STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 2, open-label, multicenter, 2-stage sequential cohort, dose escalation study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of subcutaneous SAR442501 in pediatric participants with Achondroplasia**
Protocol number:	**DRI16646**
Compound number (INN/Trademark):	**SAR442501**
Study phase:	**Phase 2**
Short title:	**Safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of SAR442501 in pediatric participants with Achondroplasia**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**22-Aug-2023**

Regulatory agency identifier number(s):

IND:	[redacted]
EudraCT/EU-trial number:	2023-503677-37
NCT:	NCT06067425
WHO:	U1111-1280-5374
EUDAMED:	Not applicable
Other:	Not applicable

Date: 22-Aug-2023 Total number of pages: 68

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

VERSION HISTORY

This statistical analysis plan (SAP) for study DRI16646 is based on the protocol dated 28-Feb-2023. This section summarizes major changes to the statistical analysis features in the SAP. This SAP is approved before the first participant is enrolled.

Major changes in statistical analysis plan

SAP version	Approval date	Changes	Rationale
1	Current version	Not applicable	Original version

1 INTRODUCTION

There are no major changes to the analyses described in the protocol. The minor changes are summarized in Section 3.10.

1.1 STUDY DESIGN

This is a Phase 2 open-label, multicenter, 2-stage sequential cohort dose escalation study in pediatric participants with genetically confirmed ACH.

The study will have 2 stages:

- In Stage 1, pediatric participants between the ages ≥3 to <12 years will enroll in a 52-week sequential cohort dose escalation period (primary treatment period) followed by an extended treatment period.
- In Stage 2, pediatric participants between the ages birth to <3 years will enroll in a 52-week sequential cohort dose escalation period (primary treatment period) followed by an extended treatment period.

In both stages, after the primary treatment period, all participants will enter the extended treatment period which will last at least for 52 weeks. The study will be closed out when the last participant has completed 52 weeks extended treatment period.

As displayed in Table 1,

- In Stage 1, the participants will be divided into 2 age groups based on the age at enrollment/randomization (ie, ≥6 to <12 years, and ≥3 to <6 years). Within each age group, there are 3 cohorts (ie, Cohort 1A, 1B and 1C for age ≥6 to <12 years, and Cohort 2A, 2B and 2C for age ≥3 to <6 years). The younger age (ie, ≥3 to <6 years) and higher dose[redacted] cohorts will be opened after DMC review of safety data of older age and lower dose group (ie, Cohort 1A will open first, followed by 1B, 1C [1B and 1C will be opened sequentially] and 2A simultaneously, then followed by Cohort 2B and 2C [2B and 2C will be opened sequentially]). Participants will be screened and assigned to the cohort open at the time when they become eligible. For participants who enter Cohort 1A and 2A (N=2 each), they will be allocated to receive SAR442501 at [redacted] twice a week. For participants who enter Cohort 1B and 2B (N=2 each), they will be allocated to receive SAR442501 at [redacted] twice a week. For participants who enter Cohort 1C and 2C (N=12 and 4, respectively), they will be[redacted] randomized to receive SAR442501 at[redacted] twice a week.
- In Stage 2, similar as in Stage 1, participants age between birth and age <3 years at the time of enrollment/randomization will be screened and assigned to the cohort (ie, Cohort 3A, 3B or 3C) which is open at the time when they become eligible. For participants who enter Cohort 3A (N=2), they will be allocated to receive SAR442501 at [redacted] twice a week. For participants who enter Cohort 3B (N=2), they will be allocated to receive SAR442501 at [redacted] twice a week. For participants who enter Cohort 3C (N=8), they will be [redacted] randomized to receive SAR442501 at[redacted] twice a week.

Table 1 - Summary of cohorts in Stage 1 and Stage 2

Stage #	Cohort name	Age group	Dose (twice weekly)	Planned sample size
1	1A	≥6 and <12 years	[redacted]	2
1	1B	≥6 and <12 years		2
1	1C	≥6 and <12 years		12 ([redacted]randomization)
1	2A	≥3 and <6 years		2
1	2B	≥3 and <6 years		2
1	2C	≥3 and <6 years		4 ([redacted]randomization)
2	3A	<3 years		2
2	3B	<3 years		2
2	3C	<3 years		8 ([redacted]randomization)

Of note, participants who discontinue study treatment or withdraw from the study before the completion of primary treatment period may be replaced by a new participant to the same cohort.

Study primary analysis will be conducted after all participants in Stage 1 and 2 have completed 52 weeks of primary treatment period.

Considering small sample size of the study, for participants who discontinued the study before the completion of 52 weeks of primary treatment period, they will be replaced by a new participant in the same age group to the study cohort.

Interim analyses will be performed when all participants in Stage 1 have completed 26, and 52 weeks or discontinued early, respectively, to support project strategic planning and further development. See details in Section 3.8.

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of 2 doses of SAR442501 administered SC twice weekly in participants from birth to <12 years of age with ACH	• The occurrence of AEs, SAEs, and AESIs during the TE period
Secondary	
• To evaluate changes in growth parameters following twice weekly SC injections of SAR442501	• Change from baseline to Week 26 and Week 52 in AGV Z-score[a] • Change from baseline to Week 26 and Week 52 in AGV (cm/year) • Change from baseline to Week 26 and Week 52 in height Z-score[a]

Objectives	Endpoints
• To evaluate changes in body proportionality following twice weekly SC injections of SAR442501 for 52 weeks	• Change from baseline to Week 26 and Week 52 in the following calculated ratios: - Upper to lower body segment ratio - Upper to lower extremity ratio - Sitting to standing height ratio (crown-to-rump length to total length for infants) - Arm span to height ratio - Upper arm to forearm length ratio - Upper leg to lower leg ratio - Head circumference to height ratio
• To evaluate changes in foramen magnum parameter via magnetic resonance imaging (MRI) following twice weekly SC injections of SAR442501 (Stage 2 only)	• Change from baseline to Week 52 in brainstem, skull, and spine morphometric and volumetric parameters in participants birth to age <3 years (Stage 2 only)
• To evaluate changes in health-related QoL as measured by the PedsQL Inventory Generic Core Scale	• Change from baseline to Week 26 and Week 52 in social, emotional, and school functioning scores as well as the Psychosocial Health Summary Score, Physical Health Summary Score, and Total Score
• To evaluate changes in fatigue as measured by the PedsQL Multidimensional Fatigue Scale	• Change from baseline to Week 26 and Week 52 in general fatigue, sleep/rest fatigue and cognitive fatigue scores and Total Score
• To evaluate changes in pain as measured by the PedsQL Pediatric Pain Questionnaire	• Change from baseline to Week 26 and Week 52 in PPQ score
• To evaluate changes in mobility as measured by the STEMS	• Change from baseline to Week 26 and Week 52 (those ages ≥5 at enrollment) in mobility and symptom rating (STEMS) score
• To collect developmental milestone data as measured by the Achondroplasia Developmental Recording Form	• Change from baseline to Week 52 (those ages birth to <3 years at enrollment) in achievement of gross motor, fine motor, communication, and feeding milestones
• To evaluate the pharmacokinetic profile of SAR442501 following twice weekly SC injections	• Plasma concentration and parameters of SAR442501
• To characterize changes from baseline in bone/collagen biomarkers following twice weekly SC injections of SAR442501	• Change from baseline to Week 26 and Week 52 in CXM, osteocalcin, bone-specific alkaline phosphatase, P1NP, CTX levels
• To evaluate the immunogenicity of SAR442501 administered as twice weekly SC injections	• Number of participants with TE anti-drug antibodies (ADA), number of treatment-induced ADAs, number of treatment-boosted ADAs from baseline to Week 26 and Week 52, ADA status at each visit, ADA titer at each visit
• To evaluate clinical signs and symptoms of foramen magnum stenosis following twice weekly injections of SAR442501 (Stage 2)	• Changes in neurological examination from baseline through Week 26 and Week 52 (Stage 2 only)

Objectives	Endpoints
Exploratory	
[redacted]	[redacted]

Abbreviations: ACH = Achondroplasia; ADA = Anti-drug antibody; AEs= adverse events; AESIs = adverse events of special interest; AGV = Annualized growth velocity; CTX = collagen-type 1 C-Telopeptide; CXM = collagen X biomarker; P1NP = procollagen type 1 N-terminal propeptide; PedsQL = Pediatric Quality of Life; PPQ= present pain and worst pain rating; MRI= magnetic resonance imaging; QoL = Quality of life; SAEs= serious adverse events; SC = subcutaneous; STEMS = Screening Tool for Everyday Mobility and Symptoms; TE = Treatment-emergent.
For China, please see Protocol Section 10.8 for details.

a Z-score takes both untreated ACH pupation and healthy population as references

b The endpoint will be analyzed for the datapoint collected at Week 52 if the participant discontinued the study at Week 52, otherwise, it will be analyzed for the datapoint collected at the visit when the participant discontinued the study.

1.2.1 Estimands

Primary estimand defined for main key efficacy endpoints are summarized in below Table 3. More details are provided in Section 3.

Table 3 - Summary of primary estimand for main endpoints

Endpoint category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary objective: To evaluate changes in growth parameters following twice weekly SC injections of SAR442501				
Secondary endpoint (Treatment policy estimand)	Change from baseline to Week 26 and Week 52 in AGV (cm/year)	ITT	Regardless of intervention discontinuation or intake of prohibited medications that may impact growth, all data collected during the analysis period will be included in the analysis (treatment policy).	Change from baseline to Week 26, and 52, respectively, in each dose group, will be analyzed from analysis of covariance (ANCOVA) adjusting for baseline age (year), baseline height Z-score, baseline AGV and treatment arm [redacted] 95% confidence intervals and nominal p-value for each dose group as well as comparisons between two dose groups will be provided for descriptive purpose. Participants who discontinued from study drug will be encouraged to remain in the study and their non-missing height measurements will continue to be used in calculating AGV. In the event that missing data occur despite all efforts, missing height and AGV will be imputed with a conservative method specified below.

Endpoint category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
				Assuming the baseline AGV z-score (by ACH population reference) is the same as the AGV z-score (by ACH population reference) at the post-baseline time interval with missing height (ie, the time interval from "Study day of last non-missing height prior to missing value" to "Target study day of missing value at the specified visit [eg, Week 26 or Week 52]"), AGV, AGV z-score by using both healthy and ACH references, height, and height z-score by using both healthy and ACH references of this specific visit of missing will be imputed.
Secondary endpoint 2 (Treatment policy estimand)	Change from baseline to Week 26 and Week 52 in AGV Z-score	The same as Change from baseline to Week 26 and Week 52 in AGV		
Secondary endpoint 3 (Treatment policy estimand)	Change from baseline to Week 26 and Week 52 in Height Z-score	The same as Change from baseline to Week 26 and Week 52 in AGV		

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Enrolled/randomized[a]	All participants from screened population who have been allocated to an intervention regardless of whether the intervention was received or not, and regardless of replacement.
Intent-to-treat (ITT)	All enrolled/randomized participants. Participants will be analyzed according to the intervention allocated.
Safety	All enrolled/randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All participants from the safety population with at least one postbaseline PK result with adequate documentation of dosing and sampling dates and times. Participants will be analyzed according to the intervention they actually received.
Pharmacodynamics (PD)	All participants from the safety population with at least one postbaseline PD parameter assessed. Participants will be analyzed according to the intervention they actually received.
ADA	All participants from the safety population treated with SAR442501 with at least one postbaseline ADA result (positive, negative or inconclusive). Participants will be analyzed according to the intervention they actually received.

Abbreviations: ADA= anti-drug antibodies; ICF= informed consent form; ITT= Intent-to-treat; PD= Pharmacodynamics; PK= Pharmacokinetic.
a The randomization is only applicable to Cohort 1C, 2C, and 3C.

Participants exposed to study intervention before or without being enrolled/randomized will not be considered enrolled/randomized and will not be included in any analysis population. The safety experience of these participants may be reported separately.

Enrolled/randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as enrolled/randomized.

For any participant enrolled/randomized more than once, only the data associated with the first randomization/enrollment (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization/enrollment will be reported separately.

For participants receiving more than one dose level of SAR442501 (eg, due to dose rechallenge) during the study, the intervention group for as-treated analyses will be the intervention group as randomized/enrollment if the participant received at least one administration as assigned at randomization/enrollment.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

Baseline

The baseline value is defined as the last available value before the first dose of study intervention. For participants enrolled/randomized but not treated, the baseline value is defined as the last available value before enrollment/randomization.

Analysis group

Unless otherwise specified, analyses will be performed

- by dose level and overall for Stage 1 (age 3 to <6 years),
- by dose level and overall for Stage 1 (age 6 to <12 years),
- by dose level and overall for Stage 1 (age 3 to <12 years),
- by dose level and overall for Stage 2 (age<3 years),
- by dose level and overall for both stages pooled (age<12 years).

For the safety analyses defined in Section 3.6, they will be analyzed in the primary analysis period and overall study treatment period (including both primary and extended treatment period), respectively. By visit tables will be considered as an exception that the analysis will be performed in the overall study treatment period only.

Growth measurements

Regarding the position of height assessment, unless otherwise specified, the height in this SAP refers to height in standing position. Specifically,

- for children who are 2 years of age or older and can stand independently, sitting and standing height will be measured. Standing height ("Height" in Standing position in eCRF growth form) will be used for the analysis of height and height z-score;
- for infants and children who are unable to stand, crown-to-rump length and total length will be measured. The total length ("Total Body Length" in eCRF growth form) will be used for the analysis of height and height z-score.

As each growth measurement (including height [in sitting position and standing position, respectively], crown rump length, upper body length, total body length, arm span, head circumference, waist circumference, mid expiration chest circumference) are planned to be measured twice, the averaged value will be used for the analysis. In case only one measurement is taken, this single measurement will be used for the analysis.

Observation period

The observation period will be divided into the following segments:

- The **pre-treatment period** is defined as the period from the date of the ICF is signed up to first investigational medicinal product (IMP) administration.
- The **study treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration +5 days.
  - **Primary treatment-emergent period**: from the first IMP administration to the first IMP administration in extended treatment period.

  For participants who didn't receive IMP administration in the extended treatment period, the primary treatment period is the same as the **study TE period**.

  Of note, the **on-treatment period** is defined as the same as TE period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint of the occurrence of AEs, SAEs, and AESIs during the TE period are detailed in Section 3.6.2 (adverse events).

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are those secondary efficacy endpoints used to analyze changes in growth parameters, body proportionality, and foramen magnum parameters. Other secondary endpoints analyses are defined in Section 3.6.3.2 (other disease specific safety assessment), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity), Section 3.7.1.3 (quality of life analyses) and Section 3.7.1.4 (biomarker analyses).

3.3.1 Key/Confirmatory secondary endpoint(s)

To evaluate changes in growth parameters following twice weekly SC injections of SAR442501, the key secondary endpoints are as follows.

- Change from baseline to Week 26 and Week 52 in AGV Z score
- Change from baseline to Week 26 and Week 52 in AGV (cm/year)
- Change from baseline to Week 26 and Week 52 in height Z-score

3.3.1.1 Definition of endpoint(s)

Annualized growth velocity (AGV)

The post-treatment AGV will be calculated from height measurements collected during the study. The baseline AGV will also be established using height measurements assessed in the longitudinal study OBS16647, before entry in study DRI16646.

For a given time interval [Date1, Date2], the AGV (cm/year) will be defined as follows:

$$\text{AGV (cm/year)} = \frac{\text{Height at Date2} - \text{Height at Date1}}{\text{Interval length in days}} \times 365.25$$

where the interval length in days is calculated as (Date2 – Date1+1) days. AGV will be calculated for the following visits:

- At baseline, using the following interval: [Date of last height measurement in study OBS16647 at least 6 months (eg, 24 weeks) prior to Date of Week 0/Day 1 (or at least 12 weeks prior to Date of Week 0/Day 1 for participants who were under 3 years of age at the time of OBS16647 enrollment), Date of Week 0/Day 1]
- At Week 13, using the following interval: [Date of Week 0/Day 1, Date of Week 13]
- At Week 26, using the following interval: [Date of Week 0/Day 1, Date of Week 26]
- At Week 39, using the following interval: [Date of Week 0/Day 1, Date of Week 39]
- At Week 52, using the following interval: [Date of Week 0/Day 1, Date of Week 52]

Of note, although the AGV at Week 13, 39 are not part of the objective, they will be calculated to understand the longitudinal pattern of AGV.

AGV Z-scores

In order to take into account the natural growth history in children and assess the treatment effect in the absence of a placebo arm, AGV values (as calculated above) will be converted into Z-scores below by corrected for age and sex, using reference data. The reference data will be taken from an untreated ACH population and healthy population, respectively. Unless LMS parameters are not available for reference, the Z-score will be calculated by LMS parameters corrected by sex and age.

$$\text{Z-score} = \frac{\text{Actual value} - \text{Reference value}}{\text{SD (Referencegroup)}} \text{ or } \begin{cases} \frac{(\frac{Actual\ value}{M})^{L}-1}{S \times L} & when\ L \neq 0 \\ \frac{ln(\frac{Actual\ value}{M})}{S} & when\ L = 0 \end{cases},$$

where SD is the standard deviation, L is the power in the Box-Cox transformation, M is the median, and S is the generalized coefficient of variation.

Specifically, in order to assess the growth in ACH population versus healthy population, for participants in age cohorts of <3 years and 3 to <6 years, the AGV Z-score will be calculated based on Table VII A and B in reference paper (1); for participants in age cohort of 6 to <12 years, AGV Z-score will be calculated based on Supplementary Table 2a in reference paper (2). AGV reference charts are also available in Section 5.8.

To confirm that the data collected are consistent with the reference ACH population, alternative Z-scores corrected for AGV will be constructed using LMS parameters generated from the growth curve work done by PEDSnet through PEDSnet (pedsnet.org) database.

Height Z-scores

Regarding the position of height assessment,

- for children who are 2 years of age or older and can stand independently, sitting and standing height will be measured. Standing height ("Height" in Standing position in eCRF growth form) will be used for the analysis of height and height Z-score;
- for infants and children who are unable to stand, these measurements will be crown-to-rump length and total length. The total length ("Total Body Length" in eCRF growth form) will be used for the analysis of height and height Z-score.

In order to assess the growth in ACH population versus healthy population, the height will be converted into Z-scores corrected for age and sex, using WHO 2006 database (3).

To confirm that the data collected are consistent with the reference ACH population, alternative Z-scores corrected for AGV will be constructed using LMS parameters generated from the growth curve work done by PEDSnet through PEDSnet (pedsnet.org) database.

3.3.1.2 Main analytical approach

Analysis population

For the above growth-related measures including AGV, AGV Z-score and height Z-score in ITT population.

Analysis of method

For AGV, AGV Z-score and height Z-score the test of null hypothesis of no change from baseline will be conducted via analysis of covariance (ANCOVA) adjusting for baseline age (year), baseline height Z-score, baseline AGV and treatment arm[redacted]

Sample SAS code for ANCOVA model

```
PROC MIXED DATA=IN;

BY AGE_GROUP;

CLASS TRT;
```

MODEL CHG = BL_AGE BASE_HEIGHT_ZSCORE BASE_AGV TRT;

LSMEANS TRT / DIFF CL;

RUN;

The variable CHG refers to change from baseline in AGV (or AGV Z-score, height Z-score) at Week 13, 26, 39 and 52, BL_AGE refers to Age at baseline (years), BASE_HEIGHT_ZSCORE and BASE_AGV refers to the baseline height Z-score and baseline AGV value (cm/year) respectively, TRT refers the dose group in [redacted], AGE_GROUP refers to the age group in <3 years, 3 to <6 years, 6 to <12 years, 3 to <12 years (for all participants in Stage 1 combined), and <12 years (for both stage combined).

Intercurrent event(s) handling strategy

Regardless of intervention discontinuation or intake of prohibited medications that may impact growth, all data collected during the analysis period will be included in the analysis (treatment policy).

Missing data handling

Participants who discontinued from study drug will be encouraged to remain in the study and their non-missing height measurements will continue to be used in calculating AGV. In the event that missing data occur despite all efforts, missing height and AGV (as well as Z-scores [regardless of using untreated ACH population, or healthy population as reference]) will be imputed with a conservative method specified below.

Missing post-baseline height at Week 13, 26, 39 or 52 will be imputed with a single value assuming that the baseline AGV z-score by using untreated ACH population as reference is the same as the AGV z-score by using untreated ACH population as reference at the post-baseline time interval with missing height (ie, time interval from “Study day of last non-missing height prior to missing value” to “Target study day of missing value”). The target study day can be found in Section 5.5.

Specifically, assuming

AGV z-score at baseline (by using untreated ACH population as reference) =AGV z-score at the time interval with missing height (by using untreated ACH population as reference), then

- Imputed AGV at the interval with missing (cm/year) = AGV z-score at baseline (by using untreated ACH population as reference) x SD of reference (by using untreated ACH population as reference) AGV at the age with missing (cm/year) + Mean of reference (by using untreated ACH population as reference) AGV at age with missing (cm/year), and
- Imputed missing height (cm) = imputed AGV at the interval with missing height (cm/year) x time interval with height missing (year) + last non missing height prior to the missing (cm)

where

- AGV z-score (by using untreated ACH population as reference) at baseline, using the time interval specified in Section 3.3.1.1
- AGV z-score (by using untreated ACH population as reference) at the time interval with height missing, using the following interval: [Study day of last non-missing height prior to missing value, Target study day of missing value]. For example, if the height is missing at Week 52 and the last available height available prior to missing is Week 39, then the interval is [Study day of Week 39, Target study day of Week 52].

With missing height imputed, the AGV and AGV Z-score (regardless of using untreated ACH population, or healthy population as reference) at the week with missing will be calculated using the time interval specified in Section 3.3.1.1.

Population level summary

The estimated least square (LS) mean, standard deviation, 95% confidence intervals and nominal p-value from ANCOVA model for each dose group as well as comparisons between two dose groups will be provided for descriptive purpose.

Descriptively summary of observed values after imputation in AGV, AGV Z-score, and height Z-score at baseline and all post-baseline visits, as well as change from baseline with assessment (eg, Week 13, 26, 39 and 52) will also be provided.

3.3.1.3 Sensitivity analyses

To support robustness of results, the analyses below will be conducted.

Treatment policy estimand with different missing data imputation method

This sensitivity analysis will use different missing data imputation method discussed below.

- Step 1: Missing data imputation
  - Step 1A, for missing height at Week 13, 26, 39 or 52 due to adverse event or lack of efficacy (ie, if the treatment discontinuation reason is adverse event or lack of efficacy, then any data which is supposed to be collected on or after treatment discontinuation will follow this category), by assuming the baseline AGV z-score is the same as the AGV z-score at the post-baseline missing data period, the same missing data handling approach will be used as in Section 3.3.1.2.
  - Step 1B, for missing height data at Week 13, 26, 39 or 52 due to any reasons other than adverse event or lack of efficacy (eg, if the treatment discontinuation reason is due to any reasons other than adverse event or lack of efficacy, then any data which is supposed to be collected after treatment discontinuation will follow this category; missing data when treatment is ongoing will also follow this category), multiple imputation with missing at random assumption will be performed for height at the specified visit to deal with missing data. The imputation model includes baseline age,

baseline height Z-score, baseline AGV and all observed height value during all the post-baseline visits up to week 52 and will be stratified by treatment group [redacted] and age group (ie, <3 years, 3 to <6 years, 6 to <12 years). Since the pattern of missing data could be non-monotone and all covariates are continuous, a MCMC method will be used. A minimum value of 0 will be specified in order to avoid negative imputed height value. Missing height values will be imputed 100 times to generate 100 complete data sets. The missing AGV and AGV Z-score will be calculated based on the imputed height.

- In summary, in those 100 complete datasets after imputation, for missing height from Step 1A, the same set will be used to generate those 100 complete datasets; for missing height from Step 1B, different 100 subsets will be used to generate those 100 complete datasets.

- Step 2: Analyze each of 100 imputed datasets with the same ANCOVA model as specified in Section 3.3.1.2 to generate the least-squares (LS) mean change from baseline for each treatment group, along with the difference in LS means between two treatment arms.
- Step 3: The estimates from the 100 analyses from Step 2 will be combined using Rubin's formulae using SAS PROC MIANALYZE.

Sample SAS code for multiple imputation

```
PROC MI DATA=IN2 OUT=IN2OUT SEED=16646 NIMPUTE=100 MINIMUM=0;

VAR BL_AGE BASE_HEIGHT_ZSCORE BASE_AGV

HEIGHT_W13 HEIGHT_W26 HEIGHT_W39 HEIGHT_W52;

By TRT AGE_GROUP;

RUN;
```

Additional sensitivity analysis may be planned if any participant received different dose level during the first 52 weeks.

3.3.1.4 Supportive analyses

Supportive analysis 1 (while on treatment estimand)

This sensitivity analysis will be the same as the main analysis approach in Section 3.3.1.2, except that height data collected after treatment discontinuation or intake of prohibited medications (eg, per medical review) that may impact growth will not be used, and no missing imputation method will be performed.

Supportive analyses 2 (external control comparison)

To support the clinical development of SAR442501 for ACH, the untreated ACH patients, from PEDSnet database, will be taken as an external control arm to compare the growth parameters and

foramen magnum with ACH participants who received SAR442501 in study DRI16646 for assessment of the treatment effect of SAR442501 in growth parameters and foramen magnum. The analysis is detailed in Section 5.7.

3.3.2 Supportive secondary endpoint(s)

To evaluate changes in body proportionality following twice weekly SC injections of SAR442501 for 52 weeks, the supportive secondary endpoints are change from baseline to Week 26 and Week 52 in the following calculated body proportionality ratios:

- Upper to lower body segment ratio
- Upper to lower extremity ratio
- Sitting to standing height ratio (crown-to-rump length to total length for infants)
- Arm span to height ratio
- Upper arm to forearm length ratio
- Upper leg to lower leg ratio
- Head circumference to height ratio

In addition, to evaluate changes in foramen magnum parameters via magnetic resonance imaging (MRI) following twice weekly SC injections of SAR442501 (Stage 2 only), change from baseline to Week 52 in bony foramen magnum cross-sectional area as well as additional brainstem, skull, and spine morphometric and volumetric parameters in participants birth to age <3 years will be performed. Based on the availability of reference growth chart, the foramen magnum parameters may be converted and analyzed in z-scores by using ACH population as reference. However, it will not be converted to z-score by using healthy references since this is not a regular exam for healthy pediatric population.

3.3.2.1 Definition of endpoint(s)

Calculated ratios:

- Upper-to-lower body segment ratio (cm/cm)

  Will be calculated by (standing height or total length - lower body segment length [cm]) divided by lower body segment length (cm)

- Upper-to-lower extremity ratio (cm/cm)

  Will be calculated by (upper arm + forearm length [cm]) divided by (upper leg + lower leg length [cm])

- Sitting-to-standing height ratio (crown-to-rump length to total length for infants) (cm/cm)

  Will be calculated by sitting height (cm) divided by standing height (cm), or crown-to-rump length (cm) divided by total length (cm).

- Arm span to height ratio (cm/cm)

  Will be calculated by arm span (cm) divided by standing height (cm), or arm span (cm) divided by total length (cm).

- Upper arm to forearm length ratio (cm/cm)

  Will be calculated by upper arm length (cm) divided by forearm length (cm).

- Upper leg to lower leg length ratio (cm/cm)

  Will be calculated by upper leg length (cm) divided by lower leg length (cm).

- Head circumference to height ratio (cm/cm)

  Will be calculated by head circumference (cm) divided by standing height (cm), or head circumference (cm) divided by total length (cm).

3.3.2.2 Main analytical approach

For those supportive secondary endpoints of body proportionality ratios, change from baseline at each post-baseline visits in ITT population will be analyzed with mixed model repeated measures analysis (MMRM) with covariates of baseline age, baseline value, visits, treatment arm, treatment arm-by-visit interaction.

To model the within subject errors, an unstructured (UN) covariance structure will first be fitted, and if the model does not converge (eg, not both Hessian and G matrix being positive definite), the model will be re-fitted using the covariance matrices of the following order specified by a decreasing number of covariance parameters until convergency is met: Heterogeneous Toeplitz (TOEPH) , Heterogeneous First-order autoregressive (ARH(1)) , Homogeneous Toeplitz (TOEP), AR(1), Heterogeneous compound symmetry (CSH), compound symmetry (CS).

The first covariance structure yielding convergence will be used in the analysis. When the unstructured covariance matrix is used, the Kenward Roger approximation (DDFM=KR in SAS PROC MIXED) will be used to estimate the denominator degrees of freedom, otherwise, denominator degrees of freedom will be estimated using the between within method (DDFM=BW in SAS PROC MIXED).

For change from baseline to Week 52 in bony foramen magnum cross-sectional area as well as additional brainstem, skull, and spine morphometric and volumetric parameters in participants birth to age <3 years, the analyses will be the same as the main analysis approach in Section 3.3.1.2, except that no imputation will be performed.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

[redacted]

3.5 MULTIPLICITY ISSUES

No adjustment for multiplicity will be conducted.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not enrolled/randomized) may be provided separately.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population. The analysis will be conducted in primary treatment period, and overall study treatment period, respectively.

Duration of IMP exposure

Duration of overall IMP exposure is defined as last IMP administration date for participants who have completed the treatment or discontinued treatment early [or data cutoff date for participants who are still ongoing the treatment] – first IMP administration date + 5 days for participants who have completed the treatment or discontinued treatment early [or + 1 day for participants who are still ongoing the treatment], regardless of unplanned intermittent discontinuations.

- **Duration of IMP exposure in primary treatment period** is defined as the first IMP administration date in extended treatment period – first IMP administration date.

  For participants who didn't receive IMP administration in the extended treatment period, the **duration of IMP exposure in primary treatment period** is the same as **the duration of overall IMP exposure**.

If the date of the last dose of IMP is missing (which only happens when subjects did not receive any recorded IMP administration), the duration of IMP will be left as missing.

Duration of IMP exposure in primary and overall treatment period, respectively, will be summarized quantitatively and categorically.

During the primary treatment period, the IMP exposure will be summarized numerically and categorically as 1 to ≤13 weeks, >13 weeks to ≤26 weeks, >26 weeks to ≤39 weeks, >39 weeks to <52 weeks, and ≥52 weeks. The IMP exposure in overall study treatment period will be summarized similarly.

Additionally, the cumulative duration of IMP exposure in primary and overall study treatment period, respectively (expressed in participant-years) will be provided.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of administrations as required by the protocol.

Percentage of overall treatment compliance for a participant is defined as the number of administrations that the participant was compliant (eg, planned and administered) divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

- **Percentage of treatment compliance in the primary treatment period** for a participant is defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP in the primary treatment period.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%, in primary and overall treatment period, respectively.

In addition, number of participants who missed ≥4 not-for-cause consecutive doses (for-cause is for the situation such as when the missed doses are required by the protocol due to an AE or SAE) and number of participants who missed ≥13 total doses during the primary treatment period will be summarized.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the overall treatment-emergent period
  - TEAEs in primary treatment period: AE that developed, worsened or became serious during the treatment-emergent primary treatment period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed.

The primary AE analyses will be on TEAEs in primary treatment period. Pre-treatment and post-treatment AEs may also be described.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 5.

Table 5 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the overall incidence
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any TEAE related to IMP as per Investigator's judgment
- Any treatment-emergent SAE
- Any treatment-emergent SAE related to IMP as per Investigator's judgment
- Any TEAE leading to permanent intervention discontinuation
- Any treatment-emergent AESI
- Any TEAE leading to death

The AE summaries of Table 6 will be generated with number (%) of participants experiencing at least one event.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, and PT
	PT
TEAE related to IMP as per Investigator's judgment	Primary SOC, and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC, and PT

Type of AE	MedDRA levels
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC, and PT
TEAE leading to permanent intervention discontinuation	Primary SOC, and PT
Pretreatment AE[a]	Primary SOC and PT
Post-treatment AE[a]	Primary SOC and PT

a Will be analyzed if deemed necessary.

Analysis of deaths

Any AE leading to death during the pre-treatment, treatment-emergent, and post-treatment period will be provided in a listing. Death as an outcome of the AE as reported by the Investigator in the AE page.

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 7. Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT if applicable. Tables will be sorted as indicated in Table 5.

Table 7 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Selection
AESI (see Protocol Section 8.4.8 for the definition)	e-CRF specific tick box on the AE page
ACH-related events of interest (See Protocol Section 8.3.5 for the definition)	e-CRF category of Achondroplasia event on the AE page
Injection site reactions	e-CRF category of Injection site reaction on the AE page

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units and conventional units, if applicable.

- Hematology:
  - Red blood cells and platelets and coagulation: Platelet count, Red blood cell (RBC) count, Hemoglobin, Hematocrit, RBC indices: Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), %Reticulocytes
  - White blood cells: white blood cell count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils

- Clinical chemistry:
  - Metabolism: glucose [non-fasting], albumin
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus (phosphate), bicarbonate, magnesium
  - Renal function: creatinine, blood urea nitrogen
  - Liver function: Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT), Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, total, direct, and indirect bilirubin
  - Pregnancy test (will be analyzed if deemed necessary): [Serum or highly sensitive urine] human chorionic gonadotropin (hCG) pregnancy test
- Endocrine: 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, Calcitonin, FGF23, Parathyroid hormone level, TSH with reflex
- Vital signs: systolic and diastolic blood pressure, heart rate, and respiratory rate
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/ Fridericia formula)

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each planned visit through the study, the last value and the worst value (minimum and/or maximum value depending on the parameter). The last and the worst value in the primary treatment period, and overall on-treatment period will be presented, respectively. These analyses will be performed using central measurements for laboratory variables.

For selected parameters of interest, mean changes from baseline with the corresponding standard error may be plotted over time.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock (also available in Table 12). For study specific safety parameters, they will be analyzed based on PCSA listing detailed in Table 13.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period in primary and overall treatment period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

3.6.3.2 Other disease specific safety assessments

The following disease specific safety assessment variables will be analyzed by visit.

- Physical examinations: head, eyes, ear, nose, throat, cardiovascular, skin, lymphatic system, respiratory system, gastrointestinal system, genitourinary system, musculo/skeletal
- Neurological examinations: mental status, motor system, sensory system, reflex, cranial nerve
- Ocular assessments (left eye and right eye respectively): visual acuity, optic fundus/optic nerve, interpretation through amsler grid, interpretation through optical coherence tomography
- Tanner stage of pubertal development in participants age>5 years: public hair stage, genitalia stage for boy, breast stage for girl
- Chest circumference (collected under “Growth measures”)
- DXA scans (Stage 1 only): bone marrow content (BMC) and bone marrow density (BMD) data (including Z-scores) for whole body less head, and the lumbar spine.
- X-ray assessment procedures: posterior-anterior (PA) X-rays of the hand and wrist to assess bone age, growth plates, hand length, and cortical thickness; anterior-posterior (AP) lower extremity X-ray to assess growth plates, tibial length, cortical thickness, and bowing; lumbar imaging X-rays to measure changes from baseline in bone morphology and pathology.

Similar analysis will be performed as in Section 3.6.3.1.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

Measured plasma concentrations and PK parameters for SAR442501 as defined in Table 8 will be summarized using descriptive statistics [eg, mean, SD, median, min-max, and coefficient of variation (%CV)]. In addition, PK analysis may be conducted using a PopPK approach. The details of the analysis will be presented in a separate PopPK analysis plan and the results will be presented in a separate PopPK report.

Table 8 - List of PK parameters and definitions

Parameters	Definition
C_{max}	Maximum concentration observed
t_{max}	Time to reach C_{max}
C_{trough}	Concentration observed just before drug administration during repeated dosing
$AUC_{0-\tau}$	Area under the concentration versus time curve over the dosing interval (T)

Potential correlations between the PK exposure of SAR442501 and changes in secondary efficacy endpoints (ie, AGV) and PD biomarkers from baseline to Week 26 and Week 52 will be explored using graphic method or regression analysis if applicable.

3.7.1.2 Immunogenicity analyses

Participant's ADA status, response variable and kinetics of ADA responses (see definitions below) will be summarized on the ADA population for each ADA assayed separately.

Kinetics of ADA responses will be described for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately. Time to ADA onset and duration of ADA will be described with minimum, Q1, median, Q3 and maximum statistics.

Peak titer will be described with minimum, Q1, median, Q3 and maximum statistics for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately.

Sample status (negative, positive, inconclusive) and titers will also be described overtime using descriptive statistics.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

Participant's ADA status

- Participants with **pre-existing ADA**s correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
    - Participants with **treatment-induced ADA**s correspond to participants with ADAs that developed during the treatment-emergent (TE) period and without pre-existing ADA (including participants without pre-treatment samples).
    - Participants with **treatment-boosted ADA**s correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A 2-fold serial dilution schema is used during titration, so at least a 4-fold increase will be considered as significant.

Kinetics of ADA response

Kinetics of ADA response will be derived for participants with treatment-induced/boosted ADA considering ADA samples collected during the TE period.

- **Time to onset of ADA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ADA.

ADA response variable:

- **ADA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.

3.7.1.3 Quality of life analyses

All analyses in quality of life will be analyzed descriptively in ITT population. For the continuous measures, change from baseline at each post-baseline visits in ITT population will be analyzed with the same mixed model repeated measures analysis (MMRM) as discussed in Section 3.3.2.2.

Changes in health-related QoL as measured by the PedsQL Inventory Generic Core Scale

The PedsQL core scale is a brief, standardized, generic instrument that is used to measure HRQOL in various pediatric conditions (4). This scale consists of 23 items across the domains of physical, social, emotional, and school functioning. The instrument uses a recall period of the past month, and responses range from "Never" to "Almost Always" on a 5-point verbal rating scale. Higher scores indicate better HRQOL and lower severity of -symptoms/problems (4).

Caregivers will complete the PedsQL Core Scale and Multidimensional Fatigue Scale parent proxy report for participants 2 years of age and older and the Pediatric Pain Questionnaire for participants 5 years of age and older. In addition, participants 8 years of age and older will complete the PedsQL child self-report for all PedsQL scales. The details of PedsQL assessment by reporter and age range are available in Table 9.

Table 9 - PedsQL assessments by reporter and age range

Version	Reporter
Child report (8 to12 years of age)	Child
Teen report (13 to 18 years of age)	Child
Parent report for toddlers (2 to 4 years of age)*	Parent
Parent report for young children (5 to 7 years of age)	Parent
Parent report for children (8 to 12 years of age)	Parent
Parent report for teens (13 to 18 years of age)	Parent

*Core Scale and Multidimensional Fatigue Scale only

To ease interpretation, the raw scores will be reversed and converted to scores scaled in 0-100 for analysis purpose by following the steps below so that higher scores indicate better quality of life scores.

Specifically, to reverse score, transform the 0-4 scale items to 0-100 as follows and Table 10:

1. To create Scale Scores (ie, in physical, social, emotional, and school functioning), if more than 50% of the items in the scale are missing, the Scale Score will not be computed. If 50% or more of the items in the scale are completed, compute the Scale Score using the sum of non-missing items scores divided by the number of items answered.
2. The PedsQL Generic Core Scales:
   - Psychosocial Health Summary Score: the mean is computed as the sum of the item scores over the number of items answered in the Emotional, Social, and School Functioning Scales;
   - Physical Health Summary Score: the same as the Physical Functioning Scale Score.
3. To create the Total Scale Score, the mean is computed as the sum of all the item scores over the number of items answered on all the Scales.

Table 10 - PedsQL raw score to scaled score conversion table

Response Choices	Never	Almost Never	Sometimes	Often	Almost Always
Raw Scores	0	1	2	3	4
0-100 Scale Scores	100	75	50	25	0

Scale Scores in social, emotional, and school functioning, Scale Psychosocial Health Summary Score, Scale Physical Health Summary Score and the Total Scale Score will be calculated based on the 0-100 scale scores. Their computed values and changes from baseline will be summarized by reporter and age range in Table 9 at Week 26 and 52.

Changes in fatigue as measured by the PedsQL Multidimensional Fatigue Scale

The PedsQL Multidimensional Fatigue Scale consists of 18 items across three domains: general fatigue, sleep/rest fatigue and cognitive fatigue (comprised of 6 items each) (5). The instrument uses a recall period of the past month, and responses range from “Never” to “Almost Always” on a 5-point verbal rating scale. Higher scores indicate lower severity of symptoms/problems (6). Mean scale scores for each domain as well as the Total Score will be calculated.

The score will be imputed and analyzed by using the same method for the PedsQL Generic Core Scales. Their computed values and changes from baseline at Week 26 and 52 in the general fatigue sale, sleep/rest fatigue scale, and cognitive fatigue scale scores and total scale score will be summarized by reporter and age range.

Changes in pain as measured by the PedsQL Pediatric Pain Questionnaire

The PedsQL Pediatric Pain Questionnaire assesses current pain and worst pain intensity in the last week using a Visual Analog Scale as well as pain location using a body diagram/map (7). Current

and worst pain are scored separately, and scoring is based on the line length to the nearest 0.5 cm (5 mm). Higher scores indicate greater levels of pain intensity. The pain location item is not scored. The PedsQL Pediatric Pain Questionnaire will only be administered in participants aged 5 years of age and older using both self-report (ages 8 and older) and parent proxy report (ages 5 and older) forms in all countries. The toddler version (2 to 4 years, parent proxy report form) will not be administered in some countries as per Protocol Section 8.2.1.1.3.

For the current pain and worst pain intensity, no imputation process is required since these are single-item VAS scales. The observed scores based on the 100 mm VAS and the change from baseline will be summarized by reporter and age range at Week 26 and 52.

Changes in mobility as measured by the STEMS

The STEMS will be completed by clinicians for participants 5 years of age and older. The STEMS captures mobility, use of mobility aides, and impact of pain and/or fatigue at the end of the day across three environments: home, school/work, and community (8). Mobility aides are recorded using a numeric 5-point rating scale where 1 = independent on all surfaces including stairs, 2 = use of sticks, 3 = use of crutches, 4 = use of wheeled walking device, and 5 = use of wheelchair or mobility scooter. Patient-reported symptoms are recorded using letters where A = no pain or fatigue, B1= pain only, B2 = fatigue, and C = pain and fatigue. This is completed for each of the three environments resulting in three scores, whereby the numeric rating reflects the use of mobility aides, and the letter reflects the symptoms. eg, 1A, 1B1, 1C.

The change from baseline in use of mobility aides (score of 1-4), and impact of pain and/or fatigue (score of A, B1, B2, C), at Week 26 and 52 respectively in each environment will be summarized descriptively for participants 5 years of age and older. The change from baseline in the composite score (eg, 1A, 1B1, 1C) may also be analyzed as part of exploratory analyses.

Changes in developmental milestone data as measured by the Achondroplasia Developmental Recording Form

For participants <3 years of age, achievement of developmental milestones will be assessed using the ACH Developmental Recording Form (ADRF). The ADRF was developed to aid clinicians in monitoring the development of young children with ACH over time across multiple skill areas (9). This form allows developmental milestones to be recorded and is not a formalized screening tool or assessment. The form measures the domains of gross motor function, fine motor function, communication, and feeding via participant reports to the Investigator. The form depicts the cumulative percentage distributions for children with ACH for each item as well as norms for reference based on the Denver II test, where available.

The proportion of participants achieve each of the milestone will be estimated using the Kaplan-Meier methodology for Stage 2 participants. The time to achieve the milestone is defined as the age in month on which the milestone achieves. If by the time of analysis, the milestone is not achieved, the participant will be considered as censoring at Week 52 or the date of last contact (if the participant is discontinued earlier from the study), whichever comes first.

The following items will be analyzed in each milestone in the subcategory of gross motor, fine motor, communication, and feeding milestones.

- Number of participants, number and percentage of censored participants, and number and percentage of participants achieve milestones at baseline, and number and percentage of participants achieve milestone by Week 52
- Among participants who didn't achieve milestones at Week 52, The median time to achieve milestones and the associated 2-sided 95% confidence intervals (CIs) estimated by Kaplan-Meier method.

[redacted]

3.7.1.4 Biomarker analyses

To characterize changes from baseline in bone/collagen biomarkers following twice weekly SC injections of SAR442501, the observed value at baseline, Week 26, Week 52, and change from baseline at Week 26 and 52 will be summarized in CXM, osteocalcin, bone-specific alkaline phosphatase, P1NP, CTX levels.

All the above biomarkers will be analyzed using PD population. Observed, change from baseline values and percent change from baseline values will be summarized at scheduled visits. Summary plots of the mean values over time for some of the biomarker endpoints may be provided if deemed necessary.

3.7.2 Subgroup analyses

As described in Section 3.1, all analyses described in this SAP will be performed by age group. In addition, the key secondary endpoints in Section 3.3.1 may also be analyzed by sex, and by dose and pooled in all Stage 1 (3 to <12 years) participants, and by sex, and by dose and pooled in all Stage 1 and 2 (<12 years) participants through the main analytical approach.

3.8 INTERIM ANALYSES

[redacted]

[redacted]

3.9 DATA MONITORING COMMITTEE (DMC)

As summarized in the DRI16646 Protocol Section 4.1 and DMC charter, DMC meetings will be held to primarily review safety data of older participants on lower dose cohort to decide if enrolling younger subjects and higher does cohort. Thus, all DMC meeting (with the exception to 2 formal interim analyses as outlined in Section 3.8) will focus on below safety data:

- Disposition
- Medical history and Demographics
- Prior and concomitant medications
- Extent of exposure
- TEAEs, TE-SAEs, TE-AESIs, and all deaths
- Clinical laboratory data, vital signs, ECG, X-Ray (after Week 52) and DXA (after Week 52)

Accordingly, all analyses specified in Section 3.6.1, Section 3.6.2, Section 3.6.3 (Clinical laboratory data, vital signs, ECG, X-Ray and DXA only), Section 5.2 and Section 5.3 will be performed by using cumulative data at the time of DMC data cutoff date.

During the formal interim analyses (ie, IA 1 and IA 2), DMC will review both safety and key efficacy data as specified in Section 3.8 in case there is a need for DMC to make recommendation based on the benefit risk ratio. PK data will be analyzed internally and may be shared with DMC if requested.

3.10 CHANGES TO PROTOCOL-PLANNED ANALYSES

- For missing data of AGV and AGV z-score, it was specified as *no imputation will be used in the analysis* as in Protocol Section 9.2.3. However, in this SAP, for the purpose of robustness assessment, both with and without imputation, will be used in analyses. They are detailed in Section 3.3.
- The AGV interval length in days will be calculated as (Date2 – Date1+1) days as defined in Section 3.3, instead of as (Date2 – Date1) days as in Protocol Section 9.2.3.
- The PD population was defined as “all participants from the ITT population with at least one postbaseline PD parameter assessed” in the protocol, however in order to align with PK population, the definition of PD population in this SAP is changed to “all participants from the safety population with at least one postbaseline PD parameter assessed” as in Table 4.
- [redacted].

4 SAMPLE SIZE DETERMINATION

The sample size was defined based on empirical considerations. No formal determination was performed. It is considered sufficient for the descriptive nature of the study regarding safety and efficacy evaluation for dose selection. Participants who discontinue study treatment or withdraw from the study may be replaced.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

%CV:	coefficient of variation
ACH:	achondroplasia
ADA:	Anti-drug antibody
AE:	adverse event
AESIs:	adverse events of special interest
AGV:	annualized growth volecity
ANCOVA:	analysis of covariance
AP:	anterior-posterior
BMC:	bone marrow content
BMD:	bone marrow density
[redacted]	
CTX:	collagen-type 1 C-Telopeptide
CXM:	collagen X biomarker
ECG:	electrocardiogram
HLT:	high level term
IA:	interim analysis
IMP:	investigational medicinal product
LLT:	lower-level term
LS:	least square
MedDRA:	medical dictionary for regulatory activities
MMRM:	mixed model repeated measures
MRI:	magnetic resonance imaging
P1NP:	procollagen type 1 N-terminal propeptide
PA:	posterior-anterior
PCSA:	potentially clinically significant abnormality
PT:	preferred term
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
STEMS:	Screening Tool for Everyday Mobility and Symptoms
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled/randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Enrolled/Randomized participants
- Enrolled/Randomized but not exposed participants
- Enrolled/Randomized and exposed participants
- Participants who is ongoing in the primary treatment period
- Participants who completed the primary treatment period as per protocol
- Participants who did not complete the primary treatment period as per protocol and main reason for permanent intervention discontinuation
- Participants who is ongoing in the extended treatment period
- Participants who completed the extended treatment period as per protocol
- Participants who did not complete the extended treatment period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed the study as per protocol
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

The number of exposed and not enrolled/randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, enrolled/randomized, with permanent full intervention discontinuation and with early study discontinuation may be provided by country and site/geographical region, country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized/enrolled population as well as displayed separately as related versus not related to COVID-19 if applicable.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized/enrolled population.

Demographic characteristics

- Age in years as quantitative variable and in categories (<3, 3 to <6, 6 to <12 years)
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown, Multiple)

Baseline characteristics

- Tanner public hair stage for participants age>5 years (Stage I, II, III, IV, V)
- Tanner genitalia stage for boys age>5 years (Stage I, II, III, IV, V)
- Tanner breast stage for girls age>5 years (Stage I, II, III, IV, V)
- Weight (kg)
- Body mass index (kg/m^2)

Baseline characteristics in growth parameters

- Height (cm)
- Height Z-score
- AGV (cm/year)
- AGV z-score
- Upper to lower body segment ratio
- Upper to lower extremity ratio
- Sitting to standing height ratio (crown-to-rump length to total length for infants)
- Arm span to height ratio
- Upper arm to forearm length ratio
- Upper leg to lower leg ratio
- Head circumference to height ratio
- Foramen magnum (age<3 years)

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Specific disease history includes medical or surgical history, and achondroplasia history. They will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the enrolled/randomized population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Handing of partial date of birth/diagnosis date

If partial date of birth/diagnosis date is collected in eCRF, for the purpose of analysis, the missing month will be imputed to June, and the missing day will be imputed to 15th. Year will not be imputed.

Handling of missing data for categorical variable

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on case report form - exposure single dose page.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment, during, or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. Further, if the primary treatment period or extension treatment period cannot be determined, then this AE will be considered as a TEAE started during primary treatment period. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of enrollment/randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose administration date should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP.

Handling of missing severity/grades of adverse events

If the severity/grade is missing for one of the occurrences of an adverse, the maximal severity on the remaining occurrences during the same period (eg, pre-treatment, treatment-emergent period, post-treatment period) will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

For PCSA including condition based only on change from baseline, the analysis is restricted to participants having a baseline and at least one post-baseline value during the analysis period.

For PCSA including two conditions one based on change from baseline and the second one on the value, the PCSA criteria will be restricted to threshold based on value only for any baseline record or in case of the first condition being missing due to missing baseline. And the analysis is restricted to participants having at least one post-baseline value during the analysis period.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG, ADA, and other safety parameter will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 APPENDIX 5 Target study day for growth measurement

Table 11 - Target study day for growth measurement

Visit	Target day	Start day	End day
Week 0	1	1	1
Week 8	57	57	57
Week 13	92	89	95
Week 26	183	180	186
Week 39	274	271	277
Week 52	365	362	366
Week 64	449	446	452
Every 12 weeks afterwards (Week [xx])	7*xx+1	7*xx-2	7*xx+4
…			

5.6 APPENDIX 6 PCSA CRITERIA

Table 12 - Criteria for Potentially Clinically Significant Abnormalities for studies in children (according to BTD-009536 Version 3.0 dated on 21-May-2014)

Parameter	Age range	PCSA	Comments
ECG parameters			Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009

Parameter	Age range	PCSA	Comments
HR	Birth/0 to 27 days old (Neonates)	≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm	
	28 days/1 month to 23 months old (Infants)	≤80 bpm and decrease from baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm	
	24 months/2 years to <6 years old (Children)	≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
	6 to <12 years old (Children)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
	12 to 16/18 years old (Adolescents)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	Birth/0 to 27 days old (Neonates)	≥120 ms	
	28 days/1 month to 23 months old (Infants)	≥140 ms	
	24 months/2 years to <6 years old (Children)	≥160 ms	
	6 to <12 years old (Children)	≥170 ms	
	12 to 16/18 years old (Adolescents)	≥180 ms	
QRS	Birth/0 to 27 days old (Neonates)	≥85 ms	
	28 days/1 month to 23 months old (Infants)	≥85 ms	
	2 to <6 years old (Children)	≥95 ms	
	6 to <12 years old (Children)	≥100 ms	
	12 to 16/18 years old (Adolescents)	≥110 ms	
QTc	Birth/0 to <12 years old (Neonates, Infants, Children)	Absolute values (ms) Borderline: 431-450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	**To be applied to QTcF** *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.
	12 to 16/18 years old (Adolescents)	Borderline: 431-450 ms (Boys); 451-470 ms (Girls) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	

Parameter	Age range	PCSA	Comments
Vital Signs			Ref. : Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
SBP	Birth/0 to 27 days old (Neonates)	≤60 mmHg and decrease from baseline ≥20 mmHg ≥85mHg and increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP or DBP ≥95th percentile for gender, age, and height on ≥3 occasions
	28 days/1 month to 23 months old (Infants)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6 years old (Children)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥101mHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50mHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54mHg and increase from baseline ≥10 mmHg	
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59mHg and increase from baseline ≥10 mmHg	
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72mHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78mHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP : St — Su ≤ - 20 mmHg DBP : St — Su ≤ - 10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4°F/38.0°C Oral or pacifier: ≥99.5°F/37.5°C Axillary or skin infrared: ≥99°F/37.2°C	Ear temperature not accurate below 6 months of age
Respiratory rate	Birth/0 to 27 days old (Neonates)	<30 per minutes >60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	<24 per minutes >40 per minutes	
	24 months/2 years to <6 years old (Children)	<22 per minutes >34 per minutes	
	6 to <12 years old (Children)	<18 per minutes >30 per minutes	
	12 to 16/18 years old (Adolescents)	<12 per minutes >20 per minutes	

Parameter	Age range	PCSA	Comments
Sa02	All age ranges	≤95%	
Weight	All ranges	≥5% weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007
Clinical Chemistry			Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005 ; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
ALT/SGPT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 6 to 50 U/L (0-5 days), 5 to 45 U/L (1-19 years)
AST/SGOT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 35 to 140 U/L (0-5 days), 15 to 55 U/L (1-9 years), 5 to 45 U/L (10-19 years)
Alkaline Phosphatase	All age ranges	≥1.5 ULN	Based on normal ranges: 145 to 420 U/L (1-9 years), 130 to 560 U/L (10-11 years), 200 to 495 U/L (Boys 12-13 years), 105 to 420 U/L (Girls 12-13 years), 130 to 525 U/L (Boys 14-15 years), 70 to 130 U/L (Girls 14-15 years), 65 to 260 U/L (Boys 16-19 years), 50 to 130 U/L (Girls 16-19 years)
Total Bilirubin	All age ranges	≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)

Parameter	Age range	PCSA	Comments
Conjugated Bilirubin	All age ranges	>35% Total Bilirubin and TBILI≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal range: 0 to 0.4 mg/dL
ALT and Total Bilirubin	All age ranges	ALT ≥3 ULN and Total Bilirubin ≥2 ULN	
CPK	All age ranges	≥3 ULN	
Creatinine	Birth/0 to <6 years old (Neonates, Infants, Children)	>53 µmol/L or 0.6 mg/dL	CF = mg x 8.8 = µmol Based on normal ranges: ≤0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years)
	6 years to <12 years old (Children)	≥90 µmol/L or 1.1mg/dL	
	12 years to 16/18 years old (Adolsecents)	≥132µmol/L or 1.5mg/dL	
Creatinine Clearance	All age ranges	50% of normal <60 ml/min/1.73m2 (After 1 year old)	Based on GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
Uric Acid	All age ranges	≤2.0 mg/dL or 119 µmol/L ≥8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL
Blood Urea Nitrogen (BUN)	Birth/0 to 27 days old (Neonates)	≥4.3 mmol/L or 12 mg/dl	CF = g x 16.66 = mmol Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age)
	28 days/1 month to 16/18 years old (Infants, Children, Adolescents)	≥6.4 mmol/L or 18 mg/dl	
Chloride	All age ranges	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1 Based on normal range: 134 to 146
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (>Infants)
	28 days/1 month to 23 months old (Infants)	≤3.5 mmol/L or 3.5 mEq/L ≥6.0 mmol/L or 6.0 mEq/L	
	24 months/2 years to 16/18 years old (Children, Adolescents)	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	CF = 1 Based on normal range: 18 to 26

Parameter	Age range	PCSA	Comments
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 8.4 to 10.9 mg/dL
Calcium ionized	All age ranges	≤1.0 mmol/L or 4.0 mg/dL ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years)
Triglycerides	All age ranges	≥4.0 mmol/L or 350 mg/dL	After >12 hours of fast) CF = g x 1.14 = mmol Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114 mg/dL (Girls 6-11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-128 mg/dL (Girls 16-19 years)
Lipasemia	All age ranges	≥2 ULN	Based on normal ranges: 3 to32 U/L (1-18 years)
Amylasemia	All age ranges	≥2 ULN	Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years)
Glucose	All age ranges	Hypoglycaemia <2.7 mmol/L or 50 mg/dL Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted)	CF = g x 5.55 = mmol Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L

Parameter	Age range	PCSA	Comments
Hematology			Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006 ; Division of Microbiology and Infections Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995
WBC	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4000 /mm3 >25.0 GIGA/L or 25 000 /mm3	To be used if no differential count available
	28 days/1 month to 23 months old (Infants)	<4.0 GIGA/L or 4000 /mm3 >20.0 GIGA/L or 20 000 /mm3	Based on normal ranges: 9000 to 30 000 /mm3 (birth), 9400 to 38 000 /mm3 (0-1 day), 5000 to 21 000 /mm3 (1 day-1 month), 6000 to 17 500 /mm3 (1 month-2 years), 5000 to 17 000 /mm3 (2-6 years), 4500 to 15 500 /mm3 (6-11 years), 4500 to 13 500 /mm3 (11-18 years)
	24 months/2 years to <6 years old (Children)	<3.0 GIGA/L or 3000 /mm3 >16.0 GIGA/L or 16 000 /mm3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5000 /mm3 >17.0 GIGA/L or 17 000 /mm3	
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5000 /mm3 >13.5 GIGA/L or 17 000 /mm3	
Lymphocytes (ALC)	Birth/0 to 27 days old (Neonates)	<1.2 GIGA/L or 1200 /mm3 >17.0 GIGA/L or 17 000 /mm3	Based on normal ranges: 2000 to 11 500 /mm3 (0-1 days), 2000 to 17 000 /mm3 (2 days-1 month), 3000 to 13 500 /mm3 (1 month-2 years), 1500 to 9500 /mm3 (2-6 years), 1500 to 8000 /mm3 (6-10 years), 1200 to 5200 /mm3 (10-18 years)
	28 days/1 month to 23 months old (Infants)	<2.0 GIGA/L or 2000 /mm3 >13.5 GIGA/L or 13 500 /mm3	
	24 months/2 years to <6 years old (Children)	<1.0 GIGA/L or 1000 /mm3 >9.5 GIGA/L or 9500 /mm3	
	6 to <12 years old (Children)	<1.0 GIGA/L or 1000 /mm3 >8.0 GIGA/L or 8000 /mm3	
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600 /mm3 >6.0 GIGA/L or 6000 /mm3	
Absolute Neutrophil Count (ANC)	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4000 /mm3 (1 day old) <1.5 GIGA/L or 1500 /mm3 (2-7 days old) <1.25 GIGA/L or 1250 /mm3 (>7 day-1 month old) >1 ULN	Based on normal ranges: 5000 to 28 000 /mm3 (0-1 day), 1000 to 10 000 (1 day-1 month), 1000 to 8500 (1-12 months), 1500 to 8500 (1 to 6 years), 1500 to 8000 (6 to 10 years), 1800 to 8000 (10 to 18 years)
	28 days/1 month to 23 months old (Infants)	<1.0 GIGA/L or 1000/mm3 (1-3 months) <1.2 GIGA/L or 1200 /mm3 (3-24 months) >1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1200 /mm3 > 1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1200 /mm3 >1 ULN	

Parameter	Age range	PCSA	Comments
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1200 /mm3 >1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500 /mm3 Or >ULN if ULN >0.5 GIGA/L or 500 /mm3	Based on normal ranges: 0 to 500 /mm3 (0-1 month), 0 to 300 /mm3 (1 month-18 years)
Hemoglobin	Birth/0 to 27 days old (Neonates)	<86 mmol/L or 12.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	CF = g x 1.55 = mmol Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5 8 years), 12.0 to 15.2 g/dL (13-18 years)
	28 days/1 month to 23 months old (Infants)	<1.40 mmol/L or 9.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	
	24 months/2 years to <16/18 years old (Children, Adolescents)	<1.55 mmol/L or10.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	
Hematocrit	Birth/0 to 27 days old (Neonates)	<0.39 l/l or 40% >0.61 l/l or 47%	CF = % x 0.01 = l/l Based on normal ranges: 45 to 61% (0-3 days), 39 to 57% (1-2 weeks), 29 to 42% (1-6 months), 33 to 38% (7 months-2 years), 34 to 39% (2-5 years), 35 to 42% (5-8 years); 36 to 47% (13-18 years)
	28 days/1 month to 23 months old (Infants)	<0.29 l/l or 29% >0.42 l/l or 42%	
	24 months/2 years to <16/18 years old (Adolescents)	<0.32 l/l or 32% >0.47 l/l or 47%	
Platelets	All age ranges	<100 GIGA/L or 100 000 /mm3 >700 GIGA/L or 700 000 /mm3	Based on normal ranges: 250 000 to 450 000 /mm3 (NN); 300 000 to 700 000 /mm3 (1-6 months), 250 000 to 600 000 /mm3 (7 months-2 years), 250 000 to 550 000 /mm3 (2-12 years), 150 000 to 450 000 /mm3 (13-18 years)
Urinalysis			Patel HP, Pediatr Clin N Am, 2006
Ketonuria	All age ranges	Presence	Semi-quantitative methods
Glycosuria	All age ranges	Presence	Semi-quantitative methods
Hematuria	All age ranges	≥1+	Semi-quantitative methods
Proteinuria	All age ranges	≥1+	Semi-quantitative methods

Table 13 - Criteria for Potentially Clinically Significant Abnormalities for studies in children (Study specific criteria)

Parameter	Age range	PCSA	Comments
Calcium	All age ranges	<LLN or > ULN	Criteria defined per study team's clinical judgement.
Phosphorous	All age ranges	<0.8 x LLN or >1.3 x ULN	Criteria defined per study team's clinical judgement.
Calcitonin	All age ranges	<LLN	Criteria defined per study team's clinical judgement.
FGF23	All age ranges	Not applicable	It is not possible to establish PCSA criteria for this.
Conjugate of TSH and free T4 (fT4)	All age ranges	TSH <LLN and fT4 >ULN TSH >ULN and fT4 <LLN TSH <LLN and fT4 <LLN	Criteria defined per study team's clinical judgement.
iPTH	All age ranges	<0.8 x LLN or >1.3 x ULN	Criteria defined per study team's clinical judgement.
1,25-dihydroxyvitamin D	All age ranges	<0.8 x LLN or >1.3 x ULN	Criteria defined per study team's clinical judgement.
25-Hydroxyvitamin D	All age ranges	<20 ng/mL	Criteria defined per study team's clinical judgement.

5.7 APPENDIX 7 ANALYSIS FOR COMPARISON WITH EXTERNAL CONTROL ARM IN GROWTH PARAMETERS AND FORAMEN MAGNUM PARAMETERS

5.7.1 Purposes

To support the clinical development of SAR442501 for ACH, the untreated ACH patients, from PEDSnet database, will be taken as external controls to compare the growth parameters and foramen magnum cross-sectional area (if available) with ACH participants who received SAR442501 in study DRI16646 for assessment of the treatment effect of SAR442501. Each of the participants in DRI16646 will be matched by age and sex with ACH patients from PEDSnet database, and all the matched ACH patients from PEDSnet will be included in the analysis as outlined Section 5.7.3 below.

5.7.2 Endpoints

- Difference in change from baseline to Week 26 and Week 52 in AGV Z-score* between participants who received SAR442501 in DRI16646 and matched untreated ACH patients from PEDSnet

  *Using reference data in healthy population and untreated ACH population.
  Refer to Section 3.3.1.1 for details.

- Difference in change from baseline to Week 26 and Week 52 in AGV (cm/year) between participants who received SAR442501 in DRI16646 and matched untreated ACH patients from PEDSnet
- Difference in change from baseline to Week 26 and Week 52 in height Z-score** between participants who received SAR442501 in DRI16646 and matched untreated ACH patients from PEDSnet

  **Using reference data in healthy population and untreated ACH population. Refer to Section 3.3.1.1 for details.
- Difference in change from baseline to Week 52 in bony foramen magnum cross-sectional area between participants who received SAR442501 in DRI16646 (birth to age <3 years [Stage 2 only]) and matched untreated ACH patients from PEDSnet
- Difference in change from baseline to Week 52 in bony foramen magnum z-score cross-sectional area between participants who received SAR442501 in DRI16646 (birth to age <3 years [Stage 2 only]) and matched untreated ACH patients from PEDSnet (Foramen magnum Z-score will be calculated based on foramen magnum growth curve [by gender] on untreated ACH patients in PEDSnet database)

5.7.3 Analyses plan

As the first step, prior to matching, comparable non-treated ACH patients from PEDSnet will be selected if meeting below criteria to align with the inclusion/exclusion criteria in DRI16646 study.

- Confirmed diagnosis of ACH (with a confirmed mutation in the FGFR3 gene if possible)
- Age <12 years old at the first height measurement in PEDSnet database, this is considered as baseline age for untreated ACH subjects
- Do not have Hypochondroplasia (or N540K mutation) or have a short stature condition other than ACH
- For selected subjects, need to exclude any height data collected after the receiving any medication or investigational product or surgery intended to affect patients' stature or body proportions, including but not limited to human growth hormone, systemic steroids, or GnRH agonist or bone-related surgery.
- For selected subject ages <3 years of age need to exclude any foramen magnum data collected after receiving any neurosurgical procedure intended to affect foramen magnum size.
- In order to have corresponding change from baseline growth data for untreated ACH subjects summarized in Section 5.7.2, need to have the corresponding height measurement (or calculated AGV, or foramen magnum cross-sectional area) while allowing approximately ±7 to ±14 days window. For example, for analysis of change from baseline at Week 26 in height Z-score, have documented height measure at least 26 weeks (±7 to ±14 days) later after the first height measurement, respectively.

As the second step, due to the concern of patient privacy protection, matching and corresponding comparative analyses will be conducted by PEDSnet as described below. Upon the completion of collecting 26 weeks and 52 weeks growth data, from the Stage 1 and 2, respectively, Sanofi will provide the following individual participant data along with dose group (low or high dose) to PEDSnet:

- Baseline data: baseline age, sex, baseline height, baseline height Z-score, baseline AGV, baseline AGV Z-score, baseline foramen magnum cross-sectional area, baseline foramen magnum cross-sectional area Z-score
- Observed/calculated value and change from baseline data for height, height Z-score, AGV, AGV Z-score at Week 26 and Week 52 respectively, foramen magnum cross-sectional area at Week 52, foramen magnum cross-sectional area Z-score at Week 52.

Once receiving the individual subject's data above from Sanofi, as a potential sensitivity analysis to use the same matched subjects as height, before performing comparative analysis for foramen magnum, missing data on foramen magnum for PEDSnet subjects who matched on height to DRI16646 Stage 2 participants may be imputed with appropriate multiple imputation approach in both treated and untreated participants. To balance the distribution of known prognostic covariates in treatment and control group, PEDSnet will perform exact matching on sex and age. In addition, as sensitivity analysis, propensity score matching with adjustment for more baseline covariates (including baseline age, baseline height and sex) will also be conducted.

For exact matching on sex and age, the goal is to do 1-to-3 match to identify up to 3 matched untreated ACH subjects based on sex and baseline age as detailed below. Matching without replacement will be conducted. If there are more than 3 untreated ACH subjects identified, then the 3 subjects with age closest to DRI16646 subjects will be chosen. Furthermore, if more than 3 matched subjects are identified for those in <3 years age cohort, then the matched subjects who also have foramen magnum collected at baseline will be preferred.

- For treated subject with baseline age <3 years old, find matched same sex untreated subjects with baseline age within ±2 months.
- For treated subjects with baseline ages 3 to 12 years old, find matched same sex untreated subjects with baseline age within ±4 months.

Of note, during the actual implementation of finding exact matched subjects, age windowing may be expanded in order to find at least 1 matched untreated ACH subjects.

For propensity score matching, a logistic regression for the treatment group (treated DRI16646 participants versus PEDSnet untreated external control patients) as the dependent variable is performed to obtain the propensity score with the baseline covariates of baseline age, sex, baseline height Z-score, and baseline AGV. The greedy nearest-neighbor matching without replacement and matching ratio of 1-to-3 to identify up to 3 matched controls will be used.

After both exact matching and propensity score matching, for each matched set, PEDSnet will conduct analyses to evaluate covariate balance after matching by providing standardized mean difference between treated and matched external control group before and after matching.

Finally, PEDSnet will perform the comparative analyses with matched ACH controls through analysis of covariance (ANCOVA) adjusted for fixed covariates of treatment (low dose, high dose, control), baseline age, baseline height Z-score and baseline AGV for the parameters mentioned above in Section. Of note, as propensity score matching does not guarantee well-matched individual pairs on the full set of covariate, it is considered that accounting for the matching in the analysis is not necessary (11, 12). The aggregated summary of comparative analyses including number of participants with value, mean, SD, min, median, max, estimated LS mean, standard error and 95% CI in each treatment group and control group separately, as well as the difference of each treated versus control in LS mean, SE, 95%CI and p-value will be provided to Sanofi.

Of note, regardless of during the exact or propensity score matching, as there is no major difference of foramen magnum development in foramen magnum, in case there is not sufficient untreated ACH patient being matched, sex may not be required as a factor for matching.

The mock data table shells are provided in a separate document.

In addition to the external comparison with untreated ACH patients from PEDSnet database as discussed above, similar analyses may be conducted by considering Vosoritide treated ACH patients as external control arm.

5.8 APPENDIX 8 HEALTHY POPULATION REFERENCES FOR AGV

Figure 1 - Healthy population reference for AGV of boys
(Applicable for participants in age cohort <3 years, and 3 to <6 years)

Age (yr.)	Centiles (cm./yr.)							SD
	3rd	10th	25th	50th	75th	90th	97th	
0·16				40·00				
0·37				30·00				
0·62	13·42	14·88	16·36	18·00	19·64	21·12	22·58	2·43
0·87	10·25	11·60	12·97	14·50	16·03	17·40	18·75	2·26
1·12	8·51	9·72	10·94	12·30	13·66	14·88	16·09	2·02
1·37	7·45	8·61	9·79	11·10	12·41	13·59	14·75	1·94
1·62	6·50	7·58	8·68	9·90	10·94	12·04	13·12	1·81
1·87	6·02	7·03	8·06	9·20	10·34	11·37	12·38	1·69
2·25	5·72	6·64	7·57	8·60	9·63	10·56	11·48	1·53
2·75	5·41	6·24	7·08	8·02	8·96	9·80	10·63	1·39
3·25	5·20	5·96	6·74	7·60	8·46	9·24	10·00	1·28
3·75	4·92	5·63	6·36	7·16	7·96	8·69	9·40	1·19
4·25	4·73	5·40	6·08	6·84	7·60	8·28	8·95	1·12
4·75	4·62	5·25	5·89	6·60	7·31	7·95	8·58	1·06
5·25	4·46	5·07	5·68	6·36	7·04	7·65	8·26	1·01
5·75	4·37	4·94	5·53	6·18	6·83	7·42	7·99	0·96
6·25	4·26	4·81	5·38	6·00	6·62	7·19	7·74	0·93
6·75	4·17	4·70	5·24	5·84	6·44	6·98	7·51	0·89
7·25	4·14	4·65	5·16	5·74	6·32	6·83	7·34	0·85
7·75	4·06	4·55	5·05	5·60	6·15	6·65	7·14	0·82
8·25	4·01	4·49	4·97	5·50	6·03	6·51	6·99	0·79
8·75	3·97	4·43	4·89	5·40	5·91	6·37	6·83	0·76
9·25	3·87	4·32	4·78	5·30	5·82	6·27	6·74	
9·75	3·71	4·20	4·67	5·20	5·72	6·18	6·67	
10·25	3·53	4·05	4·56	5·12	5·66	6·10	6·66	
10·75	3·34	3·90	4·47	5·02	5·62	6·14	6·80	
11·25	3·16	3·75	4·38	4·93	5·68	6·37	7·33	
11·75	3·03	3·64	4·36	4·93	5·93	6·99	8·40	
12·25	2·95	3·62	4·42	5·23	6·70	8·07	9·81	
12·50	2·92	3·66	4·52	5·54	7·20	8·64	10·40	
12·75	2·95	3·75	4·64	5·90	7·68	9·20	10·90	
13·00	3·00	3·87	4·80	6·30	8·13	9·70	11·15	
13·25	3·08	4·02	5·10	6·70	8·46	9·95	11·30	
13·50	3·18	4·21	5·40	7·03	8·72	10·06	11·32	
13·75	3·27	4·43	5·68	7·27	8·80	10·09	11·27	
14·00	3·33	4·57	5·89	7·30	8·72	10·02	11·08	
14·25	3·36	4·58	5·90	7·10	8·53	9·82	10·85	
14·50	3·28	4·41	5·65	6·77	8·25	9·56	10·56	
14·75	2·80	4·01	5·26	6·22	7·90	9·20	10·20	
15·00	2·09	3·49	4·76	5·84	7·46	8·78	9·77	
15·25	1·47	2·87	4·22	5·34	6·97	8·26	9·33	
15·50	1·06	2·32	3·60	4·84	6·42	7·70	8·85	
15·75	0·77	1·82	3·02	4·36	5·81	7·10	8·30	
16·00	0·54	1·40	2·48	3·86	5·20	6·45	7·73	
16·25	0·39	1·07	2·02	3·32	4·55	5·72	7·12	
16·50	0·26	0·80	1·60	2·80	3·90	5·02	6·40	
16·75		0·60	1·30	2·31	3·28	4·22	5·55	
17·00		0·44	1·03	1·88	2·60	3·40	4·60	
17·25		0·34	0·83	1·50	2·09	2·70	3·65	
17·50		0·26	0·69	1·20	1·69	2·17	2·90	
17·75		0·20	0·57	0·95	1·33	1·68	2·28	
18·00			0·47	0·74	1·03	1·30	1·75	

Figure 2 - Healthy population reference for AGV of girls
(Applicable for participants in age cohort <3 years, and 3 to <6 years)

Age (yr.)	Centiles (cm./yr.)							SD
	3rd	10th	25th	50th	75th	90th	97th	
0·16				36·00				
0·37				26·00				
0·62	14·42	15·88	17·36	19·00	20·64	22·12	23·58	2·43
0·87	11·65	13·00	14·37	15·90	17·43	18·80	20·15	2·26
1·12	9·71	10·92	12·14	13·50	14·86	16·08	17·29	2·02
1·37	8·15	9·31	10·49	11·80	13·11	14·29	15·45	1·94
1·62	7·20	8·28	9·38	10·60	11·82	12·92	14·00	1·81
1·87	6·42	7·43	8·46	9·60	10·74	11·77	12·78	1·69
2·25	5·82	6·73	7·67	8·70	9·73	10·66	11·58	1·53
2·75	5·51	6·34	7·18	8·12	9·06	9·90	10·73	1·39
3·25	5·28	6·04	6·82	7·68	8·54	9·32	10·08	1·28
3·75	4·98	5·69	6·42	7·22	8·02	8·75	9·46	1·19
4·25	4·73	5·40	6·08	6·84	7·60	8·28	8·95	1·12
4·75	4·62	5·25	5·89	6·60	7·31	7·95	8·58	1·06
5·25	4·46	5·07	5·68	6·36	7·04	7·65	8·26	1·01
5·75	4·37	4·94	5·53	6·18	6·83	7·42	7·99	0·96
6·25	4·26	4·81	5·38	6·00	6·62	7·19	7·74	0·93
6·75	4·17	4·70	5·24	5·84	6·44	6·98	7·51	0·89
7·25	4·07	4·61	5·11	5·72	6·31	6·86	7·38	
7·75	3·90	4·45	4·94	5·59	6·19	6·81	7·46	
8·25	3·71	4·30	4·80	5·45	6·12	6·85	7·71	
8·75	3·56	4·17	4·67	5·37	6·13	7·00	8·12	
9·25	3·43	4·06	4·59	5·37	6·25	7·24	8·60	
9·75	3·35	4·00	4·60	5·48	6·48	7·55	9·00	
10·25	3·30	4·02	4·74	5·73	6·78	7·90	9·36	
10·75	3·30	4·13	4·95	6·00	7·09	8·24	9·63	
11·00	3·32	4·20	5·06	6·13	7·20	8·40	9·72	
11·25	3·35	4·27	5·19	6·24	7·30	8·50	9·80	
11·50	3·36	4·33	5·29	6·31	7·39	8·60	9·86	
11·75	3·39	4·38	5·36	6·37	7·43	8·68	9·88	
12·00	3·41	4·40	5·40	6·38	7·42	8·67	9·82	
12·25	3·30	4·23	5·25	6·30	7·28	8·55	9·70	
12·50	2·84	3·84	4·96	6·13	7·10	8·36	9·55	
12·75	2·30	3·41	4·63	5·89	6·85	8·12	9·33	
13·00	1·68	2·95	4·21	5·55	6·55	7·82	9·02	
13·25	1·20	2·45	3·76	5·11	6·20	7·41	8·63	
13·50	0·82	1·95	3·20	4·60	5·75	6·93	8·05	
13·75	0·52	1·53	2·63	4·06	5·23	6·26	7·50	
14·00	0·30	1·20	2·11	3·46	4·63	5·50	6·65	
14·25		0·85	1·65	2·82	3·85	4·60	5·52	
14·50		0·58	1·24	2·15	3·08	3·73	4·55	
14·75		0·35	0·88	1·53	2·37	2·95	3·65	
15·00			0·58	1·12	1·80	2·35	3·00	
15·25			0·40	0·82	1·37	1·90	2·38	
15·50			0·24	0·58	1·03	1·50	1·93	
15·75				0·44	0·78	1·20	1·58	
16·00				0·30	0·65	0·95	1·30	

Figure 3 - Healthy population reference for AGV of boys and girls (Applicable for participants in age cohort 6 to <12 years)

	All Males							All Females						
Midpoint of Age Range	L	S	3rd	10th	50th M	90th	97th	L	S	3rd	10th	50th M	90th	97th
5.50	0.85	0.13	5.2	5.7	6.8	7.9	8.4	1.24	0.14	4.8	5.4	6.7	7.9	8.4
5.75	0.84	0.13	5.1	5.6	6.7	7.9	8.4	1.21	0.14	4.8	5.3	6.6	7.8	8.3
6.00	0.83	0.13	5.0	5.5	6.6	7.8	8.3	1.19	0.14	4.7	5.3	6.5	7.7	8.2
6.25	0.82	0.13	5.0	5.4	6.5	7.6	8.1	1.16	0.14	4.7	5.2	6.4	7.6	8.1
6.50	0.81	0.12	4.9	5.3	6.4	7.4	7.9	1.14	0.14	4.6	5.1	6.4	7.6	8.1
6.75	0.80	0.12	4.8	5.2	6.2	7.3	7.7	1.12	0.15	4.5	5.1	6.3	7.5	8.0
7.00	0.79	0.13	4.7	5.1	6.1	7.2	7.7	1.09	0.15	4.5	5.0	6.2	7.5	8.0
7.25	0.77	0.14	4.5	5.0	6.1	7.2	7.7	1.07	0.16	4.3	4.9	6.2	7.4	8.0
7.50	0.76	0.15	4.3	4.8	6.0	7.3	7.8	1.05	0.16	4.2	4.8	6.1	7.4	7.9
7.75	0.75	0.16	4.2	4.7	5.9	7.3	7.8	1.02	0.17	4.1	4.7	6.0	7.4	7.9
8.00	0.74	0.16	4.2	4.6	5.9	7.2	7.7	1.00	0.17	4.0	4.6	6.0	7.4	7.9
8.25	0.73	0.16	4.1	4.6	5.8	7.1	7.6	0.97	0.18	3.9	4.5	6.0	7.4	8.0
8.50	0.72	0.16	4.1	4.5	5.7	7.0	7.5	0.95	0.19	3.9	4.5	5.9	7.4	8.0
8.75	0.70	0.17	3.9	4.4	5.6	6.9	7.5	0.93	0.19	3.8	4.4	6.0	7.5	8.2
9.00	0.69	0.17	3.8	4.3	5.5	6.9	7.4	0.90	0.20	3.8	4.4	6.0	7.7	8.3
9.25	0.68	0.18	3.7	4.2	5.5	6.9	7.5	0.88	0.21	3.8	4.5	6.1	7.8	8.5
9.50	0.67	0.19	3.6	4.1	5.5	6.9	7.6	0.86	0.21	3.8	4.5	6.2	8.0	8.8
9.75	0.66	0.21	3.5	4.0	5.4	7.0	7.7	0.83	0.22	3.8	4.5	6.3	8.2	9.0
10.00	0.65	0.22	3.4	3.9	5.4	7.1	7.8	0.81	0.22	3.9	4.6	6.4	8.4	9.3
10.25	0.64	0.23	3.3	3.9	5.4	7.2	8.0	0.79	0.23	3.9	4.6	6.6	8.6	9.5
10.50	0.62	0.25	3.2	3.8	5.5	7.4	8.3	0.76	0.24	3.9	4.6	6.6	8.8	9.7
10.75	0.61	0.27	3.1	3.7	5.6	7.7	8.6	0.74	0.24	3.8	4.6	6.6	8.9	9.9
11.00	0.60	0.28	3.0	3.7	5.7	8.0	9.0	0.71	0.26	3.6	4.4	6.6	9.0	10.0
11.25	0.59	0.30	3.0	3.7	5.9	8.4	9.6	0.69	0.28	3.4	4.2	6.5	9.0	10.1
11.50	0.58	0.31	3.0	3.8	6.1	8.9	10.1	0.67	0.30	3.1	3.9	6.3	9.0	10.2
11.75	0.57	0.32	3.1	3.9	6.4	9.3	10.7	0.64	0.34	2.7	3.5	6.0	8.9	10.3
12.00	0.55	0.32	3.1	4.0	6.6	9.8	11.2	0.62	0.38	2.2	3.1	5.7	8.8	10.2
12.25	0.54	0.33	3.3	4.2	6.9	10.2	11.7	0.60	0.42	1.8	2.6	5.3	8.6	10.1
12.50	0.53	0.33	3.4	4.3	7.1	10.5	12.1	0.57	0.47	1.4	2.2	4.8	8.2	9.9
12.75	0.52	0.33	3.5	4.4	7.2	10.7	12.3	0.55	0.52	1.0	1.8	4.3	7.8	9.5
13.00	0.51	0.33	3.5	4.4	7.2	10.8	12.4	0.53	0.57	0.8	1.4	3.8	7.3	9.0
13.25	0.50	0.34	3.3	4.3	7.2	10.7	12.4	0.50	0.62	0.6	1.1	3.3	6.6	8.3
13.50	0.49	0.36	3.1	4.1	7.0	10.6	12.4	0.48	0.67	0.4	0.9	2.8	6.0	7.6
13.75	0.47	0.38	2.8	3.7	6.6	10.5	12.3	0.45	0.71	0.3	0.7	2.4	5.3	6.9
14.00	0.46	0.42	2.3	3.3	6.2	10.2	12.2	0.43	0.75	0.2	0.5	2.0	4.7	6.1
14.25	0.45	0.47	1.9	2.8	5.7	9.9	12.0	0.41	0.79	0.2	0.4	1.7	4.0	5.3
14.50	0.44	0.52	1.4	2.3	5.2	9.5	11.6	0.38	0.82	0.1	0.3	1.4	3.5	4.7
14.75	0.43	0.58	1.1	1.8	4.6	8.9	11.2	0.36	0.84	0.1	0.3	1.2	3.0	4.1
15.00	0.42	0.63	0.8	1.4	4.0	8.3	10.6	0.34	0.87	0.1	0.2	1.0	2.6	3.6
15.25	0.40	0.69	0.6	1.1	3.5	7.6	9.8	0.31	0.89	0.1	0.2	0.9	2.4	3.3
15.50	0.39	0.74	0.4	0.8	2.9	6.8	8.9	0.29	0.91	0.1	0.2	0.8	2.1	3.0
15.75	0.38	0.78	0.3	0.6	2.5	6.0	8.0	0.27	0.92	0.1	0.2	0.7	2.0	2.8
16.00	0.37	0.82	0.2	0.5	2.0	5.1	7.0	0.24	0.94	0.1	0.1	0.6	1.8	2.6
16.25	0.36	0.86	0.2	0.4	1.7	4.4	6.0	0.22	0.95	0.1	0.1	0.5	1.6	2.4
16.50	0.35	0.88	0.1	0.3	1.4	3.7	5.1	0.19	0.96	0.1	0.1	0.5	1.5	2.3
16.75	0.34	0.91	0.1	0.2	1.1	3.1	4.3	0.17	0.97	0.1	0.1	0.5	1.5	2.3
17.00	0.32	0.92	0.1	0.2	0.9	2.6	3.7	0.15	0.98	0.1	0.1	0.4	1.5	2.3
17.25	0.31	0.94	0.1	0.2	0.8	2.2	3.1	0.12	0.99	0.1	0.1	0.4	1.5	2.3
17.50	0.30	0.94	0.1	0.1	0.6	1.9	2.7	0.10	1.00	0.0	0.1	0.4	1.4	2.3
17.75	0.29	0.95	0.0	0.1	0.5	1.6	2.3							
18.00	0.28	0.95	0.0	0.1	0.5	1.5	2.1							
18.25	0.27	0.96	0.0	0.1	0.4	1.3	1.9							
18.50	0.25	0.96	0.0	0.1	0.4	1.2	1.7							

***The LMS method uses a Box-Cox transformation to obtain normality. The LMS parameters are the power in the Box-Cox transformation (L), the median (M), and the generalized coefficient of variation (S). For an individual height velocity measurement (HV), the HV-centile and HV-Z can be calculated using either equation 1 or 2 in the Methods section and the age- and sex-specific L, M, and S parameters* above.**

5.9 APPENDIX 9 ACH REFERENCES FOR HEIGHT AND AGV

The ACH references were calculated by PEDSnet (pedsnet.org) using cross-section of individuals of different ages in height in the PEDSnet database with 1168 ACH untreated patients considered. A popular growth curve calculation method, Super imposition by translation and rotation (SITAR), was applied. This reference is subjected to change if a more recent version is available at the time of database lock.

Table 14 - ACH reference for height and AGV of boys

	height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
0.00	48.63	5.03	4.86	52.29	0.06		NA
0.04	49.38	4.94	4.79	52.74	0.06	18.11	NA
0.13	50.88	4.76	4.66	53.64	0.06	18.01	NA
0.21	52.35	4.59	4.52	54.53	0.06	17.89	NA
0.29	53.80	4.42	4.39	55.43	0.06	17.74	NA
0.38	55.21	4.25	4.26	56.32	0.06	17.57	NA
0.46	56.49	4.70	4.12	57.21	0.06	17.15	NA
0.54	57.80	4.54	3.99	58.10	0.06	16.94	NA
0.63	59.05	4.39	3.86	58.97	0.06	16.69	NA
0.71	60.24	4.24	3.73	59.84	0.06	16.39	NA
0.79	61.34	4.09	3.59	60.69	0.05	16.06	NA
0.88	62.36	3.95	3.46	61.53	0.05	15.70	NA
0.96	63.30	3.81	3.33	62.37	0.05	15.32	NA
1.04	64.17	3.70	3.19	63.18	0.05	14.86	4.16
1.13	64.85	4.47	3.06	63.98	0.05	14.16	4.17
1.21	65.58	4.38	2.93	64.77	0.05	13.41	4.16
1.29	66.27	4.31	2.80	65.54	0.05	12.64	4.13
1.38	66.92	4.25	2.67	66.30	0.05	11.88	4.06
1.46	67.57	4.20	2.54	67.04	0.05	11.18	4.00
1.54	68.21	4.16	2.42	67.76	0.05	10.50	3.86
1.63	68.86	4.12	2.29	68.46	0.05	9.89	3.70
1.71	69.52	4.08	2.17	69.15	0.05	9.37	3.51
1.79	70.19	4.05	2.05	69.82	0.05	8.93	3.30
1.88	70.86	4.01	1.93	70.48	0.05	8.57	3.09
1.96	71.53	3.98	1.81	71.11	0.05	8.30	2.89
2.04	72.18	3.96	1.70	71.74	0.05	8.09	2.69
2.13	72.81	3.94	1.58	72.34	0.05	7.96	2.68
2.21	73.40	3.94	1.47	72.93	0.05	7.82	2.53
2.29	73.95	3.94	1.36	73.50	0.05	7.69	2.41
2.38	74.47	3.95	1.26	74.06	0.05	7.55	2.33
2.46	74.95	3.97	1.15	74.61	0.05	7.38	2.27
2.54	75.39	4.00	1.05	75.14	0.05	7.19	2.24

	height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
2.63	75.81	4.04	0.95	75.66	0.05	6.96	2.22
2.71	76.21	4.07	0.85	76.16	0.05	6.70	2.21
2.79	76.61	4.11	0.76	76.66	0.05	6.42	2.21
2.88	77.00	4.15	0.67	77.14	0.05	6.14	2.20
2.96	77.40	4.18	0.58	77.61	0.05	5.87	2.19
3.04	77.81	4.21	0.49	78.08	0.05	5.63	2.17
3.13	78.23	4.24	0.41	78.53	0.05	5.42	2.15
3.21	78.67	4.26	0.33	78.98	0.05	5.27	2.11
3.29	79.13	4.28	0.25	79.42	0.05	5.18	2.08
3.38	79.60	4.31	0.17	79.85	0.05	5.13	2.04
3.46	80.09	4.33	0.10	80.27	0.05	5.14	2.01
3.54	80.58	4.35	0.03	80.69	0.05	5.18	1.97
3.63	81.07	4.37	-0.04	81.10	0.05	5.25	1.94
3.71	81.55	4.39	-0.11	81.51	0.05	5.34	1.91
3.79	82.03	4.42	-0.17	81.91	0.05	5.42	1.88
3.88	82.49	4.45	-0.23	82.31	0.05	5.49	1.86
3.96	82.93	4.49	-0.29	82.70	0.05	5.54	1.83
4.04	83.36	4.53	-0.35	83.08	0.05	5.56	1.81
4.13	83.77	4.58	-0.41	83.47	0.05	5.54	1.79
4.21	84.16	4.63	-0.46	83.84	0.05	5.49	1.77
4.29	84.53	4.70	-0.51	84.22	0.05	5.40	1.76
4.38	84.89	4.76	-0.56	84.59	0.05	5.28	1.75
4.46	85.22	4.83	-0.61	84.96	0.05	5.14	1.74
4.54	85.55	4.90	-0.65	85.32	0.05	4.98	1.73
4.63	85.87	4.97	-0.70	85.68	0.05	4.81	1.71
4.71	86.19	5.04	-0.74	86.05	0.05	4.64	1.69
4.79	86.50	5.11	-0.78	86.41	0.05	4.48	1.67
4.88	86.82	5.17	-0.82	86.76	0.05	4.33	1.64
4.96	87.14	5.24	-0.85	87.12	0.05	4.21	1.61
5.04	87.47	5.30	-0.89	87.48	0.05	4.11	1.58
5.13	87.81	5.36	-0.92	87.84	0.05	4.04	1.55
5.21	88.16	5.41	-0.95	88.19	0.05	4.00	1.52
5.29	88.52	5.46	-0.98	88.55	0.05	3.99	1.50
5.38	88.89	5.51	-1.01	88.91	0.05	4.01	1.48
5.46	89.27	5.56	-1.04	89.27	0.05	4.05	1.47
5.54	89.67	5.60	-1.06	89.63	0.06	4.11	1.45
5.63	90.07	5.64	-1.09	89.99	0.06	4.20	1.42
5.71	90.47	5.68	-1.11	90.34	0.06	4.29	1.39
5.79	90.88	5.71	-1.14	90.70	0.06	4.38	1.35
5.88	91.30	5.74	-1.16	91.06	0.06	4.48	1.31

	height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
5.96	91.71	5.77	-1.18	91.42	0.06	4.57	1.27
6.04	92.12	5.79	-1.20	91.78	0.06	4.65	1.24
6.13	92.53	5.82	-1.23	92.13	0.06	4.72	1.20
6.21	92.93	5.85	-1.25	92.49	0.06	4.77	1.17
6.29	93.32	5.88	-1.27	92.84	0.06	4.80	1.14
6.38	93.71	5.92	-1.29	93.19	0.06	4.82	1.11
6.46	94.09	5.95	-1.31	93.54	0.06	4.81	1.08
6.54	94.46	5.99	-1.33	93.89	0.06	4.79	1.06
6.63	94.82	6.03	-1.36	94.24	0.06	4.75	1.04
6.71	95.16	6.06	-1.38	94.58	0.06	4.69	1.02
6.79	95.50	6.10	-1.40	94.93	0.06	4.62	1.01
6.88	95.84	6.13	-1.43	95.27	0.06	4.54	1.00
6.96	96.16	6.17	-1.45	95.60	0.06	4.45	1.00
7.04	96.48	6.20	-1.48	95.94	0.06	4.36	1.00
7.13	96.79	6.24	-1.50	96.28	0.06	4.26	1.01
7.21	97.10	6.28	-1.53	96.61	0.06	4.17	1.01
7.29	97.40	6.33	-1.55	96.94	0.06	4.08	1.02
7.38	97.71	6.37	-1.58	97.27	0.06	4.00	1.03
7.46	98.01	6.42	-1.61	97.60	0.06	3.92	1.03
7.54	98.32	6.46	-1.64	97.92	0.06	3.86	1.04
7.63	98.63	6.51	-1.66	98.25	0.06	3.81	1.05
7.71	98.94	6.56	-1.69	98.57	0.06	3.78	1.06
7.79	99.26	6.61	-1.72	98.90	0.06	3.75	1.07
7.88	99.58	6.66	-1.75	99.22	0.06	3.74	1.07
7.96	99.90	6.71	-1.77	99.54	0.06	3.74	1.07
8.04	100.23	6.76	-1.80	99.86	0.06	3.76	1.07
8.13	100.57	6.81	-1.83	100.18	0.06	3.78	1.07
8.21	100.90	6.85	-1.86	100.50	0.06	3.81	1.07
8.29	101.24	6.89	-1.88	100.81	0.06	3.84	1.07
8.38	101.59	6.93	-1.91	101.13	0.06	3.88	1.06
8.46	101.94	6.96	-1.94	101.44	0.06	3.92	1.05
8.54	102.28	6.99	-1.96	101.76	0.06	3.96	1.04
8.63	102.63	7.02	-1.99	102.07	0.06	4.01	1.04
8.71	102.99	7.05	-2.01	102.38	0.06	4.04	1.03
8.79	103.33	7.08	-2.04	102.69	0.06	4.08	1.02
8.88	103.68	7.11	-2.06	103.00	0.06	4.11	1.01
8.96	104.03	7.13	-2.08	103.31	0.06	4.13	1.01
9.04	104.37	7.15	-2.11	103.61	0.06	4.14	1.00
9.13	104.71	7.18	-2.13	103.91	0.06	4.15	1.00
9.21	105.05	7.20	-2.15	104.22	0.06	4.15	0.99

	height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
9.29	105.38	7.22	-2.16	104.51	0.06	4.14	0.99
9.38	105.71	7.25	-2.18	104.81	0.06	4.12	0.98
9.46	106.03	7.27	-2.19	105.11	0.06	4.09	0.98
9.54	106.34	7.29	-2.21	105.40	0.06	4.06	0.98
9.63	106.65	7.32	-2.22	105.70	0.06	4.01	0.98
9.71	106.95	7.34	-2.23	105.99	0.06	3.97	0.99
9.79	107.25	7.37	-2.24	106.28	0.06	3.91	1.00
9.88	107.54	7.39	-2.24	106.57	0.06	3.86	1.01
9.96	107.83	7.42	-2.25	106.86	0.06	3.80	1.03
10.04	108.11	7.44	-2.25	107.15	0.06	3.73	1.05
10.13	108.39	7.47	-2.24	107.44	0.06	3.67	1.07
10.21	108.66	7.50	-2.24	107.73	0.06	3.61	1.10
10.29	108.93	7.53	-2.23	108.02	0.06	3.55	1.12
10.38	109.20	7.56	-2.22	108.31	0.06	3.50	1.14
10.46	109.47	7.59	-2.21	108.60	0.06	3.45	1.17
10.54	109.74	7.62	-2.19	108.89	0.06	3.40	1.19
10.63	110.01	7.66	-2.17	109.18	0.06	3.36	1.21
10.71	110.29	7.69	-2.15	109.48	0.06	3.33	1.23
10.79	110.56	7.73	-2.12	109.78	0.06	3.31	1.25
10.88	110.84	7.77	-2.09	110.08	0.06	3.30	1.27
10.96	111.12	7.82	-2.05	110.39	0.06	3.29	1.28
11.04	111.40	7.86	-2.01	110.70	0.06	3.30	1.30
11.13	111.69	7.90	-1.97	111.01	0.06	3.31	1.32
11.21	111.99	7.95	-1.92	111.33	0.06	3.33	1.33
11.29	112.29	8.00	-1.87	111.65	0.06	3.36	1.34
11.38	112.59	8.04	-1.81	111.97	0.06	3.39	1.36
11.46	112.91	8.09	-1.75	112.30	0.06	3.43	1.37
11.54	113.22	8.14	-1.69	112.63	0.06	3.48	1.38
11.63	113.55	8.19	-1.62	112.97	0.06	3.53	1.40
11.71	113.88	8.24	-1.55	113.31	0.06	3.59	1.41
11.79	114.21	8.28	-1.48	113.66	0.06	3.65	1.42
11.88	114.55	8.33	-1.40	114.01	0.06	3.71	1.44
11.96	114.89	8.37	-1.32	114.36	0.06	3.77	1.45
12.04	115.24	8.41	-1.23	114.72	0.06	3.84	1.46
12.13	115.59	8.45	-1.14	115.08	0.06	3.90	1.47
12.21	115.94	8.49	-1.05	115.44	0.06	3.96	1.48
12.29	116.30	8.52	-0.96	115.81	0.06	4.01	1.49
12.38	116.66	8.55	-0.86	116.17	0.06	4.07	1.49
12.46	117.02	8.58	-0.76	116.54	0.06	4.12	1.50
12.54	117.38	8.60	-0.66	116.92	0.06	4.16	1.50

	height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
12.63	117.74	8.62	-0.55	117.29	0.06	4.20	1.50
12.71	118.11	8.64	-0.44	117.66	0.06	4.23	1.50
12.79	118.47	8.65	-0.33	118.04	0.06	4.26	1.50
12.88	118.82	8.66	-0.22	118.41	0.06	4.28	1.50
12.96	119.18	8.67	-0.11	118.78	0.06	4.29	1.49
13.04	119.54	8.67	0.00	119.15	0.06	4.30	1.49
13.13	119.89	8.67	0.11	119.52	0.06	4.30	1.48
13.21	120.24	8.67	0.22	119.89	0.06	4.29	1.47
13.29	120.58	8.66	0.34	120.25	0.06	4.28	1.47
13.38	120.92	8.65	0.45	120.62	0.06	4.26	1.46
13.46	121.25	8.63	0.56	120.97	0.06	4.23	1.45
13.54	121.58	8.62	0.67	121.32	0.06	4.20	1.44
13.63	121.91	8.60	0.78	121.67	0.06	4.16	1.44
13.71	122.22	8.57	0.89	122.01	0.06	4.12	1.43
13.79	122.53	8.55	1.00	122.35	0.06	4.07	1.43
13.88	122.84	8.52	1.11	122.68	0.06	4.01	1.42
13.96	123.13	8.49	1.21	123.00	0.06	3.95	1.42
14.04	123.42	8.46	1.31	123.31	0.06	3.89	1.41
14.13	123.71	8.42	1.41	123.62	0.06	3.82	1.41
14.21	123.98	8.39	1.51	123.92	0.06	3.75	1.41
14.29	124.25	8.35	1.60	124.21	0.06	3.67	1.40
14.38	124.51	8.31	1.69	124.50	0.06	3.59	1.40
14.46	124.77	8.27	1.78	124.77	0.06	3.51	1.40
14.54	125.01	8.23	1.86	125.04	0.06	3.43	1.40
14.63	125.25	8.19	1.94	125.30	0.06	3.35	1.39
14.71	125.49	8.15	2.02	125.55	0.06	3.26	1.39
14.79	125.71	8.11	2.09	125.80	0.06	3.18	1.39
14.88	125.93	8.07	2.16	126.03	0.06	3.09	1.38
14.96	126.14	8.03	2.23	126.26	0.06	3.01	1.38
15.04	126.34	7.98	2.29	126.48	0.06	2.92	1.37
15.13	126.54	7.94	2.35	126.69	0.06	2.83	1.36
15.21	126.73	7.90	2.41	126.89	0.05	2.75	1.35
15.29	126.92	7.86	2.46	127.09	0.05	2.66	1.34
15.38	127.09	7.82	2.51	127.28	0.05	2.58	1.33
15.46	127.26	7.78	2.56	127.46	0.05	2.50	1.32
15.54	127.43	7.74	2.60	127.63	0.05	2.42	1.31
15.63	127.59	7.70	2.64	127.80	0.05	2.34	1.29
15.71	127.74	7.66	2.67	127.96	0.05	2.26	1.28
15.79	127.89	7.63	2.70	128.11	0.05	2.18	1.26
15.88	128.03	7.59	2.73	128.26	0.05	2.10	1.24

	height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
15.96	128.17	7.56	2.76	128.40	0.05	2.03	1.23
16.04	128.30	7.52	2.78	128.54	0.05	1.96	1.21
16.13	128.43	7.49	2.80	128.67	0.05	1.89	1.19
16.21	128.55	7.45	2.81	128.79	0.05	1.82	1.17
16.29	128.67	7.42	2.83	128.91	0.05	1.76	1.15
16.38	128.78	7.39	2.84	129.03	0.05	1.69	1.13
16.46	128.89	7.36	2.85	129.14	0.05	1.63	1.11
16.54	129.00	7.33	2.85	129.24	0.05	1.57	1.09
16.63	129.10	7.31	2.85	129.34	0.05	1.51	1.07
16.71	129.20	7.28	2.85	129.44	0.05	1.46	1.04
16.79	129.30	7.26	2.85	129.53	0.05	1.41	1.02
16.88	129.39	7.23	2.85	129.62	0.05	1.36	1.00
16.96	129.48	7.21	2.84	129.71	0.05	1.31	0.98
17.04	129.56	7.19	2.83	129.80	0.05	1.26	0.96
17.13	129.65	7.17	2.82	129.88	0.05	1.22	0.94
17.21	129.73	7.15	2.81	129.96	0.05	1.17	0.91
17.29	129.80	7.13	2.80	130.03	0.05	1.13	0.89
17.38	129.88	7.11	2.78	130.11	0.05	1.10	0.87
17.46	129.95	7.09	2.77	130.18	0.05	1.06	0.85
17.54	130.03	7.08	2.75	130.25	0.05	1.03	0.83
17.63	130.10	7.06	2.73	130.31	0.05	0.99	0.81
17.71	130.16	7.05	2.71	130.38	0.05	0.96	0.79
17.79	130.23	7.03	2.69	130.44	0.05	0.93	0.77
17.88	130.30	7.02	2.67	130.51	0.05	0.91	0.75
17.96	130.36	7.01	2.65	130.57	0.05	0.88	0.73
18.04	130.42	7.00	2.62	130.63	0.05	0.86	0.71
18.13	130.48	6.99	2.60	130.69	0.04	0.84	0.69
18.21	130.54	6.98	2.57	130.74	0.04	0.82	0.67
18.29	130.60	6.97	2.55	130.80	0.04	0.80	0.65
18.38	130.66	6.96	2.52	130.86	0.04	0.78	0.64
18.46	130.71	6.95	2.50	130.91	0.04	0.76	0.62
18.54	130.77	6.95	2.47	130.97	0.04	0.74	0.61
18.63	130.82	6.94	2.44	131.02	0.04	0.73	0.59
18.71	130.88	6.94	2.42	131.07	0.04	0.71	0.58
18.79	130.93	6.93	2.39	131.13	0.04	0.70	0.56
18.88	130.98	6.93	2.36	131.18	0.04	0.69	0.55
18.96	131.04	6.92	2.33	131.23	0.04	0.68	0.54
19.04	131.09	6.92	2.30	131.28	0.04	0.67	0.52
19.13	131.14	6.91	2.27	131.33	0.04	0.65	0.51
19.21	131.19	6.91	2.24	131.38	0.04	0.64	0.50

	height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
19.29	131.24	6.91	2.21	131.43	0.04	0.64	0.49
19.38	131.29	6.90	2.19	131.48	0.04	0.63	0.48
19.46	131.33	6.90	2.16	131.53	0.04	0.62	0.47
19.54	131.38	6.90	2.13	131.58	0.04	0.61	0.46
19.63	131.43	6.90	2.10	131.63	0.04	0.60	0.45
19.71	131.48	6.89	2.07	131.68	0.04	0.60	0.44
19.79	131.52	6.89	2.04	131.73	0.04	0.59	0.43
19.88	131.57	6.89	2.01	131.78	0.04	0.59	0.42
19.96	131.62	6.89	1.98	131.83	0.04	0.58	0.42

a During the analysis, when the SD=NA, they will be imputed by the first SD available in this table.

Table 15 - ACH reference for height and AGV of girls

	Height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
0.00	43.31	7.33	7.98	50.86	0.06		NA
0.04	44.65	7.20	7.86	51.33	0.06	32.11	NA
0.13	47.23	6.81	7.63	52.27	0.06	31.37	NA
0.21	49.67	6.18	7.40	53.21	0.06	30.53	NA
0.29	51.78	5.95	7.16	54.15	0.06	29.06	NA
0.38	53.75	5.40	6.93	55.09	0.06	27.83	NA
0.46	55.47	4.92	6.70	56.01	0.06	26.53	NA
0.54	56.97	4.51	6.46	56.93	0.06	25.22	NA
0.63	58.27	4.18	6.23	57.83	0.06	23.93	NA
0.71	59.30	4.61	6.00	58.73	0.06	22.57	NA
0.79	60.20	5.01	5.77	59.61	0.06	21.34	NA
0.88	61.12	4.78	5.54	60.48	0.06	20.35	NA
0.96	61.97	4.59	5.31	61.33	0.06	19.48	NA
1.04	62.80	4.42	5.08	62.16	0.06	18.39	7.89
1.13	63.61	4.27	4.86	62.98	0.05	16.56	7.38
1.21	64.42	4.14	4.64	63.77	0.05	14.92	6.75
1.29	65.24	4.02	4.42	64.55	0.05	13.58	6.28
1.38	65.94	4.69	4.20	65.31	0.05	12.42	5.66
1.46	66.76	4.52	3.99	66.05	0.05	11.49	5.06
1.54	67.55	4.39	3.78	66.76	0.05	10.77	4.50
1.63	68.32	4.27	3.57	67.46	0.05	10.21	4.00
1.71	69.04	4.19	3.37	68.14	0.05	9.85	3.87
1.79	69.72	4.13	3.18	68.79	0.05	9.59	3.97
1.88	70.35	4.09	2.98	69.43	0.05	9.29	3.73
1.96	70.92	4.08	2.80	70.05	0.05	9.00	3.54

	Height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
2.04	71.44	4.09	2.61	70.65	0.05	8.69	3.39
2.13	71.91	4.12	2.44	71.23	0.05	8.34	3.25
2.21	72.34	4.15	2.26	71.79	0.05	7.95	3.13
2.29	72.74	4.20	2.10	72.34	0.05	7.52	3.02
2.38	73.10	4.24	1.94	72.87	0.05	7.16	3.65
2.46	73.45	4.29	1.78	73.38	0.05	6.70	3.54
2.54	73.79	4.34	1.63	73.89	0.05	6.24	3.41
2.63	74.13	4.38	1.49	74.38	0.05	5.81	3.26
2.71	74.48	4.42	1.36	74.86	0.05	5.43	3.09
2.79	74.83	4.45	1.23	75.33	0.05	5.11	2.92
2.88	75.21	4.48	1.10	75.80	0.05	4.85	2.73
2.96	75.60	4.51	0.99	76.25	0.05	4.68	2.54
3.04	76.02	4.53	0.88	76.70	0.05	4.57	2.35
3.13	76.46	4.55	0.77	77.14	0.05	4.54	2.18
3.21	76.91	4.57	0.68	77.57	0.05	4.57	2.02
3.29	77.39	4.59	0.58	78.00	0.05	4.65	1.87
3.38	77.88	4.60	0.50	78.43	0.05	4.77	1.75
3.46	78.38	4.62	0.42	78.84	0.05	4.92	1.64
3.54	78.88	4.64	0.34	79.26	0.05	5.09	1.54
3.63	79.39	4.66	0.28	79.67	0.05	5.26	1.45
3.71	79.89	4.67	0.21	80.07	0.06	5.42	1.37
3.79	80.39	4.69	0.16	80.47	0.06	5.56	1.29
3.88	80.88	4.71	0.10	80.86	0.06	5.67	1.22
3.96	81.35	4.73	0.06	81.25	0.06	5.75	1.15
4.04	81.81	4.75	0.01	81.64	0.06	5.80	1.08
4.13	82.26	4.76	-0.03	82.02	0.06	5.80	1.03
4.21	82.68	4.78	-0.06	82.39	0.06	5.77	0.99
4.29	83.09	4.79	-0.09	82.76	0.06	5.70	0.96
4.38	83.48	4.81	-0.12	83.13	0.06	5.60	0.93
4.46	83.85	4.82	-0.14	83.49	0.06	5.47	0.91
4.54	84.20	4.84	-0.17	83.84	0.06	5.32	0.90
4.63	84.54	4.85	-0.18	84.19	0.06	5.16	0.88
4.71	84.87	4.87	-0.20	84.54	0.06	4.98	0.86
4.79	85.19	4.88	-0.21	84.88	0.06	4.80	0.84
4.88	85.49	4.90	-0.22	85.22	0.06	4.61	0.82
4.96	85.79	4.92	-0.22	85.55	0.06	4.44	0.79
5.04	86.08	4.93	-0.23	85.89	0.06	4.27	0.77
5.13	86.37	4.95	-0.23	86.22	0.06	4.11	0.75
5.21	86.65	4.97	-0.23	86.54	0.06	3.97	0.72
5.29	86.93	5.00	-0.22	86.87	0.06	3.85	0.71

	Height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
5.38	87.21	5.02	-0.22	87.19	0.06	3.74	0.70
5.46	87.49	5.05	-0.21	87.51	0.06	3.65	0.69
5.54	87.78	5.07	-0.21	87.83	0.06	3.57	0.70
5.63	88.06	5.10	-0.20	88.15	0.06	3.52	0.71
5.71	88.35	5.13	-0.19	88.47	0.06	3.47	0.73
5.79	88.64	5.16	-0.17	88.79	0.06	3.45	0.75
5.88	88.93	5.19	-0.16	89.11	0.06	3.44	0.78
5.96	89.23	5.22	-0.15	89.43	0.06	3.43	0.80
6.04	89.53	5.25	-0.13	89.75	0.06	3.45	0.83
6.13	89.84	5.28	-0.12	90.08	0.06	3.47	0.86
6.21	90.15	5.31	-0.10	90.40	0.06	3.50	0.88
6.29	90.47	5.34	-0.09	90.73	0.06	3.53	0.90
6.38	90.79	5.37	-0.07	91.06	0.06	3.58	0.92
6.46	91.12	5.41	-0.05	91.38	0.06	3.63	0.94
6.54	91.46	5.44	-0.03	91.72	0.06	3.68	0.95
6.63	91.80	5.47	-0.01	92.05	0.06	3.74	0.96
6.71	92.15	5.49	0.00	92.38	0.06	3.80	0.97
6.79	92.50	5.52	0.02	92.72	0.06	3.86	0.97
6.88	92.86	5.55	0.04	93.06	0.06	3.93	0.96
6.96	93.22	5.57	0.06	93.40	0.06	3.99	0.96
7.04	93.58	5.59	0.08	93.74	0.06	4.05	0.95
7.13	93.95	5.61	0.10	94.09	0.06	4.12	0.94
7.21	94.33	5.63	0.12	94.43	0.06	4.18	0.92
7.29	94.70	5.65	0.14	94.78	0.06	4.23	0.91
7.38	95.07	5.67	0.16	95.12	0.06	4.28	0.89
7.46	95.45	5.68	0.18	95.47	0.06	4.33	0.88
7.54	95.83	5.69	0.20	95.82	0.06	4.37	0.86
7.63	96.20	5.71	0.21	96.17	0.06	4.40	0.84
7.71	96.58	5.72	0.23	96.52	0.06	4.43	0.83
7.79	96.95	5.73	0.25	96.86	0.06	4.45	0.81
7.88	97.32	5.74	0.27	97.21	0.06	4.46	0.79
7.96	97.68	5.75	0.29	97.56	0.06	4.47	0.77
8.04	98.05	5.76	0.31	97.90	0.06	4.46	0.75
8.13	98.40	5.77	0.33	98.25	0.06	4.45	0.74
8.21	98.76	5.78	0.35	98.59	0.06	4.43	0.72
8.29	99.11	5.79	0.37	98.93	0.06	4.41	0.70
8.38	99.45	5.80	0.39	99.27	0.06	4.38	0.68
8.46	99.79	5.82	0.41	99.61	0.06	4.34	0.67
8.54	100.13	5.83	0.43	99.95	0.06	4.30	0.65
8.63	100.46	5.85	0.45	100.29	0.06	4.26	0.64

	Height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
8.71	100.79	5.87	0.47	100.62	0.06	4.21	0.64
8.79	101.11	5.89	0.49	100.96	0.06	4.17	0.64
8.88	101.43	5.91	0.52	101.29	0.06	4.12	0.65
8.96	101.75	5.94	0.54	101.63	0.06	4.07	0.66
9.04	102.07	5.97	0.57	101.96	0.06	4.02	0.67
9.13	102.38	6.00	0.59	102.29	0.06	3.98	0.69
9.21	102.69	6.03	0.62	102.63	0.06	3.93	0.72
9.29	103.01	6.06	0.65	102.96	0.06	3.90	0.74
9.38	103.32	6.09	0.68	103.29	0.06	3.86	0.77
9.46	103.63	6.13	0.72	103.63	0.06	3.83	0.80
9.54	103.94	6.17	0.75	103.96	0.06	3.81	0.83
9.63	104.25	6.21	0.79	104.30	0.06	3.79	0.85
9.71	104.57	6.25	0.82	104.64	0.06	3.78	0.88
9.79	104.89	6.29	0.87	104.97	0.06	3.77	0.90
9.88	105.21	6.33	0.91	105.31	0.06	3.77	0.92
9.96	105.53	6.37	0.95	105.65	0.06	3.78	0.94
10.04	105.85	6.41	1.00	106.00	0.06	3.78	0.95
10.13	106.18	6.44	1.05	106.34	0.06	3.80	0.97
10.21	106.51	6.48	1.10	106.69	0.06	3.82	0.98
10.29	106.85	6.52	1.15	107.04	0.06	3.84	0.99
10.38	107.18	6.55	1.20	107.39	0.06	3.87	1.00
10.46	107.53	6.59	1.26	107.74	0.06	3.90	1.00
10.54	107.87	6.62	1.32	108.09	0.06	3.93	1.01
10.63	108.22	6.65	1.38	108.45	0.06	3.97	1.01
10.71	108.57	6.68	1.44	108.80	0.06	4.00	1.02
10.79	108.92	6.70	1.50	109.16	0.06	4.04	1.03
10.88	109.28	6.72	1.57	109.51	0.06	4.08	1.03
10.96	109.64	6.74	1.63	109.87	0.06	4.11	1.04
11.04	110.00	6.76	1.70	110.23	0.06	4.14	1.05
11.13	110.36	6.77	1.77	110.59	0.06	4.18	1.06
11.21	110.72	6.79	1.83	110.94	0.06	4.20	1.08
11.29	111.07	6.80	1.90	111.30	0.06	4.23	1.09
11.38	111.43	6.80	1.97	111.65	0.06	4.25	1.11
11.46	111.79	6.81	2.04	112.00	0.06	4.26	1.12
11.54	112.14	6.81	2.11	112.35	0.06	4.27	1.14
11.63	112.49	6.81	2.18	112.70	0.06	4.27	1.16
11.71	112.84	6.81	2.25	113.04	0.06	4.27	1.18
11.79	113.18	6.80	2.32	113.38	0.06	4.26	1.21
11.88	113.52	6.80	2.38	113.72	0.06	4.24	1.23
11.96	113.86	6.79	2.45	114.05	0.06	4.22	1.25

	Height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
12.04	114.19	6.78	2.51	114.37	0.06	4.19	1.27
12.13	114.51	6.77	2.58	114.69	0.05	4.15	1.29
12.21	114.82	6.76	2.64	115.00	0.05	4.11	1.32
12.29	115.13	6.75	2.70	115.31	0.05	4.06	1.34
12.38	115.43	6.73	2.76	115.61	0.05	4.00	1.35
12.46	115.73	6.72	2.81	115.91	0.05	3.94	1.37
12.54	116.01	6.70	2.87	116.19	0.05	3.87	1.39
12.63	116.29	6.69	2.92	116.47	0.05	3.80	1.40
12.71	116.56	6.67	2.97	116.74	0.05	3.72	1.41
12.79	116.82	6.65	3.02	117.00	0.05	3.63	1.42
12.88	117.07	6.63	3.06	117.26	0.05	3.54	1.43
12.96	117.31	6.62	3.10	117.50	0.05	3.45	1.44
13.04	117.54	6.60	3.14	117.74	0.05	3.35	1.44
13.13	117.76	6.58	3.17	117.97	0.05	3.25	1.45
13.21	117.97	6.56	3.20	118.19	0.05	3.15	1.45
13.29	118.18	6.54	3.23	118.40	0.05	3.04	1.44
13.38	118.37	6.53	3.25	118.61	0.05	2.94	1.44
13.46	118.55	6.51	3.27	118.80	0.05	2.83	1.44
13.54	118.73	6.49	3.29	118.99	0.05	2.72	1.43
13.63	118.90	6.47	3.30	119.16	0.05	2.61	1.42
13.71	119.06	6.46	3.31	119.33	0.05	2.50	1.41
13.79	119.21	6.44	3.31	119.49	0.05	2.40	1.40
13.88	119.36	6.43	3.31	119.64	0.05	2.29	1.39
13.96	119.49	6.41	3.31	119.79	0.05	2.19	1.37
14.04	119.62	6.40	3.30	119.92	0.05	2.09	1.36
14.13	119.75	6.39	3.29	120.05	0.05	1.99	1.34
14.21	119.86	6.37	3.28	120.18	0.05	1.89	1.32
14.29	119.97	6.36	3.26	120.29	0.05	1.80	1.30
14.38	120.08	6.35	3.24	120.40	0.05	1.71	1.28
14.46	120.17	6.34	3.21	120.50	0.05	1.62	1.26
14.54	120.27	6.33	3.19	120.60	0.05	1.53	1.24
14.63	120.35	6.32	3.15	120.69	0.05	1.45	1.22
14.71	120.44	6.31	3.12	120.78	0.05	1.38	1.20
14.79	120.52	6.30	3.08	120.86	0.05	1.30	1.18
14.88	120.59	6.30	3.04	120.93	0.05	1.23	1.15
14.96	120.66	6.29	3.00	121.00	0.05	1.17	1.13
15.04	120.73	6.28	2.95	121.07	0.05	1.10	1.10
15.13	120.79	6.28	2.90	121.13	0.05	1.04	1.08
15.21	120.85	6.27	2.85	121.19	0.05	0.99	1.06
15.29	120.91	6.27	2.79	121.24	0.05	0.94	1.03

	Height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
15.38	120.96	6.26	2.74	121.30	0.05	0.89	1.01
15.46	121.02	6.26	2.68	121.35	0.05	0.84	0.98
15.54	121.07	6.25	2.62	121.39	0.05	0.80	0.96
15.63	121.12	6.25	2.56	121.44	0.05	0.76	0.94
15.71	121.17	6.25	2.50	121.48	0.05	0.73	0.91
15.79	121.21	6.24	2.43	121.52	0.05	0.70	0.89
15.88	121.26	6.24	2.37	121.56	0.05	0.67	0.86
15.96	121.30	6.24	2.30	121.59	0.05	0.64	0.84
16.04	121.34	6.24	2.23	121.63	0.05	0.62	0.81
16.13	121.39	6.23	2.17	121.66	0.05	0.60	0.79
16.21	121.43	6.23	2.10	121.70	0.05	0.58	0.77
16.29	121.47	6.23	2.03	121.73	0.05	0.56	0.74
16.38	121.51	6.23	1.96	121.76	0.05	0.55	0.72
16.46	121.55	6.23	1.89	121.79	0.05	0.53	0.70
16.54	121.59	6.23	1.82	121.82	0.05	0.52	0.68
16.63	121.63	6.22	1.75	121.85	0.05	0.51	0.66
16.71	121.67	6.22	1.68	121.88	0.05	0.50	0.64
16.79	121.71	6.22	1.60	121.91	0.05	0.49	0.62
16.88	121.75	6.22	1.53	121.94	0.05	0.49	0.60
16.96	121.78	6.22	1.46	121.97	0.05	0.48	0.58
17.04	121.82	6.22	1.39	122.00	0.05	0.48	0.57
17.13	121.86	6.22	1.32	122.03	0.05	0.48	0.55
17.21	121.90	6.22	1.25	122.06	0.05	0.47	0.54
17.29	121.94	6.22	1.17	122.09	0.05	0.47	0.52
17.38	121.98	6.21	1.10	122.11	0.05	0.47	0.51
17.46	122.02	6.21	1.03	122.14	0.05	0.47	0.49
17.54	122.06	6.21	0.96	122.17	0.05	0.47	0.48
17.63	122.10	6.21	0.89	122.20	0.05	0.47	0.47
17.71	122.14	6.21	0.82	122.23	0.05	0.47	0.46
17.79	122.18	6.21	0.74	122.26	0.05	0.47	0.45
17.88	122.22	6.21	0.67	122.29	0.05	0.47	0.44
17.96	122.26	6.21	0.60	122.32	0.05	0.47	0.43
18.04	122.30	6.21	0.53	122.35	0.05	0.47	0.42
18.13	122.34	6.21	0.46	122.38	0.05	0.48	0.41
18.21	122.38	6.20	0.39	122.41	0.05	0.48	0.40
18.29	122.42	6.20	0.32	122.44	0.05	0.48	0.40
18.38	122.46	6.20	0.25	122.47	0.05	0.48	0.39
18.46	122.50	6.20	0.18	122.50	0.05	0.49	0.38
18.54	122.55	6.20	0.11	122.53	0.05	0.49	0.38
18.63	122.59	6.20	0.04	122.56	0.05	0.49	0.37

	Height (cm)					AGV (cm/year)[a]	
Age (year)	Mean	SD	L	M	S	Mean	SD
18.71	122.63	6.20	-0.03	122.59	0.05	0.49	0.37
18.79	122.67	6.20	-0.10	122.62	0.05	0.50	0.36
18.88	122.72	6.20	-0.16	122.65	0.05	0.50	0.36
18.96	122.76	6.20	-0.23	122.69	0.05	0.50	0.35
19.04	122.80	6.20	-0.30	122.72	0.05	0.51	0.35
19.13	122.85	6.20	-0.37	122.75	0.05	0.51	0.34
19.21	122.89	6.20	-0.44	122.79	0.05	0.51	0.33
19.29	122.94	6.20	-0.50	122.82	0.05	0.51	0.33
19.38	122.98	6.20	-0.57	122.85	0.05	0.52	0.32
19.46	123.02	6.20	-0.64	122.89	0.05	0.52	0.32
19.54	123.07	6.20	-0.71	122.92	0.05	0.52	0.31
19.63	123.11	6.20	-0.77	122.95	0.05	0.53	0.31
19.71	123.16	6.20	-0.84	122.99	0.05	0.53	0.30
19.79	123.20	6.20	-0.91	123.02	0.05	0.53	0.29
19.88	123.25	6.20	-0.98	123.06	0.05	0.53	0.29
19.96	123.30	6.20	-1.04	123.09	0.05	0.54	0.28

a During the analysis, when the SD=NA, they will be imputed by the first SD available in this table.

6 REFERENCES

1. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. Arch Dis Child. 1966;41(220):613-35.

2. Kelly A, Winer KK, Kalkwarf H, Oberfield SE, Lappe J, Gilsanz V, et al. Age-based reference ranges for annual height velocity in US children. J Clin Endocrinol Metab. 2014;99(6):2104-12.

3. WHO (World Health Organization), Multicentre Growth Reference Study Group. WHO Child growth standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development. [Online]. 2006 [cited 2023 Aug 21]. Available from: URL:https://www.who.int/tools/child-growth-standards/standards/length-height-for-age

4. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999;37(2):126-39.

5. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer. 2002;94(7):2090-106.

6. Mapi Research Trust, Varni JW. Scaling and Scoring of the Pediatric Quality of Life Inventory™, Version 20. Availbale from: URL: https://www.pedsql.org/PedsQL-Scoring.pdf

7. Varni JW, Thompson KL, Hanson V. The Varni/Thompson Pediatric Pain Questionnaire. I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis. Pain. 1987;28(1):27-38.

8. Ireland PJ, Savarirayan R, Pocovi T, Tate T, Coussens M, Tofts L, et al. Development of the Screening Tool for Everyday Mobility and Symptoms (STEMS) for skeletal dysplasia. Orphanet J Rare Dis. 2021;16(1):40.

9. Ireland PJ, Donaghey S, McGill J, Zankl A, Ware RS, Pacey V, et al. Development in children with achondroplasia: a prospective clinical cohort study: Development in Children with Achondroplasia. Dev Med Child Neurol. 2012 ;54(6):532-7.

10. Gater A, Reaney M, Findley A, Brun-Strang C, Burrows K, Nguyên-Pascal M-L, et al. Development and first use of the Patient's Qualitative Assessment of treatment (PQAT) questionnaire in type 2 diabetes mellitus to explore individualised benefit-harm of drugs received during clinical studies. Drug Saf. 2020;43(2):119-34.

11. Schafer JL, Kang J. Average causal effects from nonrandomized studies: a practical guide and simulated example. Psychol Methods. 2008;13(4):279-313.

12. Stuart E.A. Matching methods for causal inference: A review and a look forward. Stat Sci. 2010;25(1):1-21.

Signature Page for VV-CLIN-0652139 v1.0
dri16646-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]