powder | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| | Solution | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| V02 | Powder | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| | Solution | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| .. | Powder | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |
| | Solution | XX | XX | XXX.X | XX.X | XXX | XXX.X | XXX.X | XXX.X | XXX |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS)**

| Difference between visits | N | Mean difference (cm) | 95% confidence interval for mean difference |
|---|---|---|---|
| V02 - V01 | XX | XX.XX | [ XX.XX; XX.XX ] |
| V03 - V01 | XX | XX.XX | [ XX.XX; XX.XX ] |
| .. - V01 | XX | XX.XX | [ XX.XX; XX.XX ] |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)**

| Difference between visits | by | N | Mean difference (cm) | 95% confidence interval for mean difference |
|---|---|---|---|---|
| V02 - V01 | Males | XX | XX.XX | [ XX.XX; XX.XX ] |
| | Females | XX | XX.XX | [ XX.XX; XX.XX ] |
| V03 - V01 | Males | XX | XX.XX | [ XX.XX; XX.XX ] |
| | Females | XX | XX.XX | [ XX.XX; XX.XX ] |
| .. - V01 | Males | XX | XX.XX | [ XX.XX; XX.XX ] |
| | Females | XX | XX.XX | [ XX.XX; XX.XX ] |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)**

| Difference between visits | by | N | Mean difference (cm) | 95% confidence interval for mean difference |
|---|---|---|---|---|
| V02 - V01 | Powder | XX | XX.XX | [ XX.XX; XX.XX ] |
| | Solution | XX | XX.XX | [ XX.XX; XX.XX ] |
| V03 - V01 | Powder | XX | XX.XX | [ XX.XX; XX.XX ] |
| | Solution | XX | XX.XX | [ XX.XX; XX.XX ] |
| .. - V01 | Powder | XX | XX.XX | [ XX.XX; XX.XX ] |
| | Solution | XX | XX.XX | [ XX.XX; XX.XX ] |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-1.3.1 SUMMARY OF HEIGHT STANDARD DEVIATION SCORE (HSDS) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-1.3.2 SUMMARY OF HSDS BY VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.3.3 SUMMARY OF HSDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.3.4 SUMMARY OF HSDS BY COMPLETERS, TOTAL, AND VISIT FOR PATIENTS WITH AND WITHOUT POSITIVE ANTI-RHGH ANTIBODIES (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Present patient with and without positive anti-rhGH antibodies instead of sex. Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.4.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HSDS BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.4.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HSDS BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-1.4.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HSDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.5.1 SUMMARY OF HEIGHT VELOCITY (HV) BY COMPLETERS, TOTAL AND VISIT (FAS)**

| Visit | Basis | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| 01 | historical data | XX | XX | XX.XX | X.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| 02 | visit 01 | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| .. | visit 01 | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit. Please add confidence interval for means here.

**TABLE 14.2-1.5.2 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)**

| Visit | Basis | by | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| V01 | historical data | Males | XX | XX | XX.XX | X.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| V02 | V01 | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| .. | V01 | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit. Please add confidence interval for means here.

**TABLE 14.2-1.5.3 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)**

| Visit | Basis | by | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| V01 | historical data | Powder | XX | XX | XX.XX | X.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| V02 | V01 | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| .. | V01 | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.6.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV BY COMPLETERS, TOTAL AND VISIT (FAS)**

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.6.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)**

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.6.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV BY COMPLETERS, TOTAL ANDVISIT AND INITIAL TREATMENT (FAS)**

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-1.7.1 SUMMARY OF HV SDS (CS) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.5.1 SUMMARY OF HEIGHT VELOCITY (HV) BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-1.7.2 SUMMARY OF HV SDS (CS) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.5.2 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.7.3 SUMMARY OF HV SDS (CS) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.5.3 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.7.4 SUMMARY OF HV SDS (CS) BY COMPLETERS, TOTAL, AND VISIT FOR PATIENTS WITH AND WITHOUT POSITIVE ANTI-RHGH ANTIBODIES (FAS)

See shell for TABLE 14.2-1.5.2 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

Programming note: Present patient with and without positive anti-rhGH antibodies instead of sex. Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.8.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV SDS (CS) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.8.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV SDS (CS) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-1.8.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV SDS (CS) BY, COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-1.9.1 SUMMARY OF HV SDS (PC) BY COMPLETERS, TOTAL AND VISIT (FAS)**

See shell for TABLE 14.2-1.5.1 SUMMARY OF HEIGHT VELOCITY (HV) BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

**TABLE 14.2-1.9.2 SUMMARY OF HV SDS (PC) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)**

See shell for TABLE 14.2-1.5.2 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

**TABLE 14.2-1.9.3 SUMMARY OF HV SDS (PC) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)**

See shell for TABLE 14.2-1.5.3 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

**TABLE 14.2-1.9.4 SUMMARY OF HV SDS (PC) BY COMPLETERS, TOTAL, AND VISIT FOR PATIENTS WITH AND WITHOUT POSITIVE ANTI-RHGH ANTIBODIES (FAS)**

See shell for TABLE 14.2-1.5.2 SUMMARY OF HV BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

Programming note: Present patient with and without positive anti-rhGH antibodies instead of sex. Please add one column 'Status' (value: Completers, Total) before column Visit.

**TABLE 14.2-1.10.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV SDS (PC) BY COMPLETERS, TOTAL AND VISIT (FAS)**

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

**TABLE 14.2-1.10.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV SDS (PC) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)**

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-1.10.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HV SDS (PC) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.1.1 SUMMARY OF IGF-1 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-2.1.2 SUMMARY OF IGF-1 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-2.1.3 SUMMARY OF IGF-1 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.1.4 SUMMARY OF RELATIVE CHANGE FROM BASELINE OF IGF-1 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-2.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-2.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-2.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-2.3.1 SUMMARY OF IGFBP-3 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-2.3.2 SUMMARY OF IGFBP-3 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-2.3.3 SUMMARY OF IGFBP-3 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.3.4 SUMMARY OF RELATIVE CHANGE FROM BASELINE OF IGFBP-3 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.4.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGFBP-3 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.4.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGFBP-3 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

**TABLE 14.2-2.4.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGFBP-3 SERUM LEVELS (NMOL/L) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)**

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

### TABLE 14.2-2.5 SHIFT TABLE FOR IGF-1 BY COMPLETERS AND TOTAL (FAS)

Programming note: Please add one column 'Status' (value: Completers, Total) before column Comparison.

### TABLE 14.2-2.6 SHIFT TABLE FOR IGFBP-3 BY COMPLETERS AND TOTAL (FAS)

Programming note: Please add one column 'Status' (value: Completers, Total) before column Comparison.

### TABLE 14.2-2.7 SHIFT TABLE FOR IGF-1 IN PATIENTS WITH POWDER TREATMENT BY COMPLETERS AND TOTAL (FAS)

Programming note: Please add one column 'Status' (value: Completers, Total) before column Comparison.

### TABLE 14.2.2.8 SHIFT TABLE FOR IGFBP-3 IN PATIENTS WITH POWDER TREATMENT BY COMPLETERS AND TOTAL (FAS)

Programming note: Please add one column 'Status' (value: Completers, Total) before column Comparison.

### TABLE 14.2-2.9 SHIFT TABLE FOR IGF-1 IN PATIENTS WITH SOLUTION TREATMENT BY COMPLETERS AND TOTAL (FAS)

Programming note: Please add one column 'Status' (value: Completers, Total) before column Comparison.

### TABLE 14.2.2.10 SHIFT TABLE FOR IGFBP-3 IN PATIENTS WITH SOLUTION TREATMENT BY COMPLETERS AND TOTAL (FAS)

| Comparison (Compared vs Baseline) | Baseline | Compared Visit | | | | |
|---|---|---|---|---|---|---|
| | | Low | Normal | High | Missing | Total |
| V02 vs V01 | Low | XX | XX | XX | XX | XX |
| | Normal | XX | XX | XX | XX | XX |
| | High | XX | XX | XX | XX | XX |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX | XX | XX | XX | XX |

| Comparison (Compared vs Baseline) | Baseline | Compared Visit | | | | |
|---|---|---|---|---|---|---|
| | | Low | Normal | High | Missing | Total |
| V03 vs V02 | Low | XX | XX | XX | XX | XX |
| | Normal | XX | XX | XX | XX | XX |
| | High | XX | XX | XX | XX | XX |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX | XX | XX | XX | XX |
| V.. vs V.. | Low | XX | XX | XX | XX | XX |
| | Normal | XX | XX | XX | XX | XX |
| | High | XX | XX | XX | XX | XX |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX | XX | XX | XX | XX |

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Comparison.

### TABLE 14.2-2.11.1 SUMMARY OF IGF-1/IGFBP-3 RATIO (NG/MCG) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit

### TABLE 14.2-2.11.2 SUMMARY OF IGF-1/IGFBP-3 RATIO (NG/MCG) BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit

### TABLE 14.2-2.11.3 SUMMARY OF IGF-1/IGFBP-3 RATIO (NG/MCG) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.12.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1/IGFBP-3 RATIO (NG/MCG) BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.12.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1/IGFBP-3 RATIO (NG/MCG) BY VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.12.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1/IGFBP-3 RATIO (NG/MCG) BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.13.1 SUMMARY OF IGF-1 SDS BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-2.13.2 SUMMARY OF IGF-1 SDS BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.13.3 SUMMARY OF IGF-1 SDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.14.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1 SDS BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.14.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1 SDS BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.14.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1 SDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.15.1 SUMMARY OF IGFBP-3 SDS BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit. Please add confidence interval for means here.

### TABLE 14.2-2.15.2 SUMMARY OF IGFBP-3 SDS BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.15.3 SUMMARY OF IGFBP-3 SDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.16.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGFBP-3 SDS BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.16.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGFBP-3 SDS BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.16.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGFBP-3 SDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.17.1 SUMMARY OF IGF-1/IGFBP-3 RATIO SDS BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.1.1 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.17.2 SUMMARY OF IGF-1/IGFBP-3 RATIO SDS BY COMPLETERS, TOTAL AND VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.1.2 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.17.3 SUMMARY OF IGF-1/IGFBP-3 RATIO SDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.1.3 SUMMARY OF HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.18.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1/IGFBP-3 RATIO SDS BY COMPLETERS, TOTAL AND VISIT (FAS)

See shell for TABLE 14.2-1.2.1 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL AND VISIT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.18.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1/IGFBP-3 RATIO SDS BY COMPLETERS, TOTAL, VISIT AND SEX (FAS)

See shell for TABLE 14.2-1.2.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND SEX (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-2.18.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN IGF-1/IGFBP-3 RATIO SDS BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS)

See shell for TABLE 14.2-1.2.3 ANALYSIS OF MEAN CHANGE FROM BASELINE IN HEIGHT BY COMPLETERS, TOTAL, VISIT AND INITIAL TREATMENT (FAS).

Programming note: Please add one column 'Status' (value: Completers, Total) before column Visit.

### TABLE 14.2-3.1 SUMMARY OF THE DEVELOPMENT OF [redacted] HEIGHT AGE IN COMPARISON WITH CHRONOLOGICAL AGE BY COMPLETERS AND TOTAL (FAS)

| | Visit | by | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chronological age* (years) | V01 | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Total | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | V05 | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Total | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | … | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Total | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |

[redacted]

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Height age§ (years) | V01^ | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Total | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | V05& | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | | Total | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| … | Males | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Females | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Powder | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Solution | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |
| | Total | XX | XX | XX.XX | X.XX | XX.X | XX.X | XX.X | XX.X | XX.X |

* Chronological age determined using date of x-ray

[redacted]

^ Height age determined using height data from the measurement performed closest to pretreatment x-ray date

[redacted]

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Visit.

**TABLE 14.2-3.2 ANALYSIS OF MEAN CHANGE FROM BASELINE IN [redacted] AND HEIGHT AGE BY COMPLETERS AND TOTAL (FAS)**

| Parameter | Difference between visits | by | N | Mean difference | 95% Confidence interval for mean difference |
|---|---|---|---|---|---|
| [redacted] | | | | | |
| Height age (years) | V05 - V01 | Males | XX | X.XX | [ X.XX; X.XX ] |
| | | Females | XX | X.XX | [ X.XX; X.XX ] |
| | | Powder | XX | X.XX | [ X.XX; X.XX ] |
| | | Solution | XX | X.XX | [ X.XX; X.XX ] |
| | | Total | XX | X.XX | [ X.XX; X.XX ] |
| | … | Males | XX | X.XX | [ X.XX; X.XX ] |
| | | Females | XX | X.XX | [ X.XX; X.XX ] |
| | | Powder | XX | X.XX | [ X.XX; X.XX ] |
| | | Solution | XX | X.XX | [ X.XX; X.XX ] |
| | | Total | XX | X.XX | [ X.XX; X.XX ] |

[redacted].

Programming note: Please add one column ‘Status’ (value: Completers, Total) before column Parameter.

**TABLE 14.2-3.3 SUMMARY OF THE MEAN RATIOS FOR THE COMPARISON OF CHANGES IN [redacted] HEIGHT AGE, AND CHRONOLOGICAL AGE (FAS)**

| | Individual ratio of changes derived between visits | By | N | Missing | Mean | SD | Min | Q1 | Median | Q3 | Max | p-value # |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] / ΔCA | V05 - V01 | Males | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Females | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Powder | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Solution | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Total | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | V.. - V01 | Males | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Females | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Powder | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Solution | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Total | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| ΔHA / ΔCA | V05 - V01 | Males | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Females | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Powder | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Solution | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Total | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | V.. - V01 | Males | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Females | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Powder | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Solution | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |

| | Individual ratio of changes derived between visits | By | N | Missing | Mean | SD | Min | Q1 | Median | Q3 | Max | p-value # |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| ΔHA / [redacted] | V.. - V01 | Males | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Females | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Powder | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Solution | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Total | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | V09 - V01 | Males | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Females | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | Powder | XXX | XXX | X.XX | X.XX | X.X | X.X | X.XX | X.X | X.X | X.XXXX |
| | | XXX | XXX | XXX | X.XX | X.XX | X.X | X.XX | X.X | X.X | X.X | XXX |
| | | XXX | XXX | XXX | X.XX | X.XX | X.X | X.XX | X.X | X.X | X.X | XXX |

[redacted]; HA - Height Age; CA - Chronological Age
# two-sided p-value for t-test with null hypothesis that ratio equals 1

Programming note: Please add one column ‘Status’ (value: Completers, Total) before first column.

TABLE 14.2-3.4 SUMMARY OF OVERWEIGHT PATIENTS BY SEX AND VISIT (FAS)

| | | | | | Number of patients (%) | |
|---|---|---|---|---|---|---|
| **Sex** | **Visit** | **Total** | **Missing** | **N** | **Normal** | **Overweight*** |
| Male | Baseline | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) |
| | V02 | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) |
| | … | | | | | |
| Female | Baseline | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) |
| | V02 | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) |
| | … | | | | | |
| Total | Baseline | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) |
| | V02 | XXX | XXX | XXX | XXX (XX.X%) | XXX (XX.X%) |
| | … | | | | | |

* Defined by international cut off points for BMI for overweight by sex and age at visit. The cut-off point is defined by the percentile that passes through BMI at 25 kg/m² at age 18.

## 5.3 Figures

**FIGURE 14.2-2.22 Mean IGFBP-3 SDS serum levels over time, means ± 95% CI (FAS)**

## 5.4 Safety Tables including shells

## TABLE 14.3-1.1 GENERAL SUMMARY OF ADVERSE EVENTS (SAF)

| | Number of patients (%) (N=277) | | Number of adverse events (%) | |
|---|---|---|---|---|
| Any adverse events | XXX | (XX.X%) | XXX | (XX.X%) |
| Relationship to study drug | | | | |
| Not suspected | XXX | (XX.X%) | XXX | (XX.X%) |
| Suspected | XXX | (XX.X%) | XXX | (XX.X%) |
| Missing | XXX | (XX.X%) | XXX | (XX.X%) |
| Intensity | | | | |
| Mild | XXX | (XX.X%) | XXX | (XX.X%) |
| Moderate | XXX | (XX.X%) | XXX | (XX.X%) |
| Severe | XXX | (XX.X%) | XXX | (XX.X%) |
| Missing | XXX | (XX.X%) | XXX | (XX.X%) |
| Serious adverse event | | | | |
| No | XXX | (XX.X%) | XXX | (XX.X%) |
| Yes | XXX | (XX.X%) | XXX | (XX.X%) |
| Missing | XXX | (XX.X%) | XXX | (XX.X%) |
| Outcome | | | | |
| Resolved | XXX | (XX.X%) | XXX | (XX.X%) |
| Ongoing | XXX | (XX.X%) | XXX | (XX.X%) |
| Missing | XXX | (XX.X%) | XXX | (XX.X%) |
| Action taken | | | | |
| Nothing | XXX | (XX.X%) | XXX | (XX.X%) |
| Study drug dosage adjusted/temporarily interrupted | XXX | (XX.X%) | XXX | (XX.X%) |
| Study drug permanently discontinued due to this AE | XXX | (XX.X%) | XXX | (XX.X%) |
| Concomitant medication given | XXX | (XX.X%) | XXX | (XX.X%) |
| Non-drug therapy given | XXX | (XX.X%) | XXX | (XX.X%) |
| Hospitalization/prolonged hospitalization | XXX | (XX.X%) | XXX | (XX.X%) |
| Missing | XXX | (XX.X%) | XXX | (XX.X%) |

No AEs (including SAEs) that started prior to start of treatment are included.

**TABLE 14.3-1.2 INCIDENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY, ALL ADVERSE EVENTS (SAF)**

TABLE 14.3-1.2.1 INCIDENCE OF ADVERSE EVENTS FOR OVERWEIGHT* PATIENTS AT BASELINE BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY, ALL ADVERSE EVENTS (SAF)

Defined by international cut off points for BMI for overweight by sex and age at baseline. The cut-off point is defined by the percentile that passes through BMI at 25 kg/m² at age 18..

Programming note: Same table shell as Table 14.3-1.2 will be used.

**TABLE 14.3-1.3 INCIDENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY, DRUG-RELATED ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.4 INCIDENCE OF SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY (SAF)**

**TABLE 14.3-1.5 INCIDENCE OF DRUG-RELATED SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY (SAF)**

**TABLE 14.3-1.6 INCIDENCE OF NON-SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY (SAF)**

| | Intensity | | | | | |
|---|---|---|---|---|---|---|
| Novartis MedDRA version<br>System Organ Class<br>Preferred Term | Mild | Moderate | Severe | Missing | Total number of patients | Patients per patient years# |
| Blood and lymphatic system disorders | | | | | | |
| Any AE | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Anaemia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Eosinophilia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Leukopenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Lymphadenitis | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Lymphadenopathy | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Neutropenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Splenomegaly | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |

| Novartis MedDRA version System Organ Class Preferred Term | Intensity Mild | Moderate | Severe | Missing | Total number of patients | Patients per patient years# |
|---|---|---|---|---|---|---|
| Thrombocytopenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Thrombocytosis | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Cardiac disorders | | | | | | |
| Any AE | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| … | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |

No AEs (including SAEs) that started prior to start of treatment are included.

# Patient years = XXX.XXX

Patient years are calculated as years of exposure (i.e. total sum of the number of years that each patient was treated).

**TABLE 14.3-1.7 OCCURRENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY, ALL ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.8 OCCURRENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY, DRUG-RELATED ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.9 OCCURRENCE OF SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY (SAF)**

**TABLE 14.3-1.10 OCCURRENCE OF DRUG-RELATED SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY (SAF)**

**TABLE 14.3-1.11 OCCURRENCE OF NON-SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND INTENSITY (SAF)**

| | | Intensity | | | | | |
|---|---|---|---|---|---|---|---|
| SOC | Preferred term | Mild | Moderate | Severe | Missing | Total | Events per Patient Year |
| SOC1 | ANY | XX | XX | XX | XX | XX | X.XXX |
| | Preferred Term 1 | XX | XX | XX | XX | XX | X.XXX |
| | Preferred Term 2 | XX | XX | XX | XX | XX | X.XXX |
| | Preferred Term X | XX | XX | XX | XX | XX | X.XXX |
| | … | … | … | … | … | … | … |
| SOC2 | ANY | XX | XX | XX | XX | XX | X.XXX |
| | Preferred Term 1 | XX | XX | XX | XX | XX | X.XXX |
| | Preferred Term 2 | XX | XX | XX | XX | XX | X.XXX |
| | Preferred Term X | XX | XX | XX | XX | XX | X.XXX |
| | … | … | … | … | … | … | … |
| … | … | … | … | … | … | … | … |

No AEs (including SAEs) that started prior to start of treatment are included.

# Patient years = XXX.XXX

Patient years are calculated as years of exposure (i.e. total sum of the number of years that each patient was treated).

**TABLE 14.3-1.12 INCIDENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME, ALL ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.13 INCIDENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME, DRUG-RELATED ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.14 INCIDENCE OF SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME (SAF)**

**TABLE 14.3-1.15 INCIDENCE OF DRUG-RELATED SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME (SAF)**

| | Outcome | | | | | |
|---|---|---|---|---|---|---|
| Novartis MedDRA version<br>System Organ Class<br>Preferred Term | Resolved | Ongoing | Fatal | Missing | Total number of patients | Patients per patient years# |
| Blood and lymphatic system disorders | | | | | | |
| Any AE | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Anaemia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Eosinophilia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Leukopenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Lymphadenitis | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Lymphadenopathy | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Neutropenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Splenomegaly | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Thrombocytopenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Thrombocytosis | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Cardiac disorders | | | | | | |
| Any AE | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| … | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |

No AEs (including SAEs) that started prior to start of treatment are included.

# Patient years = XXX.XXX

Patient years are calculated as years of exposure (i.e. total sum of the number of years that each patient was treated).

**TABLE 14.3-1.16 OCCURRENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME, ALL ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.17 OCCURRENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME, DRUG-RELATED ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.18 OCCURRENCE OF SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME (SAF)**

**TABLE 14.3-1.19 OCCURRENCE OF DRUG-RELATED SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND OUTCOME (SAF)**

| | Outcome | | | | | |
|---|---|---|---|---|---|---|
| Novartis MedDRA 19.1<br>System organ class<br>Preferred Term | Resolved | Ongoing | Fatal | Missing | Total | Events per patient year# |
| Blood and lymphatic system disorders | | | | | | X.XXX |
| ANY | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Anaemia | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Eosinophilia | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Leukopenia | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Lymphadenitis | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Lymphadenopathy | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Neutropenia | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Splenomegaly | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Thrombocytopenia | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Thrombocytosis | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Cardiac disorders | XXX | XXX | XXX | XXX | XXX | X.XXX |
| ANY | XXX | XXX | XXX | XXX | XXX | X.XXX |
| … | | | | | | |

No AEs (including SAEs) that started prior to start of treatment are included.

# Patient years = XXX.XXX

Patient years are calculated as years of exposure (i.e. total sum of the number of years that each patient was treated).

**TABLE 14.3-1.20 INCIDENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN, ALL ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.21 INCIDENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN, DRUG-RELATED ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.22 INCIDENCE OF SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN (SAF)**

**TABLE 14.3-1.23 INCIDENCE OF DRUG-RELATED SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN (SAF)**

| | Action taken | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Novartis MedDRA 19.1 System Organ Class Preferred Term | Nothing | Study drug dosage adjusted /tempo-rarily inter-rupted | Study drug perma-nently disc-ontinued due to this AE | Conco-mitant medi-cation given | Non-drug therapy given | Hospital-ization/ prolonge d hospital-ization | Missing | Patients per patient years# |
| Blood and lymphatic system disorders | | | | | | | | |
| Any AE | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Anaemia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Eosinophilia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Leukopenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Lymphadenitis | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Lymphadenopathy | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| Neutropenia | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | XX (XX.X%) | X.XXX |
| … | | | | | | | | |

No AEs (including SAEs) that started prior to start of treatment are included.

# Patient years = XXX.XXX

Patient years are calculated as years of exposure (i.e. total sum of the number of years that each patient was treated).

**TABLE 14.3-1.24 OCCURRENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN, ALL ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.25 OCCURRENCE OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN, DRUG-RELATED ADVERSE EVENTS (SAF)**

**TABLE 14.3-1.26 OCCURRENCE OF SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN (SAF)**

**TABLE 14.3-1.27 OCCURRENCE OF DRUG-RELATED SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS, PREFERRED TERM, AND ACTION TAKEN (SAF)**

| | Action taken | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Novartis MedDRA 19.1<br>System organ class<br>Preferred Term | Nothing | Study drug dosage adjusted /temporarily interrupted | Study drug permanently discontinued due to this AE | Concomitant medication given | Non-drug therapy given | Hospitalization/ prolonged hospitalization | Missing | Total | Events per patient year# |
| Blood and lymphatic system disorders | | | | | | | | | |
| ANY | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Anaemia | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Eosinophilia | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Leukopenia | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Lymphadenitis | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Lymphadenopathy | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Neutropenia | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Splenomegaly | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Thrombocytopenia | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Thrombocytosis | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Cardiac disorders | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| ANY | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| Bradycardia | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |
| … | XXX | XXX | XXX | XXX | XXX | XXX | XXX | XXX | X.XXX |

No AEs (including SAEs) that started prior to start of treatment are included.

# Patient years = XXX.XXX

Patient years are calculated as years of exposure (i.e. total sum of the number of years that each patient was treated).

## TABLE 14.3-2.1 CONVERSION FACTORS FOR LABORATORY PARAMETERS

| | Parameter | Unit measured | Conversion factor | Unit derived |
|---|---|---|---|---|
| Hematology | Hematocrit | % / 100 | | Value |
| | Hemoglobin | g/dl | 10 | g/l |
| | MCHC | g/dl | 10 | g/l |
| Blood chemistry | Total protein | g/dl | 10 | g/l |
| | Creatinine | mg/dl | XX.X | umol/l |
| | Total bilirubin | mg/dl | XX.X | umol/l |
| | Urea | mg/dl | X.XXX | mmol/l |
| … | … | … | … | … |

**TABLE 14.3-2.2 SUMMARY OF HEMATOLOGY DATA (SAF)**

| Parameter (unit) | Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin (g/l) | V01 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V03 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V05 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | … | | | | | | | | | |
| Hematocrit (l/l) | V01 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V03 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V05 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | … | | | | | | | | | |
| … | … | … | … | … | … | … | … | … | … | … |

**TABLE 14.3-2.3 SUMMARY OF BLOOD CHEMISTRY (SAF)**

| Parameter (unit) | Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter1 (unit1) | V01 | XX | XX | XXX.XX | XX.XX | XX.X | XXX.XX | XXX.XX | XXX.XX | XX.X |
| | V03 | XX | XX | XXX.XX | XX.XX | XX.X | XXX.XX | XXX.XX | XXX.XX | XX.X |
| | V05 | XX | XX | XXX.XX | XX.XX | XX.X | XXX.XX | XXX.XX | XXX.XX | XX.X |
| | … | | | | | | | | | |
| Parameter2 (unit2) | V01 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V03 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V05 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | … | | | | | | | | | |
| … | … | … | … | … | … | … | … | … | … | … |

**TABLE 14.3-2.4 SUMMARY OF CARBOHYDRATE METABOLISM INCL. OGTT DATA (SAF)**

**TABLE 14.3-2.5 SUMMARY OF ABSOLUTE CHANGES FROM BASELINSE OF CARBOHYDRATE METABOLISM INCL. OGTT DATA (SAF)**

**TABLE 14.3-2.6 SUMMARY OF RELATIVE CHANGES FROM BASELINSE OF CARBOHYDRATE METABOLISM INCL. OGTT DATA (SAF)**

| Parameter (unit) | Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter 1 (unit1) | V01 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V03 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V05 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | … | | | | | | | | | |
| Parameter 2 (unit2) | V01 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V03 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V05 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | … | | | | | | | | | |
| … | … | … | … | … | … | … | … | … | … | … |

## TABLES 14.3-2.7 SHIFT TABLES FOR CARBOHYDRATE METABOLISM (SAF)

## TABLE 14.3-2.7.1 SHIFT TABLE FOR $HbA_{1C}$ (SAF)

## TABLE 14.3-2.7.2 SHIFT TABLE FOR FASTING GLUCOSE (SAF)

## TABLE 14.3-2.7.3 SHIFT TABLE FOR FASTING INSULIN (SAF)

| Comparison (Baseline vs Compared) | Base Visit | Low | Normal | High | Missing | Total |
|---|---|---|---|---|---|---|
| V01 vs V03 | Low | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Normal | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | High | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| V01 vs V05 | Low | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Normal | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | High | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| V… vs V.. | Low | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Normal | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | High | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |

**TABLE 14.3-2.8 SUMMARY OF HOMA AND QUICKI SCORES (SAF)**

**TABLE 14.3-2.9 SUMMARY OF ABSOLUTE CHANGES FROM BASELINE OF HOMA AND QUICKI SCORES (SAF)**

**TABLE 14.3-2.10 SUMMARY OF RELATIVE CHANGES FROM BASELINE OF HOMA AND QUICKI SCORES (SAF)**

**TABLE 14.3-2.11 SUMMARY OF THYROID PANEL DATA (SAF)**

| Parameter (unit) | Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter1 (unit1) | V01 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V03 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V05 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | … | | | | | | | | | |
| Parameter2 (unit2) | V01 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V03 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V05 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | … | | | | | | | | | |
| … | … | … | … | … | … | … | … | … | … | … |

## TABLES 14.3-2.12 SHIFT TABLES FOR THYROID PANEL DATA (SAF)

## TABLE 14.3-2.12.1 SHIFT TABLE FOR FREE THYROXINE (T4) (SAF)

## TABLE 14.3-2.12.2 SHIFT TABLE FOR THYROID STIMULATING HORMONE (TSH) (SAF)

| Comparison (Baseline vs Compared) | Base Visit | Low | Normal | High | Missing | Total |
|---|---|---|---|---|---|---|
| V01 vs V03 | Low | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Normal | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | High | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| V01 vs V05 | Low | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Normal | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | High | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| V01 vs V.. | Low | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Normal | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | High | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | Missing | XX | XX | XX | XX | XX |
| | Total | XX ( XX.X%) | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |

**TABLE 14.3-2.13 SUMMARY OF URINALYSIS DATA (SAF)**

| Parameter (unit) | Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter 1 (unit1) | V01 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V03 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V05 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | … | | | | | | | | | |
| Parameter 2 (unit2) | V01 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V03 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V05 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | … | | | | | | | | | |
| … | … | … | … | … | … | … | … | … | … | … |

**TABLES 14.3-2.14 SHIFT TABLES FOR URINALYSIS DATA (SAF)**

**TABLE 14.3-2.14.1 SHIFT TABLE FOR PROTEIN (SAF)**

**TABLE 14.3-2.14.2 SHIFT TABLE FOR GLUCOSE (SAF)**

**TABLE 14.3-2.14.3 SHIFT TABLE FOR KETONES (SAF)**

**TABLE 14.3-2.16.4 SHIFT TABLE FOR BILIRUBIN (SAF)**

| Comparison (Baseline vs Compared) | Base Visit | Negative | + | ++ | + | ++ | Missing | Total |
|---|---|---|---|---|---|---|---|---|
| V01 vs V03 | Negative | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | + | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | ++ | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | +++ | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | ++++ | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | Missing | XX | XX | XX | XX | XX | XX | XX |
| | Total | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| V.. vs V… | Negative | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | + | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | ++ | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | +++ | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | ++++ | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |
| | Missing | XX | XX | XX | XX | XX | XX | XX |

| Comparison (Baseline vs Compared) | Base Visit | Negative | + | ++ | + | ++ | Missing | Total |
|---|---|---|---|---|---|---|---|---|
| | Total | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XXX (XX.X%) | XX | XXX (XX.X%) |

**TABLE 14.3-3.1 SUMMARY OF VITAL SIGNS (SAF)**

| Parameter (unit) | Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter1 (unit1) | V01 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V03 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | V05 | XX | XX | XXX.XX | XX.XX | XXX | XXX.XX | XXX.XX | XXX.XX | XXX |
| | … | | | | | | | | | |
| Parameter2 (unit2) | V01 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V03 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | V05 | XX | XX | X.XX | X.XXX | X.XX | X.XX | X.XX | X.XX | X.XX |
| | … | | | | | | | | | |
| … | … | … | … | … | … | … | … | … | … | … |

**TABLE 14.3-3.2 SUMMARY OF PHYSICAL EXAMINATION (SAF)**

| Body System | Visit | Total | Missing | N | Significant findings Number of patients (%) Yes | No |
|---|---|---|---|---|---|---|
| General appearance | SCR | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V01 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V02 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V03 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V04 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V05 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V06 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V07 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V08 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | … | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| Head | SCR | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V01 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V02 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V03 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V04 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V05 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V06 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V07 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | V08 | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |
| | … | XXX | XXX | XXX | XX (XX.X%) | XX (XX.X%) |

**TABLE 14.3-3.3 SHIFT TABLE FOR PHYSICAL EXAMINATION BY BODY SYSTEM (SAF)**

| Body System | Comparison (Baseline vs Compared) | Base Visit | Normal | Abnormal | Missing | Total |
|---|---|---|---|---|---|---|
| General appearance | V01 vs V02 | Normal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Abnormal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Missing | XX | XX | XX | XX |
| | | Total | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| | V01 vs V03 | Normal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Abnormal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Missing | XX | XX | XX | XX |
| | | Total | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| | ... | ... | ... | ... | ... | ... |

| Body System | Comparison (Baseline vs Compared) | Base Visit | Normal | Abnormal | Missing | Total |
|---|---|---|---|---|---|---|
| Head | V01 vs V02 | Normal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Abnormal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Missing | XX | XX | XX | XX |
| | | Total | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| | V01 vs V03 | Normal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Abnormal | XX ( XX.X%) | XX ( XX.X%) | XX | XX ( XX.X%) |
| | | Missing | XX | XX | XX | XX |
| | | Total | XX ( XX.X%) | XX ( XX.X%) | XX | XXX (100.0%) |
| | ... | ... | ... | ... | ... | ... |

**TABLE 14.3-3.4 SUMMARY OF BODY WEIGHT (SAF)**

**TABLE 14.3-3.5 SUMMARY OF BMI (SAF)**

**TABLE 14.3-3.6 SUMMARY OF BMI SDS (SAF)**

| | Visit | N | N miss | Mean | SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| BMI SDS | 01 | XX | XX | XX.X | X.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | 02 | XX | XX | XX.X | X.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | 03 | XX | XX | XX.X | X.X | XX.X | XX.X | XX.X | XX.X | XX.X |
| | … | XX | XX | XX.X | X.X | XX.X | XX.X | XX.X | XX.X | XX.X |

**TABLE 14.3-3.7 SUMMARY OF PATIENTS WITH LABORATORY PARAMETERS FULLFILING THE DEFINITION OF DIABETES MELLITUS (DM) (SAF)**

| | Total | Number of patients with DM (%) | Number of patients without DM finding (%) |
|---|---|---|---|
| Female | XXX | XX (XX.X%) | XX (XX.X%) |
| Male | XXX | XX (XX.X%) | XX (XX.X%) |
| Total | XXX | XX (XX.X%) | XX (XX.X%) |

DM is defined as fulfilment of one of the following criteria:

1. FPG ≥126 mg/dl (≥7.0 mmol/l) during safety lab assessment or as -10min value of OGTT
2. 2-h plasma glucose ≥ 200 mg/dl (≥11.1 mmol/l) during OGTT
3. $HbA_{1C} \geq 6.5\%$

Patients not fulfilling at least one criteria on at least one visit are considered as patients without DM finding

**TABLE 14.3-3.7.1 SUMMARY OF OVERWEIGHT* PATIENTS AT BASELINE WITH LABORATORY PARAMETERS FULLFILING THE DEFINITION OF DIABETES MELLITUS (DM) (SAF)**

| Sex | Total | Number of patients with DM (%) | Number of patients without DM finding (%) |
|---|---|---|---|
| Female | XXX | XX (XX.X%) | XX (XX.X%) |
| Male | XXX | XX (XX.X%) | XX (XX.X%) |
| Total | XXX | XX (XX.X%) | XX (XX.X%) |

* Defined by international cut off points for BMI for overweight by sex and age at baseline. The cut-off point is defined by the percentile that passes through BMI at 25 kg/m² at age 18.

DM is defined as fulfilment of one of the following criteria:

1. FPG ≥126 mg/dl (≥7.0 mmol/l) during OGTT or safety lab assessment
2. 2-h plasma glucose ≥ 200 mg/dl (≥11.1 mmol/l) during OGTT
3. $HbA_{1C} \geq 6.5\%$

Patients not fulfilling at least one criteria on at least one visit are considered as patients without DM finding

## TABLE 14.3-3.8 SUMMARY OF PATIENTS WITH LABORATORY PARAMETERS FULLFILING THE DEFINITION OF IMPAIRED GLUCOSE TOLERANENCE (IGT) (SAF)

| | Total | Number of patients with IGT (%) | Number of patients without IGT finding (%) |
|---|---|---|---|
| Female | XXX | XX (XX.X%) | XX (XX.X%) |
| Male | XXX | XX (XX.X%) | XX (XX.X%) |
| Total | XXX | XX (XX.X%) | XX (XX.X%) |

IGT is defined as fulfilment of all of the following criteria:

1. FPG < 126 mg/dl (<7.0 mmol/l) during OGTT or safety lab assessment
2. 2-h plasma glucose between 140 – 200 mg/dl (≥7.8 and <11.1 mmol/l) during OGTT

Patients not fulfilling all criteria on at least one visit are considered as patients without IGT finding

## TABLE 14.3-3.9 SUMMARY OF PATIENTS WITH LABORATORY PARAMETERS FULLFILING THE DEFINITION OF IMPAIRED FASTING GLUCOSE (IFG) (SAF)

| | Total | Number of patients with IFG (%) | Number of patients without IFG finding (%) |
|---|---|---|---|
| Female | XXX | XX (XX.X%) | XX (XX.X%) |
| Male | XXX | XX (XX.X%) | XX (XX.X%) |
| Total | XXX | XX (XX.X%) | XX (XX.X%) |

IFG is defined as fulfilment of all of the following criteria:

1. FPG 110 - 125 mg/dl (6.1 - 6.9 mmol/l) during OGTT or safety lab assessment
2. 2-h plasma glucose < 140 mg/dl (<7.8 mmol/l) during OGTT

Patients not fulfilling all criteria on at least one visit are considered as patients without IFG finding.

**TABLE 14.3-3.10 SUMMARY OF ANTI-HGH ANTIBODIES (SAF)**

| Visit | Total | Missing | N | Number of patients with positive test result (%) |
|---|---|---|---|---|
| V01 | XXX | XXX | XXX | XX (XX.X%) |
| V02 | XXX | XXX | XXX | XX (XX.X%) |
| V03 | XXX | XXX | XXX | XX (XX.X%) |
| V04 | XXX | XXX | XXX | XX (XX.X%) |
| V05 | XXX | XXX | XXX | XX (XX.X%) |
| V07 | XXX | XXX | XXX | XX (XX.X%) |
| V… | XXX | XXX | XXX | XX (XX.X%) |

**TABLE 14.3-3.11 SUMMARY OF ANTI-HCP ANTIBODIES (SAF)**

| Visit | Total | Missing | N | Number of patients with positive test result (%) |
|---|---|---|---|---|
| V01 | XXX | XXX | XXX | XX (XX.X%) |
| V02 | XXX | XXX | XXX | XX (XX.X%) |
| V03 | XXX | XXX | XXX | XX (XX.X%) |
| V04 | XXX | XXX | XXX | XX (XX.X%) |
| V05 | XXX | XXX | XXX | XX (XX.X%) |
| V07 | XXX | XXX | XXX | XX (XX.X%) |
| V… | XXX | XXX | XXX | XX (XX.X%) |
| Total* | XXX | XXX | XXX | XX (XX.X%) |

* including all final assessments

## 5.5 Listings

16.2.1 Discontinued patients (FAS)

16.2.2 Protocol deviations (FAS)

16.2.3 Medical history (FAS)

16.2.4 Compliance and/or drug concentration data

16.2.4.1 Dose changes (FAS)

16.2.5 Adverse events listings

16.2.5.1 All adverse events (FAS)

16.2.5.2 All fatal adverse events (FAS)

16.2.5.3 All adverse events belonging to MedDRA High Level Term Diabetes mellitus (incl. subtypes) (FAS)

16.2.5.4 All adverse events belonging to MedDRA High Level Term Hyperglycemia Condition NEC (FAS)

16.2.5.5 All adverse events belonging to MedDRA System Organ Class Neoplams benign, malignant and unspecified (incl. cysts ans polyps) (FAS)

16.2.5.6 All adverse events of special interest (FAS)

16.2.6 Laboratory measurements

16.2.6.1 HbA1c (FAS)

16.2.6.2 Glucose (FAS)

16.2.6.3 Insulin (FAS)

16.2.6.4 Oral Glucose Tolerance Test (OGTT) (FAS)

16.2.6.5 HOMA and QUICKI Score (FAS)

16.2.6.6 Positive hGH-Antibodies results (FAS)

16.2.6.7 Positive HCP-Antibodies results (FAS)

# 6 Literature

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Elmlinger MW, Kühnel W, Weber MM, Ranke MB (2004) Reference ranges for two automated chemiluminescent assays for serum insulin-like growth factor I (IGF-1) and IGF binding protein 3 (IGFBP-3), Clinical Chemistry and Laboratory Medicine, 42(6), 654-64.

# 7 Appendices

## 7.1 Appendix A

Height Reference Tables for Boys and Girls, Prader Standards (1989)

## 7.2 Appendix B: Height SDS

The following national references for the calculation of Height SDS will be used:

| Country | Calculation | Literature reference |
|---|---|---|
| Belgium | Median, 3rd Percentile | Data manually extracted from Flemish Growth Charts 2 – 20 years. H/1-20040916-EP/2-20 – Vrije Universiteit Brussel, Antropogenetica & Katholieke Universiteit Leuven, Jeugdgezondheidszorg – vub, kul © 2005 www.vub.ac.be/groeicurven (Mean of three measurements) |
| Czech republic | Mean, SD | Celostatni antropologicky vyzkum detí a mladeze 2001, Ceska republika J Vignerova, P.Blaha, Praha 2006 |
| Georgia | Mean, SD | Prader A, Largo RH, Molinari L, et al (1989) Physical growth of Swiss children from birth to 20 years of age. Helv Paediat Acta; 43 Suppl 52:1-125 |
| Germany | Mean, SD | Reinken L., van Oost, G.: Longitudinale Körperentwicklung gesunder Kinder von 0 bis 18 Jahren; Klin Pädiatr 204, 129-133 (1992) |
| Hungary | Mean, SD | Joubert Joubert K., Darvay S., Gyenis G., Éltetö Ö., Mag K., van't Hof M., Ágfalvi R.: Az Országos Longitudinális Gyermeknövekedés-vizsgálat eredményei születéstöl 18 éves korig. I. Központi Statisztikai Hivatal - Népességtudományi Kutatóintézet (Hungarian Central Statistical Office - Demographic Research Institute, 2006) |
| Poland | Median, 3rd Percentile | Iwona Palczewska, Zofia Niedzwiecka:<br>Medycyna - Wieku Rozwojowego<br>Dawniej Problemy Medycyny Wieku Rozwojowego<br>Suplement I do nr 2 kwiecien-czerwiec tom V 2001 Warszawa ISSN 1428-345X<br>Developmental Period Medicine<br>Instytut Matki i Dziecka |
| Romania | Mean, SD | Prader A, Largo RH, Molinari L, et al (1989)] Physical growth of Swiss children from birth to 20 years of age. Helv Paediat Acta; 43 Suppl 52:1-125 |

## 7.3 Appendix C: BMI SDS

As the probability distribution of the BMI is skewed, a satisfying description of the BMI needs additional characterization of the skewness. This is usually done by the LMS method (Cole and Green 1992). If the same reference for height and weight also included BMI reference values they were used. If the reference for height and weight does not include BMI reference values they were appropriately derived from height and weight. For patients older than the maximal age for that a reference is given, the reference for the oldest patients will be used.

The following references for the calculation of BMI SDS will be used in each country:

| Country | Literature reference |
|---|---|
| Belgium | Prader A, Largo RH, Molinari L, et al (1989)] Physical growth of Swiss children from birth to 20 years of age. Helv Paediat Acta; 43 Suppl 52:1-125 |
| Czech republic | Bláha P, Vignerová et al (2003)] Celostátní antropologický výzkum dětí a mládeže 2001. Ces-slov Pediat; 58 (12):766-70 |
| Germany | Prader A, Largo RH, Molinari L, et al (1989)] Physical growth of Swiss children from birth to 20 years of age. Helv Paediat Acta; 43 Suppl 52:1-125 |
| Georgia | Prader A, Largo RH, Molinari L, et al (1989)] Physical growth of Swiss children from birth to 20 years of age. Helv Paediat Acta; 43 Suppl 52:1-125 |
| Hungary | Prader A, Largo RH, Molinari L, et al (1989)] Physical growth of Swiss children from birth to 20 years of age. Helv Paediat Acta; 43 Suppl 52:1-125 |
| Poland | Palczewska I, Niedzwiecka Z (2001)] Wskazniki rozwoju somatycznego dzieci i mlodziezy Warszawskiej. Med Wieku Rosz; 2, suppl. 1. |
| Romania | Prader A, Largo RH, Molinari L, et al (1989)] Physical growth of Swiss children from birth to 20 years of age. Helv Paediat Acta; 43 Suppl 52:1-125 |

## 7.4 Appendix D

Peak Height Velocity Centered Height Velocity Reference Tables for Boys and Girls Cross-Sectional Height Velocity Reference Tables for Boys and Girls, Prader Standards (1989).