Statistical Analysis Plan

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Protocol Title:	*An International, Prospective Registry Investigating the Natural History of Children with Achondroplasia*
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Approvals

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Document History

Not applicable.

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1. Overview

This master statistical analysis plan (SAP) describes the planned analysis and reporting for Pfizer protocol number C4181001 (An International, Prospective Registry Investigating the Natural History of Children with Achondroplasia), dated 31-Jan-2019, version 2.0.

This study uses a primary master SAP and may require supplemental SAPs as well. An advantage of this study design is its ability to answer questions that emerge during the course of the study[1]. Subsequent and supplemental SAPs - triggered by new research questions emerging after the initial master SAP - can be developed when enough data become available, including data from other studies, to analyze a particular research question not included in this master SAP.

Reference materials for this statistical plan include the protocol, the anthropometric manual, and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the Food and Drug Administration, European Medicines Agency, and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[2]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[3] and the Royal Statistical Society[4], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. CCI [redacted]

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any inferential or descriptive analysis of data pertaining to Pfizer's study C4181001.

2. Study Objectives and Endpoints

2.1. Study Objectives

To investigate the natural history of children with achondroplasia in terms of:

- anthropometric characteristics
- achondroplasia-related symptoms, tests, and treatments
- biomarkers of bone growth

2.2. Study Endpoints

2.2.1. Safety Endpoints

Not applicable.

2.2.2. Efficacy Endpoints

Not applicable.

2.2.3. Anthropometric Endpoints

2.2.3.1. Anthropometric Measurements

Anthropometric measurements will be done at all study visits and measurement results will be reported in the electronic case report form (eCRF). Anthropometric measurements will be performed according to the study-specific Anthropometric Measurement Manual.

The anthropometric endpoints of the study include specific measurements assessed at every visit or yearly. Moreover, the anthropometric manual requires performing 3 valid measurements for all endpoints during a visit, with the exception of body weight.

Table 1: Anthropometric Measurements

Measurements	Unit	Age group	Visit	# of valid measurements
Standing height	cm	≥2 years	Every visit	3
Height in supine position	cm	<2 years	Every visit	3
Sitting height	cm	≥2 years	Every visit	3
Crown-rump length	cm	<2 years	Every visit	3
Knee height	cm	All	Every visit	3
Head Circumference	cm	All	Every visit	3
Arm Span	cm	All	Every visit	3
Elbow extension angle	degrees	All	Every visit	3
Knee extension angle	degrees	All	Every visit	3
Body weight	kg	All	Every visit	1
Forehead Results	cm	All	Every visit	3
Top of nose results	cm	All	Every visit	3
Base of nose results	cm	All	Every visit	3
Waist circumference	cm	All	Yearly	3
Chest circumference	cm	All	Yearly	3

2.2.3.2. Derived Anthropometric Endpoints

Five additional anthropometric endpoints will be derived:

.

1. Height Growth (HG)

$$HG_i = \frac{OH_i - OH_0}{RH_i - RH_0}$$

where:

OH_i = Observed Height in cm at visit i

OH_0 = Observed Height in cm at baseline

RH_i = Achondroplasia Reference Height at i (Merker at al., 2018)[9]

RH_0 = Achondroplasia Reference Height at baseline

HG will be calculated every 3 months after baseline.

2. Sitting height/standing height (%)

The ratio (%) between the sitting height and the standing height will be calculated for all subjects.

3. Arm span/standing height (%)

The ratio (%) between the arm span and the standing height will be calculated for all subjects.

4. Difference between arm span and standing height (cm)

The difference between the arm span and the standing height will be calculated as:

arm span (cm) – standing height (cm)

5. Height Standard Deviation Score (SDS)

The SDS for a given height or length in cm will be calculated using the LMS method

$$SDS = \frac{\left(\frac{height\ in\ cm}{M}\right)^{L} - 1}{LS}, \quad L \neq 0$$

$$SDS = \frac{1}{S}\ln\left(\frac{height\ in\ cm}{M}\right), \quad L = 0$$

where L, M, and S are the interpolated values between the neighbouring values from the standard tables corresponding to the gender and to the exact age of the child. If the month is missing in the date of birth then the SDS will be set to missing.

L, M, and S, provided in the standard tables, are the tabulated fitted values of Box-Cox power, median, and coefficient of variation corresponding to the standard population, respectively.

If L=1 the formula for calculating the SDS can be written as:

$$SDS = \frac{\text{observed value - median value of the reference population}}{\text{standard deviation value of the reference population}}$$

where the median value is M and the standard deviation is MxS.

The same method will be applied for both the standing height and the recumbent length.

4.1 SDS with reference to normal population

The height-for-age SDS with reference to the normal population will be calculated using the 'WHO Child Growth Standards'[5-7] from birth to 5 years and the 'WHO Reference 2007 for boys and girls, 5-19 years'[6] for children older than 5 years.

The tables of the WHO Child Growth Standards are accessible in electronic format at www.who.int/childgrowth/standards/en; and the tables of the WHO Reference 2007 can be found at www.who.int/growthref.

The following datasets available from the WHO websites will be used:

- lhfa_boys_p_exp.txt
- lhfa_girls_p_exp.txt
- hfa_boys_perc_WHO2007_exp.txt
- hfa_girls_perc_WHO2007_exp.txt

The WHO standard tables assume that L=1 for all ages.

All SDS for children below 24 months are length-based and height-based otherwise. This means for children aged below 24 months (<731 days) and measured standing, the height will be converted to recumbent length by adding 0.7 cm; and for children aged 24 months or above who are measured in recumbent position, the length will be converted to standing height by subtracting 0.7 cm.

4.2 SDS with reference to achondroplasia population

The height-for-age SDS with reference to the achondroplasia population will be calculated on tabulations of population means (M), standard deviations (MxS), and coefficient of variation (S) Merker at al. (2018)[9]. Descriptive statistics and fitted values of L, M, and S for age are summarized in Supporting Information Table 2[9].
L, M, and S values for finer ages values (age in exact years) will be interpolated between the neighbouring table values. The Merker standard tables assume that L=1 for all ages.

The same method for the standing height and the recumbent length will be applied. No adjustment to convert standing height and recumbent length will be applied when calculating the SDS with reference to the achondroplasia population.

Appendix 2 shows the calculation of the SDS for 3 examples.

2.2.4. Achondroplasia-Related Symptoms, Test, and Treatment

Achondroplasia-related symptoms will be collected according to relevant body systems and severity (mild, moderate, and severe).

Achondroplasia-related tests and treatment are also collected in the eCRF.

After the initial report on an important medical symptom, test, or treatment, the investigator should follow-up on the severity status of the medical symptoms, determine whether the symptom is ongoing or is resolved, and assess the outcome of a potential treatment until the child's participation in the study has ended.

2.2.5. Non-achondroplasia-Related Conditions of Medical Significance

Information concerning the diagnosis of any non-achondroplasia-related conditions of medical significance, including start and stop dates, should be reported. Information may be provided by parent(s) / legal guardian(s) or by the child if this is applicable.

3. Overall Study Design and Plan

This is a registry study in children with achondroplasia, aged 0-10 years, to be conducted at multiple clinical centers in several countries. Childrens' information will be collected in the registry at baseline and at every 3-month interval visits, for a maximum of 5 years. There will be a Screening visit, a Baseline visit, 3-month interval visits, a yearly visit (±3 weeks), and a Final visit.

The children may continue study participation until:

- Growth plates are considered to have fused, defined as standing height gain less than 1 cm within the last 6 months
- The child has reached the end of puberty (Tanner Stage V)

- The child is enrolled in an interventional study
- The child has participated in the study for 5 years
- The child is considered lost to follow-up

3.1. Overall Design

CCI [redacted]

[redacted]

The study will enroll participants in the following approximate proportions:

- 40% 0-5y
- 40% 5-10y
- 20% 10-15y

3.3. Study Population

Children between 0 years and 15 years of age with achondroplasia documented by clinical diagnosis.

3.4. Treatments Administered

No investigational treatment will be administered.

3.5. Method of Assigning Subjects to Treatment Groups

No investigational treatment will be administered.

3.6. Blinding and Unblinding

Not applicable.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 2.

Table 2: Schedule of Events

Procedure	Screening Visit[a] (Visit 0)	Baseline Visit (Visit 1)[b]	Every 3 Months[c] (±3 weeks)	Every year (±3 weeks)	Final Visit[c,d] (±3 weeks)
Informed consent and assent (as applicable)	X				
Eligibility criteria	X	X			
Demographics	X				
Medical and surgical history	X	X			
Physical examination		X	X		X
Waist circumference		X		X	X
Genetic confirmation of achondroplasia[e]		(X)			
Anthropometric measurements		X	X		X
Achondroplasia-related symptoms, tests, and interventions		X	X		X
Non-achondroplasia-related symptoms, tests, and treatments[f]		X	X		X
Tanner stage of puberty[g]		X	X		X
Collection of blood sample[h]		X		X	X

a. Within 1 month before Baseline visit.
b. Screening visit and Baseline visit can be combined, if applicable.
c. Visits are scheduled relative to the date of the Baseline visit.
d The Final visit is conducted after termination criteria are met or after a decision to withdraw the child from the study.
e. If not available in medical records, then the result of genetic testing should be available as soon as possible, but not later than at the Final Visit.
f. Any non-achondroplasia-related important medical conditions and any treatment based on the medical judgment of the investigator that may affect the child's growth trajectory.
g. Only for children ≥7 years of age (providing the investigator confirms there is no suspicion of a diagnosis of precocious puberty).
h. Fasting blood sample for biomarker analyses is required to be drawn in the morning. Sampling can be done, e.g., at a separate visit in the clinic, in the home by a visiting nurse, or at a local laboratory, whatever is most convenient and appropriate for the child's well-being.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher).

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, number of missing values (if applicable), mean, standard deviation (SD), median, minimum, and maximum. Continuous variables may be classed into groups and analyzed as a categorical variable when appropriate.

Categorical (qualitative) variable summaries will include the number of subjects (n) with non-missing values, number of missing values, frequency, and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population with non-missing data.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

4.2. Data Snapshot and Data Monitoring

Data snapshot will be performed on a regular basis. This SAP describes the analytical principles and statistical techniques to be employed for both data snapshots and final analysis.

The sponsor may also request additional analysis during the study to analyze a particular research question that emerges during the course of the study.

A data safety monitoring board will not be used in this study.

5. Analysis Populations

All analyses will be conducted on all enrolled children. The enroll set includes consented, screened, and eligibility-verified children.

Data after procedures or treatments that may affect height growth will be excluded from the analysis of anthropometric parameters. The Sponsor will review the subject-level data on an ongoing basis, providing information about procedures or treatment that may affect growth velocity.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The observation recorded at Baseline visit (Visit 1) will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Handling of Dropouts or Missing Data

In general, no data will be imputed. Missing intermediate or final measurements of the anthropometric measurements will not be replaced by imputed values.

6.1.3. Analysis Visit Windows

As per the protocol, a window of ±3 weeks is allowed for the follow-up visits (Visits 2 to 20), while the Screening visit is planned within 1 month before the Baseline visit.

Statistical analyses will be based on scheduled visits collected in the eCRF without further realignment.

6.1.4. Pooling of Sites

Sites will not be taken into account in the analyses. Therefore, the question of pooling of sites is not applicable.

6.1.5. Derived Variables

The following derived and computed variables have been initially identified as important for the descriptive summaries:

1. Height Growth (HG)Height Standard Deviation Score (SDS) with reference to normal population
2. Height SDS with reference to achondroplasia population
3. Sitting height/standing height (%)
4. Arm span/standing height (%)
5. Difference between arm span (cm) and standing height (cm)
6. Change from baseline = (value at current timepoint – value at baseline)
7. Average of valid anthropometric measurements. When it is required to perform 3 valid measurements, the average of the 3 will be used in descriptive summaries. If 1 or 2

valid measurement are missing, the average will include only non-missing values. If all 3 measurements are missing then the average will be missing as well.

8. Age at baseline

   Age at baseline = (date of informed consent – date of birth)/365.25

   Age will be rounded using 2 decimal places. If the day of birth is missing, but the month and year are present, age will be calculated based on day 1 if the month and year match the month/year of informed consent, or 15 if not. If the month is missing, age will be set to missing.

9. Exact age at each visit

   - Exact age in years = (date of visit – date of birth)/365.25
   - Exact age in month = (date of visit – date of birth)/30.4375
   - Exact age in days = (date of visit – date of birth)

   The exact age (2 decimal places if in months, 3 decimal places if in years) will be used to calculate the height-for-age SDS. The use of the 2 date variables (date of birth and date of visit) for calculating the exact age of the child is the recommended approach as best practice. If the day is missing for the date of birth, 15 will replace it, unless the month and year of birth match the month and year of informed consent in which case the first of the month will be used. If the month is missing for the date of birth, the exact age values and the height-for age SDS will be set to missing.

10. Age groups at each visit. Three age groups will be identified: <2 years, 2-10 years, and ≥10 years. Children may move from an age group to the next one during the study.

6.1.6. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

6.1.7. COVID-19

A Coronavirus Disease 2019 (COVID-19) Continuity Plan has been to mitigate the negative effects of the COVID-19 pandemic on the conduct of this natural history registry.

The impact of COVID-19 on this study and participants will be described in tables and listings, and in the CSR.

The following aspects will be summarized when due to COVID-19:

- Subject who early terminated the study

- Changes to visit windows to accommodate delays for some assessments
- Protocol deviations

The situation is rapidly evolving and further updates to the COVID-19 Continuity Plan and to this SAP are possible and likely.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

The total number of subjects for each one of the following categories will be presented in tables:

- Consented subjects
- Screened subjects and reason for screening failure
- Enrolled subjects
- Completed subjects and reason for completion
- Reasons for study discontinuation

In summary tables for disposition of subjects, a breakdown by gender will be given.

The reason given for screening failure will be summarized in a separate table for screen failures.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for exact age at the Baseline visit, gender, race, ethnicity, and achondroplasia familiarity will be presented by gender.

For the continuous variables, the number of non-missing values and the mean, SD, minimum, median, and maximum will be tabulated.

The number and percent of subjects reporting various medical and surgical histories, grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (coded using MedDRA v.20.0), will be tabulated by gender. Medical and surgical histories by SOC and PT will be sorted in order of descending frequency in the overall group of the SOC and then by descending frequency orders of the PT within each SOC.

8. Analysis of the Anthropometric Endpoints

Descriptive summaries of the observed value and change from baseline will be calculated for the anthropometric endpoints. For continuous variables, number of non-missing values, number of

missing values, the mean, SD, minimum, median, and maximum will be tabulated by gender. Subgroup analysis will be performed by age group at each visit.

Angles are circular quantities and are usually described using polar coordinates since the arithmetic mean may not be appropriate. However, angles for elbow and knee extension measure the deviation from a completely straight elbow or knee and are not circular quantities. The elbow extension angle and the knee extension angle will be summarized using the same descriptive statistics described for other anthropometric endpoints.

Height growth, height SDS, ration between sitting and standing heights, and ratio between arm span and standing height will be plotted against age separately by gender.

8.1. Height SDS

As a complementary descriptive analysis the height SDS will be analyzed using a Mixed Model for Repeated Measure (MMRM) based on the restricted maximum likelihood (REML) approach.

Although the SDS is calculated standardizing for age and gender, the model will include a fixed effect of gender (binary) and a random effect of age (continuous) and a random intercept for each subject.

An unstructured covariance structure will be used to model the within-subject errors. If the analysis fails to converge, simpler structures (e.g. spatial power, ante-dependent, first autoregressive) will be tested; the covariance structure converging to the best fit, as determined by Akaike's information criterion will be used. Only the final model will be included in the TLFs.

The main goal of this model is to characterize the within-subject variability, the between-subjects variability, and to address any residual effect of gender and age.

Moreover, predicted trajectories of height SDS over age will be presented in a plot separately by gender.

8.2. Difference between Arm Span and Standing Height

The difference between the arm span and the standing height will be analyzed using the methods described in Section 8.1.

9. Safety Analysis

9.1. Related Symptoms, Tests, and Treatments

The number and percent of subjects reporting symptoms related to achondroplasia will be tabulated by gender, body system, and severity. The number and percent of subjects for each test and treatment related to achondroplasia will be described by gender.

9.2. Non-Achondroplasia-Related Conditions of Medical Significance

The non-achondropasia-related conditions of medical significance will be listed.

9.3. Physical Examinations

The number and percent of subjects with normal, abnormal, and clinical significant results will be calculated for each body system by visit and gender.

9.4. Collection of Blood Sample and X-ray of knees

The number and percent of subjects with blood sample collection, X-Ray of knees, and tibiofemoral angles measured will be described by visit and gender. Descriptive summaries of the tibiofemoral angles will be calculated and presented in a table.

9.5. Concomitant Medication

Concomitant medications will be summarized descriptively by anatomical therapeutical chemical (ATC) level 2 and PT and gender using counts and percentages.

Prior medications will be presented only in listings separately from concomitant medications. Medications that started prior to date of informed consent will be considered prior medications. Any medications continuing or starting post the date of informed consent will be considered concomitant. If a medication starts prior to the date of the informed consent and continues after the date of the informed consent, it will be considered both prior and concomitant.

Medications will be coded using ATC classification level 2 (WHO-DD v. March 2017).

10. Changes from Planned Analysis

No change have been planned.

11. Other Planned Analysis

Pubertal status for boys and girls will be described using number and percent of subjects reporting various categories by visit and age group at each visit. Only children ≥7 years of age will be included in the analysis, providing the investigator confirms there is no suspicion of a diagnosis of precocious puberty.

Descriptive summaries will be calculated for the biomarkers of bone growth. Longitudinal modeling of biomarkers of bone growth will done in a manner similar to modeling of anthropometric parameters. Additional analyses for the biomarkers of bone growth may be requested and described in a separate analysis plan.

12. References

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7. WHO Child Growth Standards: length /height-for-age, weight-for-age, weight-for-length, weight-forheight and body mass index-for-age. Methods and development. Geneva, Switzerland: World Health Organization, 2006.
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9. Merker A, Neumeyer L, Hertel NT, Grigelioniene G, Mäkitie O, Mohnike K, Hagenäs L. Growth in achondroplasia: Development of height, weight, head circumference, and body mass index in a European cohort. Am J Med Genet A. 2018 Aug;176(8):1723-1734. doi: 10.1002/ajmg.a.38853. Epub 2018 Aug 2.

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (case report form [CRF] page or listing number).

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number C4181001. The table numbers and page numbers are placeholders only and will be determined when the tables are produced.

Table 3: Demographic Data Summary Tables and Figures

Table/Figure Number	Population(s)	Table/Figure Title / Summary	Supporting Listing
14.1 Baseline and Demographic Data Summary Tables			
14.1.1	All Subjects	Subject Disposition	16.2.1.1 16.2.1.2
14.1.2	Screen Failures	Reason for Screen Failure	16.2.1.3
14.1.3.1	Enrolled Subjects	Summary of Demographics and Baseline Characteristics	16.2.4.1
14.1.3.2	Enrolled Subjects	Genetic Confirmation of Achondroplasia	16.2.4.4
14.1.3.3	Enrolled Subjects	Medical and Surgical History by System Organ Class and Preferred Term	16.2.4.2

Table 4: Anthropometric Data

Table Number	Population(s)	Table Title / Summary	Supporting Listing
14.2 Anthropometric Tables			
14.2.1.1	Enrolled Subjects	Standing Height in Children Aged ≥2 Years by Visit	16.2.6.1
14.2.1.2	Enrolled Subjects	Height in Supine Position in Children Aged <2 Years by Visit	16.2.6.1
14.2.1.3	Enrolled Subjects	Sitting Height in Children Aged ≥2 Years by Visit	16.2.6.1
14.2.1.4	Enrolled Subjects	Crow-rump Length in Children Aged <2 Years by Visit	16.2.6.1
14.2.1.5	Enrolled Subjects, Age groups	Knee Height by Visit	16.2.6.1
14.2.1.6	Enrolled Subjects, Age groups	Head Circumference by Visit	16.2.6.1
14.2.1.7	Enrolled Subjects, Age groups	Arm Span by Visit	16.2.6.1
14.2.1.8	Enrolled Subjects, Age groups	Elbow Extension Angle by Visit	16.2.6.1
14.2.1.9	Enrolled Subjects, Age groups	Knee Extension Angle by Visit	16.2.6.1
14.2.2	Enrolled Subjects, Age groups	Body Weight by Visit	16.2.6.2
14.2.3.1	Enrolled Subjects, Age groups	Cranial Series - Forehead Results by Visit	16.2.6.3
14.2.3.2	Enrolled Subjects, Age groups	Cranial Series - Top of Nose Results by Visit	16.2.6.3
14.2.3.3	Enrolled Subjects, Age groups	Cranial Series - Base of Nose Results by Visit	16.2.6.3
14.2.4.1	Enrolled Subjects, Age groups	Waist Circumference by Visit	16.2.6.4
14.2.4.2	Enrolled Subjects, Age groups	Chest Circumference by Visit	16.2.6.4
14.2.5.1.1	Enrolled Subjects, Age groups	Height Growth by Visit	16.2.6.5
14.2.5.1.2	Enrolled Subjects	Statistical Analysis of Height Growth: MMRM	16.2.6.5
14.2.5.2	Enrolled Subjects	Height Standard Deviation Score with Reference to Normal Population by Visit	16.2.6.6
14.2.5.3	Enrolled Subjects	Height Standard Deviation Score with Reference to Achondroplasia Population by Visit	16.2.6.6
14.2.5.4	Enrolled Subjects, Age groups	Ratio Between Sitting Height and Standing Height by Visit	16.2.6.7
14.2.5.5	Enrolled Subjects, Age groups	Ratio Between Arm Span and Standing Height by Visit	16.2.6.7
14.2.6.1.1	Enrolled Subjects, Age groups	Difference Between Arm Span and Standing Height Growth by Visit	16.2.6.5
14.2.6.1.2	Enrolled Subjects	Statistical Analysis of Height Growth: MMRM	16.2.6.5

Table 5: Safety Data

Table Number	Population(s)	Table Title / Summary	Supporting Listing
14.3 Safety Data			
14.3.6 Other Safety Data Summary Tables			
14.3.6.1.1	Enrolled Subjects	Achondroplasia-Related Symptoms by Body System and Severity	16.2.7.1
14.3.6.1.2	Enrolled Subjects	Achondroplasia-Related Tests	16.2.7.2
14.3.6.1.3	Enrolled Subjects	Achondroplasia-Related Treatments	16.2.7.3
14.3.6.2	Enrolled Subjects	Non-Achondroplasia-Related Conditions of Medical Significance	16.2.7.4
14.3.6.3	Enrolled Subjects	Abnormal and Clinically Significant Physical Examination Results	16.2.9.1
14.3.6.4.1	Enrolled Subjects, Age groups	Pubertal Status for Boys by Visit	16.2.9.2
14.3.6.4.2	Enrolled Subjects, Age groups	Pubertal Status for Girls by Visit	16.2.9.3
14.3.6.5	Enrolled Subjects	Concomitant Medications by ATC Level 2 and Preferred Term	16.2.9.4
14.3.6.6	Enrolled Subjects	Blood Sample Collection and X-Ray of Knees	16.2.9.5 16.2.9.6

13.2. Planned Listing Descriptions

The following are planned data and subject data listings for protocol number C4181001.

In general, 1 listing will be produced per CRF domain. All listings will be sorted by gender, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for a subject will be kept on 1 page if possible, rather than splitting a subject's information across pages.

Table 6: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings **16.2.1 Subject Discontinuation/Completion**		
Listing 16.2.1.1	All Subjects	Informed Consent and Assignment to Enrolled Population
Listing 16.2.1.2	Enrolled Subjects	Study Completion Status
Listing 16.2.1.3	Screen Failures	List of Reasons for Screening Failure
Listing 16.2.1.4	All Subjects	Visit Dates
16.2.2. Protocol Deviations		
Listing 16.2.2.1	Enrolled Subjects	Major Protocol Deviations
16.2.3 Exclusion from the Analysis of Anthropometric Parameters		
Listing 16.2.3.1	Enrolled Subjects	Exclusion from the Analysis of Anthropometric Parameters
16.2.4 Demographic and Other Baseline Characteristics		
Listing 16.2.4.1	Enrolled Subjects	Demographic Data and Baseline Characteristics
Listing 16.2.4.2	Enrolled Subjects	Medical and Surgical History
Listing 16.2.4.3	Enrolled Subjects	Prior Medications
Listing 16.2.4.4	Enrolled Subjects	Genetic Confirmation of Achondroplasia
16.2.6 Individual Anthropometric Data		
Listing 16.2.6.1	Enrolled Subjects	Anthropometric Measurements
Listing 16.2.6.2	Enrolled Subjects	Body Weight
Listing 16.2.6.3	Enrolled Subjects	Anthropometric Measurements - Cranial Series
Listing 16.2.6.4	Enrolled Subjects	Anthropometric Measurements of Waist and Chest Circumference
Listing 16.2.6.5	Enrolled Subjects	Annual Growth Velocity
Listing 16.2.6.6	Enrolled Subjects	Height Standard Deviation Score
Listing 16.2.6.7	Enrolled Subjects	Ratios: Sitting Height/Standing Height and Arm Span/Standing Height
16.2.7 Symptoms, Tests, and Treatments Listing		
Listing 16.2.7.1	Enrolled Subjects	Achondroplasia-Related Symptoms
Listing 16.2.7.2	Enrolled Subjects	Achondroplasia-Related Tests
Listing 16.2.7.3	Enrolled Subjects	Achondroplasia-Related Treatments

Data Listing Number	Population	Data Listing Title / Summary
Listing 16.2.7.4	Enrolled Subjects	Non-Achondroplasia-Related Conditions for Clinical Relevance
16.2.9 Other Clinical Observations and Measurements		
Listing 16.2.9.1	Enrolled Subjects	Physical Examination Results
Listing 16.2.9.2	Enrolled Subjects	Pubertal Status for Boys
Listing 16.2.9.3	Enrolled Subjects	Pubertal Status for Girls
Listing 16.2.9.4	Enrolled Subjects	Concomitant Medications
Listing 16.2.9.5	Enrolled Subjects	Blood Sample Collection
Listing 16.2.9.6	Enrolled Subjects	BX-Ray of Knees
Listing 16.2.9.7	Enrolled Subjects	List of Patients Who Were Affected by COVID-19

13.3. Planned Figure Descriptions

The following are planned summary figures for the study.

Table 7: Planned Figures

Figure Number	Population	Figure Title/Summary	Supporting listing
14.2.1	Enrolled	Height Growth by Age and Gender	16.2.6.5
14.2.2	Enrolled	Height Standard Deviation Scores by Age and Gender	16.2.6.6
14.2.3	Enrolled	Ratio between Sitting Height and Standing Height by Age t and Gender	16.2.6.7
14.2.4	Enrolled	Ratio between Arm Span and Standing Height by Age and Gender	16.2.6.7
14.2.5	Enrolled	Predicted Height SDS by Age and Gender	

14. Tables, Listings, and Listing Shells

14.1. Standard Layout for all Tables, Listings, and Figures

Table and listing shells are provided as a separate document.

Note that programming notes may be added if appropriate after each table, listing, and figure shell.

The final statistical tables will be produced in the format of the shells and will additionally include “double” page numbering in the format “page xx of yy.” The first page numbering will count all pages of the document continuously and the second numbering will count the pages for each table separately. The final statistical output will be provided as fully bookmarked pdf file, including a table of contents.

No shells are provided for figures.

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
AGV	Annual Growth Velocity
ATC	anatomical therapeutic chemical
CRF	case report form
CSR	clinical study report
eCRF	electronic case report form
HG	height growth
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
PT	preferred term
SAP	statistical analysis plan
SD	standard deviation
SDS	Standard Deviation Score
SOC	system organ class
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

Appendix 2: Calculation of the Height-for-Age SDS

This section shows how to calculate the SDS for 3 subjects:

Subject ID	001	002	003
Gender	Male	Male	Female
Date of birth	15 Dec 2005	15 Dec 2015	15 Dec 2015
Date of measurement	04 Sep 2013	07 Jul 2017	25 Aug 2018
Age in years	7.721	1.561	2.694
Age in months	92.65	18.727	32.3285
Age in days	2820	570	984
Height or Length in cm	103.2	65.2	74.4
Type of measure	Standing Height	Length in supine position	Length in supine position

For Subject 003 aged <24 months, the length in supine position is converted to standing height by subtracting 0.7 cm. The standing height for Subject 003 is 73.7 cm. The estimated standing height will be used to calculate the SDS with reference to the WHO population, while the observed length in supine position will be used to estimate the SDS with reference to the Achondroplasia population.

The L, M, and S values corresponding to the neighbouring tables values are:

	WHO Reference Population				Merker Reference Population			
Subject ID	Age	L	M	S	Age	L	M	S
001	92 months	1	125.4545	0.04406	7.0 years	1	95.8	0.039666
	93 months	1	125.9104	0.04414	8.0 years	1	99.6	0.041165
002	570 days*	1	82.9759	0.0331	1.5 years	1	69.8	0.032951
	-	-	-	-	2.0 years	1	72.9	0.032922
003	984 days*	1	92.433	0.03939	2.5 years	1	74.3	0.37685
	-	-	-	-	3.0 years	1	76.8	0.038220

***For children aged 0-5 years, the WHO Standard Table provides age in days (0 to 1856) and there is no need for linear interpolation.**

The interpolated L, M, and S values and the SDSs are:

	WHO Reference Population				
Subject ID	Age	L	M	S	SDS
001	92.65 months	1	125.7503201	0.04411191	-4.06525
002	570 days	1	82.9759	0.0331	-6.48984
003	984 days	1	92.433	0.03939	-5.14511
	Merker Reference Population				
Subject ID	Age	L	M	S	SDS
001	7.721 years	1	98.53880903	0.040746134	1.160922
002	1.561 years	1	70.17556468	0.032947718	-2.15194
003	2.694 years	1	75.2702	0.038220	-0.30250