

Protocol C4181008

**A PHASE 2 STUDY OF LONG-TERM SAFETY, TOLERABILITY, PK AND
EFFICACY OF RECIFERCEPT IN ACHONDROPLASIA**

**Statistical Analysis Plan
(SAP)**

Version: 1

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Version History

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 21 Dec 2020	1 09 Nov 2020	N/A	N/A

1. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4181008. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

1.1. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary:	Primary:	Primary:
<ul style="list-style-type: none"> Evaluate the long-term safety and tolerability of recifercept doses and dosing regimes in participants aged ≥ 15 m to < 12 years with achondroplasia. 	N/A.	Long-term Safety and tolerability of recifercept as assessed through frequency and severity of AEs/SAEs.
<ul style="list-style-type: none"> To assess long-term efficacy of recifercept to increase height growth in children with achondroplasia. 	<ul style="list-style-type: none"> The primary efficacy estimand is intended to provide a population level estimate of the effect of the IP on a continuous endpoint. <p>Population-level summary: ratio between participants in the trial and a reference population [Merker et al, 2018]¹ in growth of height at 24 month; ratio between treated and reference population is observed change-from-baseline of treated participants standardized by reference participant given age and gender.</p>	<ul style="list-style-type: none"> Increase in height growth above expected in reference population [Merker et al, 2018].¹
Secondary:	Secondary:	Secondary:
<ul style="list-style-type: none"> To evaluate the PK of recifercept in children aged ≥ 15m to ≤ 12 years old with achondroplasia. 		Population PK characterization in children aged ≥ 15 m to < 12 years old with achondroplasia. CL/F and other PK parameters of recifercept to assess exposures in different age group.

Objectives	Estimands	Endpoints
<ul style="list-style-type: none"> To assess efficacy of recifercept to improve achondroplasia-related complications. 		<ul style="list-style-type: none"> Sitting height/standing height ratio. Arm span to height/length difference. Knee height:lower segment ratio. Occipito-frontal circumference. Ratio of occipito-frontal distance to occipito-mid-face measurements. z-score of the above proportionality and skull morphology where achondroplasia reference datasets exist (occipito-frontal circumference, arm span, sitting height). Fixed flexion angles at elbow. Polysomnography parameters in those with pre-existing sleep-disordered breathing at the time of enrollment. BMI. Waist:chest circumference ratio.
<ul style="list-style-type: none"> Assess change in individual safety parameters. 		<ul style="list-style-type: none"> Change from baseline in safety labs, vital signs, physical examination. Rate of ADAs.
<p>CCI [REDACTED]</p>	<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>	<p>[REDACTED]</p>

1.1.1. Primary Estimand(s)

The primary estimand is defined according to the primary objective and is in alignment with the primary endpoint. It includes the following 4 attributes:

- Population: Patients with achondroplasia, as defined by inclusion/exclusion criteria;
- Variable: Height Growth at 24 months;
- Height Growth = (Observed Change from Baseline (from study C4181005) in standing height (cm))/(Expected Change from Baseline (cm)[Merker et al, 2018]¹)



- Intercurrent event(s): Withdrawal and all events leading to missing data will be excluded from efficacy analysis and will not have their data imputed;
- Population-level summary: Mean Height growth at 24 months adjusted for age and gender.

1.1.2. Secondary Estimand(s)

The secondary efficacy estimand comprises the following 4 attributes:

- Population: Patients with achondroplasia, as defined by inclusion/exclusion criteria;
- Variable: Change from baseline to 24 months in the difference between arm span (cm) and standing height (cm);
- Intercurrent event: Withdrawal and all events leading to missing data will be excluded from efficacy analysis and will not have their data imputed;
- Population-level summary: Mean change-from-baseline of arm span/standing height difference at 24 months adjusted for age and gender.

1.2. Study Design

This is a Phase 2 open label extension study to assess the long-term safety, tolerability, PK and efficacy of recifercept.

Approximately 63 children from the Phase 2 C4181005 study will be offered to participate who, in the opinion of the investigator, continue to have a positive risk:benefit profile. Participants will be children diagnosed with achondroplasia aged $\geq 15\text{m}$ - ≤ 12 years (inclusive). All participants will continue to receive 1 of 3 doses of recifercept (1 mg/kg QW, 2 mg/kg BIW or 1.5 mg/kg QD) until a therapeutic dose is identified for up to 24 months.

Enrollment of participants will follow their completion of the C4181005 Phase 2 study and only be offered to those who, in the opinion of the investigator, continue to have a positive risk: benefit profile. PK and immunogenicity samples will be collected to assess long-term safety of recifercept.

Once a final therapeutic dose has been identified, the Pfizer IRC may decide to extend the study treatment duration and data collection (including final adult height) period beyond 24 months. Any significant changes to the protocol will be made via substantial protocol amendment.

2. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

2.1. Primary Endpoint(s)

Safety

Safety and tolerability of recifercept as assessed through frequency and severity of AEs/SAEs.

Efficacy

Increase in height growth above expected in reference population [Merker et al, 2018].

2.2. Secondary Endpoint(s)

Safety

- Change from baseline in safety labs, vital signs, physical examination.
- Rate of anti-drug antibodies.

Efficacy

- Sitting height/standing height ratio.
- Arm span to height/length difference.
- Knee height:lower segment ratio.
- Occipito-frontal circumference.
- Ratio of occipito-frontal distance to occipito-mid-face measurements.
- z-score of the above proportionality and skull morphology where achondroplasia reference datasets exist (occipito-frontal circumference, arm span, sitting height).
- Fixed flexion angles at elbow.
- Polysomnography parameters in those with pre-existing sleep-disordered breathing at the time of enrollment.
- Body mass index (BMI).
- Waist:chest circumference ratio.

Pharmacokinetic

Population PK characterization in children aged >2 to <11 years old with achondroplasia. Clearance (CL/F) and other PK parameters of recifercept to assess exposures in different age group.



2.4. Baseline Variables

The following baseline variables will be summarized for each treatment group (per [Section 3](#)). Details of summary analyses are described in [Section 5.5.1](#).

Demographic characteristics:

- Baseline age
- Gender (female vs. male);
- Race (white, black, Asian, other);
- Baseline body weight;
- Baseline height (cm);
- Baseline Body Mass.

The baseline data measured at Day 1 are:

- Vital signs
- Physical Examinations

The following variables are to have their baseline value defined as latest screening result relative to Day 1:

- Medical history & demography, Height/Weight.
- Neurological Examinations
- Vital Signs/Physical Examinations with missing Day 1 values

Where Day 1 result is missing, baseline data will be defined as the latest result from C4181005 prior to enrollment, where available.

Medical history and concomitant medications ongoing from the C4181005 study will be reentered in C4181008 with the start date from when they entered into the C4181008 study.

2.5. Safety Endpoints

- laboratory data
- vital signs data
- physical examination

2.5.1. Adverse Events

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, washout or follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

Any resolved AEs from study C4181005 will be reported as medical history. On-going AEs will be captured as ongoing with the start date from when they entered into the C4181008 study.

2.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, and blood chemistry safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be defined as the measurement on Day 1.

2.5.3. Physical Examination

Physical examination assessments will be performed as described in the protocol. Baseline will be defined as the last pre-dose measurement on Day 1.

3. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Full Analysis Set (FAS)/Safety	All participants receiving at least one dose of recifercept. Participants will be analyzed according to the dose they actually received.
Randomized (RAS)	All participants receiving at least one dose of recifercept. Participants will be analyzed according to the dose assigned from C4181005.
Per-Protocol Analysis Set (PPAS)	All participants receiving at least one dose of recifercept and have complete data at baseline through end of study or subject discontinuation and without protocol deviations that were thought to impact the efficacy evaluation during the treatment period. Participants will be analyzed according to the randomized intervention. Participants will be analyzed according to the dose assigned from C4181005.
PK Concentration set	All participants who received at least one dose of recifercept and have at least one evaluable concentration.

4. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis will be performed after all study participants completed treatment and follow-up period, and the CSR will be issued after them.

4.1. Hypotheses and Decision Rules

There are no statistical hypotheses for this protocol.

4.2. General Methods

Data will be presented – ie, listed and summarized – by dose group, block and overall. Data summaries may also be grouped by gender. Continuous data will be summarized comprising mean, median, standard deviation, minimum and maximum. Categorical and binary data are summarized will be done via percentages.

4.2.1. Analyses for Longitudinal Continuous Endpoints

Mixed-effect, repeated measures (MMRM) models will be used. The fixed effects of treatment, visit, treatment-by-visit interaction, age and gender will be included. Visit will be modeled as a categorical covariate. (If the model does not converge then Visit will be modeled as a continuous covariate.) Unstructured covariance matrix will be assumed for the model errors. Compound symmetry covariance matrix will be used if the model with unstructured variance covariance doesn't converge.

When modeling the change from baseline values, the variable for visit will start with the first post-baseline visit. At each visit, estimates of least square mean (LSM) values and the LSM differences between treatment groups will be derived from the model. The corresponding p-values and 95% confidence intervals will also be derived from the model.

4.3. Methods to Manage Missing Data

In general, for descriptive statistics missing values will not be imputed. In addition, for safety endpoints missing values will not be imputed. Other methods for handling missing values are discussed below. Missing data methods for baseline values are discussed in [Section 2.4](#).

4.3.1. PK and CCI Data

Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification). For population PK modeling, BLQ will be handled by the Pfizer standard processes.

Deviations, Missing Concentrations and Anomalous Values

In summary tables of concentration data by dose, visit day and time, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

A concentration has been collected as ND (ie not done) or NS (ie no sample),

A deviation in sampling time (15% beyond the sampling time window) is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

Pharmacokinetic Parameters

Nonlinear mixed effect modeling will be performed to evaluate pharmacokinetic parameters including clearance, area under the curve at steady state over the dosing interval for recifercept. Additional details on the population PK modeling will be described in the population modeling analysis plan.

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥ 3 evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as dosing error), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5. ANALYSES AND SUMMARIES

5.1. Primary Endpoint(s)

5.1.1. Increase in height growth above expected in reference population

5.1.1.1. Main Analysis

- Estimand strategy: Hypothetical ([Section 1.1.1](#)).
- Analysis set: FAS ([Section 3](#)).
- Analysis methodology: Change from baseline relative to Merker (2018) will be analyzed using MMRM including data from Months 3-24 with gender (and possibly age), and whether a subject has switched doses of recifercept as covariates, subject (and/or time) as a random effect and an unstructured covariance matrix ([Section 4.2.1](#)).
- Intercurrent events and missing data: Data after study drug discontinuation and rescue will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for observed standing height and change from baseline will be presented for each treatment arm.
- The least-squares (LS) means, the 95% confidence interval for the LS means, the difference between the LS means for each pair of treatment groups, and the corresponding 95% confidence interval will be presented for change from baseline in standing height for all postbaseline visits.

5.1.1.2. Sensitivity/Supplementary Analyses

The main analysis will be repeated by using the per-protocol analysis set (PPAS) as defined in [Section 5.1.1.1](#). It will use the same methodology and summary as the main analysis.

5.2. Secondary Endpoint(s)

5.2.1. Arm span to height/length difference

5.2.1.1. Main Analysis

- Estimand strategy: Hypothetical ([Section 1.1.1](#)).
- Analysis set: FAS ([Section 3](#)).

- Analysis methodology: Change from baseline for Arm span to height/length difference will be analyzed MMRM including data from Months 3-24 with gender and whether a subject has switched doses of recifercept as covariates, subject (and/or time) as a random effect and an unstructured covariance matrix ([Section 4.2.1](#)).
- Intercurrent events and missing data: Data after study drug discontinuation and rescue will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for observed standing height and change from baseline will be presented for each treatment arm.

The least-squares (LS) means, the 95% confidence interval for the LS means, the difference between the LS means for each pair of treatment groups, and the corresponding 95% confidence interval will be presented for change from baseline in standing height for all postbaseline visits.

5.2.1.2. Sensitivity/Supplementary Analysis

The main analysis will be repeated by using the per-protocol analysis set (PPAS) as defined in [Section 5.2.1.1](#).

5.2.2. Sitting height/standing height ratio

- Analysis set: FAS ([Section 3](#)).
- Intercurrent events and missing data: Data after study drug discontinuation and rescue will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and postbaseline visits for observed sitting height/standing height ratio and change from baseline will be presented for each treatment arm.

5.2.3. Knee height:lower segment ratio

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.4. Occipito-frontal circumference

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.5. Ratio of occipito-frontal distance to occipito-mid-face measurements

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.6. Z-score of the above proportionality and skull morphology where achondroplasia reference datasets exist (occipito-frontal circumference, arm span, sitting height)

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.7. Fixed flexion angles at elbow

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.8. Polysomnography parameters in those with pre-existing sleep-disordered breathing at the time of enrolment

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.9. BMI

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.10. Waist:chest circumference ratio

The analysis set, analysis methodology and intercurrent events and missing data are the same as [Section 5.2.2](#).

5.2.11. Population PK characterization in children aged ≥ 2 to < 11 years old with achondroplasia.

The analysis set for this endpoint will be the PK concentration set ([Section 3](#)); nonlinear mixed effect modeling will be performed to evaluate pharmacokinetic parameters. Additional details on the population PK modeling will be described in the population modeling analysis plan.

5.2.12. Rate of anti-drug antibodies

- Analysis set: FAS

Response rates of the development of anti-recifercept antibodies (ADA) and NAb. The percentage of subjects with positive ADA and NAb will be summarized by dose and cohort. For subjects with positive ADA or NAb, the magnitude (titer), time of onset and duration of ADA/NAb response will also be described, if data permit. The impact of ADA and NAb on PK and/or safety may also be assessed, if data permit. This may include:

- Spaghetti plots of individual intact and total recifercept concentration time profile, grouped by ADA/NAb status, produced separately by cohort.
- Table summaries of intact and total recifercept concentrations at visit and time by ADA and NAb status by cohort.

5.3. Other Endpoint(s)

5.3.1. CoIX

The analysis set, analysis methodology are the same as [Section 5.2.2](#), while intercurrent events and missing data follow methods detailed in [Section 4.3.1](#)

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.4. Subset Analyses

Not applicable.

5.5. Baseline and Other Summaries and Analyses

5.5.1. Baseline Summaries

Demographics and baseline disease characteristics defined in [Section 2.4](#) will be summarized by treatment group according to Pfizer standards.

5.5.2. Study Conduct and Participant Disposition

Subjects evaluation, disposition, discontinuation will be summarized according to Pfizer standards. .

5.5.3. Study Treatment Exposure

The exposure to study drug will be summarized by total number of applications, the total number of days of dosing, the number and the proportion of participants who are compliant with the dosing regimen.

5.5.4. Concomitant Medications and Nondrug Treatments

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to Pfizer standard.

5.5.5. Tanner Stage

Tanner stage and the change from baseline will be summarized at each visit by dose and gender.

5.6. Safety Summaries and Analyses

All safety analyses will be performed on the safety population and summarized in accordance with Pfizer Data Standards.

All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants.

Safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations, where appropriate. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, blood pressure, pulse rate, etc.) will be summarized using N, mean, median, standard deviation, etc. Change from baseline (CFB) in laboratory data, and vital signs will also be summarized. Participant listings will be produced for the safety endpoints accordingly.

5.6.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

5.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is defined as the last visit prior to Day 1.

5.6.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure, oral temperature, and pulse rate will be summarized by treatment in accordance with the sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in [Section 2.4](#).

Mean changes from baseline for supine systolic and diastolic blood pressure, oral temperature, and pulse rate for each treatment will be plotted against time post-dose. On each plot there will be 1 line for each treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum absolute values and changes from baseline for vital signs will also be summarized descriptively by treatment, using categories as defined in [Appendix 5](#). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

5.6.4. Electrocardiograms

A single 12-lead ECG will be obtained on all subjects at screening. A listing of clinical ECGs -- comprising QT, heart rate, QTcB, QTcF, PR, RR and QRS – will be presented.

5.6.5. Physical Examination

Physical examination assessments will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in [Section 2.4](#).

5.6.6. Neurological Examination

Neurological examination will be listed and summarized by treatment. Baseline is as defined in [Section 2.4](#).

6. INTERIM ANALYSES

Not applicable.

7. REFERENCES

1. Merker A, Neumeyer L, Hertel NT, et al. Growth in achondroplasia: development of height, weight, head circumference, and body mass index in a European cohort. *Am J Med Genet A* 2018; 176(8):1723-34

8. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from baseline to Month 24 in mean standing height	Summary	FAS	Separately for observed data and imputed data.	N/A
	Main analysis	FAS	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	MMRM with terms time,dose, gender & age
	Sensitivity/supplementary analysis	PPAS	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	MMRM with terms time,dose, gender & age
Change from baseline to Month 12 in mean arm span-height difference	Summary	FAS	Separately for observed data and imputed data.	N/A
	Main analysis	FAS	All data collected will be included regardless of intercurrent events. Missing data will be not be imputed.	MMRM with terms time,dose, gender & age
	Sensitivity/supplementary analysis	PPAS	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	MMRM with terms time,dose, gender & age

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Visit Label	Target Day	Start Day	End Day
Day 1	Day 1	Day 1	Day 1
Day 4	Day 4	Day 2	Day 6
Day 8	Day 8	Day 7	Day 9
Day 15	Day 15	Day 10	Day 19
Day 29	Day 29	Day 20	Day 39
Month 2	Day 61	Day 40	Day 75
Month 3	Day 91	Day 76	Day 105
Month 4	Day 121	Day 106	Day 135
Month 5	Day 151	Day 136	Day 165
Month 6	Day 181	Day 166	Day 195
Month 7	Day 211	Day 196	Day 225
Month 8	Day 241	Day 226	Day 255
Month 9	Day 271	Day 256	Day 285
Month 10	Day 301	Day 286	Day 315
Month 11	Day 331	Day 316	Day 345
Month 12	Day 361	Day 346	Day 375
Month 13	Day 391	Day 376	Day 405
Month 14	Day 421	Day 406	Day 435
Month 15	Day 451	Day 436	Day 465
Month 16	Day 481	Day 466	Day 495
Month 17	Day 511	Day 496	Day 525
Month 18	Day 541	Day 526	Day 555
Month 19	Day 571	Day 556	Day 585
Month 20	Day 601	Day 586	Day 615
Month 21	Day 631	Day 616	Day 645

Month 22	Day 661	Day 646	Day 675
Month 23	Day 691	Day 676	Day 705
Month 24	Day 721	Day 706	Day 735

Appendix 2.2. Endpoint Derivations

Height Growth

The primary efficacy endpoint is H defined by the following:

$$H_{ijkl} = \frac{Y_{ijkl} - Y_{i0kl}}{Z_{jl} - Z_{0l}},$$

where Y_{ijkl} is the observed standing height for the i th subject, at month j on dose k with gender factor l ($j=0$ denotes baseline measurement) and Z_{jl} is the mean expected standing height based on Merker for subject i 's age.

Mean expected standing height from Merker is sorted by 6 months up to age 4, while means expected values for children > 4 years are sorted per annum. Linear interpolation will be employed to calculate mean expected values so that mean standing height are sorted at 6 month intervals for children > 4 years. SAS code for the linear interpolation calculation will be provided in Appendix 4.

Appendix 2.3. Definition of Protocol Deviations That Relate to Statistical Analyses/Populations

Appendix 3. Data Set Descriptions

Appendix 4. Statistical Methodology Details

Linear Interpolation

Linear interpolation will be employed to provide mean expected standing height values at 6 month interval for children > age 4. The SAS code is as follows:

```
proc expand data=mydata out=LinInterp;  
    convert exp_mean=linear / method=join;  
    id age;  
run;
```

MMRM

MMRM will be used for height growth and arm span-height difference. The SAS code is as follows:

```
proc mixed data=mydata;  
    class dose gender month;  
    model height = dose month gender age/s;  
    random int month / type=un sub=subject;  
    lsmean dose;  
run;
```

Appendix 5. Categorical Classes for Vital Signs of Clinical Concern

Categories for Vital Signs

Systolic BP (mm Hg)	min. < 90
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Systolic BP (mm Hg) change from baseline	max, decrease ≤ 30	max, increase ≤ 30
Diasstolic BP (mm Hg)	min. < 50	
Diastolic BP (mm Hg) change from baseline	max, decrease ≤ 20	max, increase ≤ 20
Supine pulse rate (bpm)	min. < 40	max. > 120

Appendix 6. List of Abbreviations

	Term
Abs	absolute
AE	adverse event
ANOVA	analysis of variance
BLQ	below the limit of quantitation
BP	blood pressure
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
FAS	full analysis set
LLOQ	lower limit of quantitation
LOCF	last observation carried forward

	Term
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
N/A	not applicable
CCI	
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PR interval	time from the beginning of the P wave to the beginning of QRS complex
PT	preferred term
QRS	a combination of the Q wave, R wave and S wave
QTc	corrected QT
QTcB	corrected QT (Bazzett method)
QTcF	corrected QT (Fridericia method)
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGS	Statistical Guidance Standards
SOP	standard operating procedure