Sandoz Biopharmaceuticals Clinical Development

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Long-term safety follow-up after growth treatment (rhGH) of short children born Small for Gestational Age (SGA)

SAP – Detailed Statistical Methodology

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2.0	28-Nov-2018	Section 4.3 protocol deviations have been added according to the decisions made at data review meeting.

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
FPG	Fasting pPlasma glucose
GH	Growth hormone
GT	Glutamyltransferase
HbA_{1C}	Glucose glycosylated hemoglobin
HOMA	Homeostasis model assessment
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
OGTT	Oral glucose tolerance test
QUICKI	Quantitative insulin sensitivity check index
RBC	Red blood cell count
rhGH	Recombinant human growth hormone
SAE	Serious adverse event
SAF	Safety population
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
WBC	White blood cell count

[redacted]

1 Introduction

This study is performed as part of the Marketing Authorization Holder's post-marketing pharmacovigilance plan to investigate the long-term safety, in particular the diabetogenic potential and immunogenicity of recombinant human growth hormone (rhGH) therapy in short children born small for gestational age (SGA). Children born SGA who were treated in study EP00-401 with growth hormone due to short stature will be followed up for 10 years after stop of rhGH treatment. Patients will be monitored for safety.

2 Statistical and analytical plans

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

2.1 Study documents and general considerations

This document describes the procedures and conventions to be used in the final analyses with data of all patients who were included into study EP00-402.

The study is based on the

- study protocol V 1.0, dated 16 Mar 2007,
- Amendment no. 01, dated 12 Mar 2012 incorporated into protocol v 1.0 leading to protocol v 2.0, dated 12 Mar 2012,
- Amendment no. 02, dated 9 May 2012 incorporated into protocol v2.0 leading to protocol v3.0, dated 9 May 2012,
- Amendment no. 03, dated 6 Jun 2013 incorporated into protocol v3.0 leading to protocol v 4.0, dated 6 Jun 2013,
- Amendment no. 04, dated 14 July 2014 incorporated into protocol v4.0 leading to protocol v5.0, dated 14 July 2014.

This study was terminated by the sponsor [redacted] Following decision of study termination all patients were called in for a last visit (documented on the final visit page of the case report form (CRF)).

Raw data listings, summary tables, graphs and statistical tests will be generated by means of the program SAS 9.3 or higher.

The following descriptive statistical parameters will be shown in summary tables

- Continuous variables: n (valid cases), n (missing data), mean, median, standard deviation (SD), min, max, quartiles
- 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 quartiles will be reported to one decimal place greater than the precision of data as collected. Standard deviation will be

[redacted]

presented in two decimal place greater than the data and minimum/ maximum values will be reported with the same precision, as they were collected. This rule is only valid if values are not converted for the summary.

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 for 10 years after the end of treatment.

The secondary objectives of this study are:

- to report the incidence of anti-rhGH antibodies 6 months after termination of growth hormone treatment
- evaluate final height in follow-up period
- to evaluate IGF-I and IGFBP-3 levels for 10 years after end of growth hormone 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) and oral glucose tolerance test (OGTT)).

Specifically of interest is, number and percentage of patients developing overt type II diabetes mellitus after the end of GH treatment, characterized by fulfilment of the following criteria:

- FPG $\geq$ 126 mg/dl (7.0 mmol/l) during blood sampling and/or during OGTT
- 2-h plasma glucose $\geq$ 200 mg/dl (11.1 mmol/l) during OGTT

Documented confirmation on diagnosis of diabetes mellitus by investigator during OGTT will also be considered to qualify incidence of elevated glucose values as development of overt type II diabetes mellitus.

Fasting plasma glucose as well as an OGTT will be measured at baseline (i.e. final visit of EP00-401), 6 months, 1, 5 and 10 years after the end of treatment.

Additional criteria – carbohydrate metabolism

Additionally, long term effect of growth hormone (GH) treatment on carbohydrate metabolism is also assessed by

- Change from baseline in FPG, baseline and 2hr plasma glucose (during an OGTT), fasting plasma insulin and glucose glycosylated hemoglobin (HbA_{1C}) at 6 months, 1, 5 and 10 years after the end of treatment.

[redacted]

- **Insulin resistance** will be estimated at baseline, 6 months, 1, 5 and 10 years after the end of treatment, using both the homeostasis model assessment (HOMA; Matthews et al. 1985) and quantitative insulin sensitivity check index (QUICKI; Katz et al. 2000):

$$\text{HOMA} = \frac{\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mg/dl)}}{405.41^*}$$

*use constant 22.5 instead of 405.41 if glucose concentration is reported in mmol/L

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

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.

Potential of GH-treatment induced insulin resistance will be captured through change from baseline in HOMA and QUICKI at 6 months, 1, 5 and 10 years after the end of treatment

2.3.2 Secondary Endpoints

2.3.2.1 Safety endpoints

Criteria for assessing long term safety of GH treatment focusing on the secondary objectives are:

- **Immunogenicity:** Number and percentage of patients developing anti-rHGH antibodies through the follow-up period after end of GH treatment is the secondary safety endpoint associated with monitoring and assessing immunogenicity.

  Patients will be screened for anti-rhGH antibodies at baseline and 6 months after the end of treatment. Only in case of positive antibodies measurements in previous visit follow-up measurements are planned after 1 year, 5 years and 10 years. Positive antibodies are defined as values above 1.76. Unscheduled visits will be excluded from the analysis**.**

- **Laboratory evaluations – safety parameters:** Change from baseline (Shift from baseline, as applicable) at 6 months, 1 year, 5 years and 10 years after end of GH treatment in laboratory safety parameters as follows:

  - Hematology: Hemoglobin, hematocrit, white blood cell count (WBC, total and differential), red blood cell count (RBC), platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), erythrocyte sedimentation rate (ESR).
  - Biochemistry: Creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (gamma-GT), alkaline phosphatase, total bilirubin, albumin, total protein, HDL, LDL, sodium, potassium, chloride, uric acid, fasting total cholesterol, fasting triglycerides, calcium, phosphorus.
  - Thyroid function: Free thyroxine and thyroid stimulating hormone.
  - Urinalysis: pH, glucose, ketones, bilirubin, protein.

[redacted]

- Number and percentage of patients with Adverse Events and Serious Adverse Events
- Change from baseline in vital signs parameters (blood pressure, pulse rate) and body weight, BMI, and BMI SDS will be assessed at each visit (baseline, 6 months, 1, 5, and 10 years after termination of treatment). BMI is calculated by [weight in kg] divided by [height in m]^2. For further details on the calculation of BMI SDS, see Section 5.1.
- Number and percentage of patients with significant finding in any body systems: head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculo-skeletal system, skin, lymph nodes, central nervous system, and where appropriate, others. Physical examinations are performed at baseline, 6 months, 1 year, 5 and 10 years after end of treatment.

2.3.2.2 Efficacy Endpoints

Secondary efficacy endpoints of this study include:

- **Pharmacodynamic endpoints** Change from baseline in hGH-induced serum IGF-I and serum IGFBP-3 levels, as well as the respective serum IGF-I level SDS and serum IGFBP-3 level SDS, at 6 months, 1, 5 and 10 years after the end of treatment. For further details on the calculation/derivation of the serum IGF-I level SDS and the serum IGFBP-3 level SDS, see Section 5.3.
- **Height measurement related endpoints** include height, height SDS, final height, and final height SDS. Height will be measured according to the usual clinical practice at all visits including baseline, 6 months, 1, 5, and 10 years after the end of treatment. Height SDS will be calculated/derived from the height measurement for all visits including baseline, 6 months, 1, 5, and 10 years after the end of treatment. For further details on the calculation/derivation of height SDS, see Section 5.2. The final height is defined as the respective maximum value of height. Final height SDS is the respective SDS value for maximum value of height. For further details on the calculation/derivation of final height and final height SDS, Section 5.2.

2.4 Statistical methods planned in the protocol

Planned analyses are described in Section 10 of the protocol. Safety and efficacy endpoints will be summarized descriptively.

2.5 Determination of sample size

All patients who participated in the EP00-401 study and received at least one dose of study medication are intended to enter the observational period.

2.6 Definitions of analysis sets

The **safety population** (SAF) comprises all who enter the observational period i.e. at least one visit date additional to visit F0 or an adverse event starting or worsening on or after baseline have to be documented. The SAF population will be the basis for all safety analyses.

[redacted]

The **full analysis set** (FAS) population comprises all patients who received at least one dose of study medication, as defined for the final analysis of study EP00-401. All baseline and efficacy analyses will be summarized for the FAS. Only patients from SAF will be included.

2.7 Subgroup analyses

No subgroup analyses will be performed.

3 Changes to planned analyses

It has been decided prospectively that a per-protocol analysis will not be performed since the study focuses on long-term safety monitoring for which the safety set will be the primary analysis population.

4 Statistical analyses

4.1 General considerations

Data transfer from EP00-401

Some information for analyses planned in the protocol is not provided in the CRF of this follow-up study, but in the CRF of study EP00-401 only. Therefore, the following variables provided in the CRF of EP00-401 will be transferred to this study:

- age at final visit
- gender and race
- physical examination and pubertal status at final visit
- height, height Standard Deviation Score (SDS) at final visit
- weight and BMI, BMI SDS at final visit
- fasting plasma glucose, OGTT results, fasting plasma insulin, HbA_{1C} at final visit
- IGF-I, IGFBP-3, IGF-1 SDS, and IGFBP-3 SDS at final visit
- anti-rhGH antibody testing at final visit
- safety lab at final visit
- blood pressure and pulse at final visit
- exposure to study drug

Data of study EP00-401 will be transferred to EP00-402 on the same date the EP00-402 database is locked. In general, analysis data (i.e. data created for the analysis of EP00-401) will be transferred not the original CRF data.

Study days, baseline and visits

Study days are defined as date of assessment minus date of baseline visit.

Baseline is defined as final visit of study EP00-401. If no date of final visit is available, the date of F0 baseline visit of study EP00-402 will be used instead.

[redacted]

Analyses by visits will be based on CRF visits, i.e. F1 Month 6, F2 1 Year, F3 5 Years, and F4 10 Years/Final. The CRF visit F4 10 Years/Final will be presented as EOS (termination visit).

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 listed by parameter and will provide CRF unit, SI unit and conversion factor. If albumin is given in %, the respective values will be converted to g/l using total protein values.

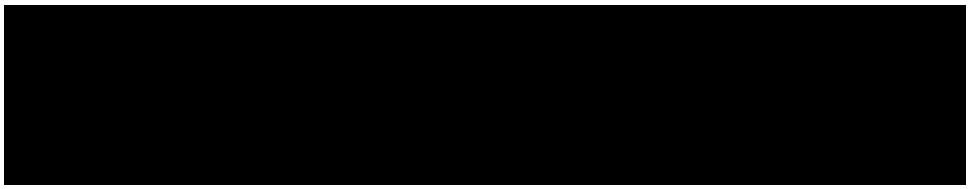
4.2 Disposition of patients

Number of patients enrolled in the study will be summarized by site and for overall population along with number of patients at different visits. A summary for number and percentage of patients included in each analysis set will be provided separately. Patients prematurely discontinuing the study will be descriptively summarized by presenting number and percentage of such patients both in overall population and also by primary reason for discontinuation. Premature study discontinuations will also be listed at a patient level quoting site number and primary reason of discontinuation.

4.3 Protocol deviations

Number of protocol deviations as well as the number and percentage of patients with protocol deviations will be summarized overall and by protocol deviation category and classified reason for exclusion/protocol deviation for all enrolled patients. The summary of reported protocol deviations will be presented according to the following categories as agreed during data review meeting –

- Inclusion/exclusion criteria
- Withdrawal/ termination criteria met, but subject not discontinued
- Failure to perform key procedures
  - Lab values not taken
  - Study assessment not done
  - visit window (deviation from protocol specified visit schedule)
- GCP–related deviation



In addition all protocol deviations will be listed on a subject level.

According to the decisions made during the data review meeting prior to DBL, following patient will be excluded from the appropriate analyses sets with details as below:

Table 4-1 Summary of patients excluded from analysis set(s)

Patient	Analysis set excluded from	Reason for exclusion
[redacted]	SAF/ FAS	[redacted]

4.4 Demographics and baseline characteristics

4.4.1 Demographics

Following demographic and baseline characteristics are summarized for patients in full analysis set (FAS).

Continuous variables: Age at baseline, baseline height, baseline height SDS (for further details: Section 5.2), baseline weight, BMI and BMI SDS at baseline (for further details: Section 5.1). BMI is calculated by [weight in kg] divided by [height in m]^2.

Categorical variables: Gender, ethnic origin

These demographic/ baseline characteristics will also be listed at a patient level including informed consent dates/days of first legal guardian, second legal guardian and child.

4.4.2 Pubertal status

The number and percentage of pubertal patients evaluated at each Tanner stage (Tanner Stages 1-5) will be summarized by gender and visit.

4.4.3 Concomitant medication

Information on administration of any medications, except investigational medicinal products, should have been reported in the appropriate section of the CRF, along with dose information, dates of administration and reason for use. Any diagnostic, therapeutic or surgical procedure should have also have been recorded, including the date, indication, descriptions of the procedure and clinical findings.

Concomitant medication will be coded according to WHO-DRL. For version and used update strategy for coding see coding guideline for this study. All documented concomitant medication data will be summarized separately by Anatomical Therapeutic Chemical (ATC) term (level 2) and preferred term, providing the number and % of patients to whom medication was administered. This summary will be prepared for the FAS analysis set.

[redacted]

4.5 Exposure to study drug

4.5.1 Treatment exposure

The extent of exposure in the EP00-401 study will be analyzed using descriptive statistics.

According to the SAP for interim analysis of study EP00-401 exposure will be assessed as follows:

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 months 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 months as follows:

- Exposure (months) = Exposure (days)*12/365.25.

4.5.2 Study exposure

Study exposure for patients entering the observation period for EP00-402 study is calculated as:

Study exposure (days) = Date of final visit – Date of baseline visit +1

Study exposure (days) will be converted to months as treatment exposure and will be summarized in a similar manner.

4.6 Analysis of primary endpoint

Patients in the safety set (SAF) are considered for analyzing the primary endpoint (and related endpoints).

4.6.1 Developing type II diabetes mellitus

Development of type II diabetes mellitus is the primary outcome measure, characterized by fulfilment of the following criteria:

- FPG ≥ 126 mg/dl (7.0 mmol/l) during blood sampling and/or during OGTT
- 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT
- Investigator documenting diagnosis of diabetes mellitus during OGTT

Accordingly, if lab values are elevated (both 2-hr plasma glucose and FPG) above the specified threshold for overt diabetes and investigator confirms with 'Yes' (question on OGTT page), consider the case for diabetes. But in case, 2-hr plasma glucose is elevated (overt) and FPG is normal/ impaired then investigator's response on diagnosis of diabetes will be considered only.

No inferential statistics is planned for this endpoint and results will only be interpreted in a descriptive manner.

[redacted]

4.6.2 Additional criteria - carbohydrate metabolism

Absolute values as well as absolute and relative changes from baseline for fasting plasma glucose, OGTT parameters, fasting insulin, and HbA_{1C} values will be summarized descriptively by visit.

The effect of Omnitrope® treatment on HOMA and QUICKI scores, calculated subsequent for each plasma glucose and insulin measurement, will be evaluated at each visit using descriptive statistics for the observed values along with the absolute and relative changes from baseline.

HbA1c, glucose and insulin data will be listed per parameter, center and patient number and will include: visit, sample date/day, fasting status, parameter result in CRF and SI unit, reference range in CRF and SI unit, outside reference range indicator, clinical significance and a column containing comments. Results of OGTT will be listed by center, patient number and will include: visit, sample date/day, fasting glucose at baseline (-10 minutes) and at 120 minutes in CRF and SI unit, a column providing if diabetes mellitus was diagnoses during OGTT, and comments. Assessed HOMA and QUICKI scores will be listed by center, patient number and visit. Additionally, fasting status and sample date/day will be provided.

4.7 Analysis of secondary endpoints

4.7.1 Safety evaluations

4.7.1.1 Immunogenicity

The number and percentage of patients with positive anti-rhGH antibodies (ABs) will be tabulated by visit. For patients with positive anti-rhGH results, all results of anti-rhGH testing will be listed by center, patient number, and visit and will include: parameter, value, unit (if available), and assessment if positive or negative

4.7.1.2 Safety parameters - Laboratory evaluations

Change from baseline (Shift from baseline) in hematology, biochemistry, thyroid function, and urinalysis parameters will be displayed by visit using descriptive statistics and/ or frequency tables depending on the type of variable (continuous or discrete).

4.7.1.3 (Serious) Adverse events

AEs are coded according to Novartis MedDRA, Version 19.1 or higher.

Only adverse event starting or worsening during study EP00-402 will be presented. Adverse events with missing or incomplete start dates not clearly attributable as starting/worsening prior to study EP00-402 will be included in the analysis.

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.

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

[redacted]

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.

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) 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 12 x {(number of events) / (months of study exposure)}.

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.

All AE data will be listed, sorted by site code, patient number, and MedDRA preferred term. This list will include: adverse event, MedDRA system organ class, MedDRA preferred term, start and stop date/day, intensity, outcome, relationship to study drug, actions taken, and a variable indicating whether an AE was considered a serious adverse event (SAE). Further, a variable identifying if an AE started or worsened on or after baseline is provided.

4.7.1.4 Vital signs / weight

Absolute values as well as absolute and relative changes from baseline for vital signs (systolic and diastolic blood pressure, pulse) and body weight, BMI, and BMI SDS will be presented by visit. Vital signs will be listed by center, patient number and visit and will include examination date/day, sitting pulse, and systolic and diastolic blood pressure.

4.7.1.5 Physical examination

The number and percentage of patients with significant findings will be summarized for each body system by visit for all non-missing patient evaluation data. Results of physical examination will be listed by center, patient number and visit and will include: examination date/day, weight, height, pubertal status, body system and if significant findings were identified, and if significant findings for other body systems were documented, specification will be given.

[redacted]

4.7.2 Efficacy evaluations

4.7.2.1 IGF-I and IGFBP-3 serum levels

The effect of treatment on serum IGF-I, IGF-I SDS, IGFBP-3 and IGFBP-3 SDS levels will be evaluated using descriptive statistics for the observed values at each visit together with the absolute and relative changes as compared to baseline.

4.7.2.2 Height measurements

The effect of treatment on height and height SDS will be evaluated by presenting absolute values for the observed values of height and height SDS at each visit. The effect of treatment on final height and final height SDS will be evaluated by presenting descriptive statistics for absolute values as well as absolute and relative changes from baseline of final height and final height SDS. The descriptive statistics for final height and final height SDS will only be calculated for the following patients:

- patients who completed study EP00-401
- females who discontinued study EP00-401 prematurely and are at least 16 years old when assessing final height
- males who discontinued study EP00-401 prematurely and are at least 18 years old when assessing final height.

4.8 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.

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

4.9 Analyses during an ongoing study

No interim analysis was finalized when the study was prematurely terminated.

[redacted]

5 References for SDS calculations

5.1 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.

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

Country	Literature reference
[redacted]	

5.2 Height SDS

Standard Deviation Scores (SDS) are the relative deviation from the mean value of normally growing children of same gender and chronological age. In general, the SDS values for height will be calculated according to the following formula SDS= (X1-X2)/SD, where X1 means the measured value, X2 the mean value for the relevant chronological age and gender, and SD the standard deviation for the relevant chronological age and gender applying the references as outlined below. If respective national references are provided as median and 3rd 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 chronologcial age and gender, and X4 the 3rd percentile for the relevant chronological age and gender applying the references as outlines below. Resulting SDS values will be rounded to two digits. In case age is higher than maximum age in the respective reference, maximal age will be used for the calculation.

[redacted]

Standardization of patients' height will be performed using the following national reference:

Country	Calculation	Literature reference
[redacted]		

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. Final height SDS will be calculated according to national reference ranges (using the reference values for 18 year olds or older age if available).

5.3 IGF-1 and IGFBP-3 SDS

Standardization of patients' IGF-1 and IGFBP-3 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 gender, X3 the –2 SD value for the relevant chronological age and gender, and X4 the +2 SD value for the relevant chronological age and gender 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

[redacted]

patients with an age between two mids of age intervals, mean, -2 SD, and +2 SD values will be interpolated.

6 LITERATURE

Cole and Green (1992) Smoothing reference centile curves: the LMS method and penalized likelihood. Statistics in Medicine, 11, 1305-1319.

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Katz A et al (2000). Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrin Metab; 85: 2402-10

Matthews DR et al (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia; 28:412-9

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