**Protocol C4181005**

# A PHASE 2 MULTIPLE DOSE, RANDOMIZED STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF RECIFERCEPT IN CHILDREN WITH ACHONDROPLASIA

**Statistical Analysis Plan**
**(SAP)**

**Version:** **2**

**Date:** 16 Aug 2022

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## APPENDICES

# 1. VERSION HISTORY

**Table 1. Summary of Changes**

| Version/ Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 1<br>21 Dec 2020 | 1<br>09 Nov 2020 | N/A | N/A |
| 2<br>16 Aug 2022 | 3<br>23 Mar 2022 | Addition of PK cohort; Clinical Outcome Assessment changes | • Added specification and analysis of (Primary) PK endpoints (Section 3.1.1 & Section 6.1.2)<br>• Added 2 analysis sets to accompany the PK cohort (Section 4)<br>• Added language on CHAQ data (Section 5.3.2)<br>• Futility language removed (Section 7.1) |

# 2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4181005. 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.

## 2.1. Study Objectives, Endpoints, and Estimands

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| • Evaluate the safety and tolerability of recifercept doses and dosing regimes in participants aged ≥2 to <11 years with achondroplasia. | N/A | Safety and tolerability of recifercept as assessed through frequency and severity of AEs/SAEs. |
| • To assess efficacy of recifercept to increase height growth in children with achondroplasia. | • The primary efficacy estimand is intended to provide a population level estimate of the effect of recifercept on a continuous endpoint.<br><br>Population-level summary: ratio between participants in the trial and a reference population [Merker et al, 2018][1] in growth of height at 12 month; ratio between treated and reference population is observed change-from-baseline of treated participants standardized by reference participant given age and gender. | • Increase in height growth above expected in reference population [Merker et al, 2018][1] |
| **Secondary:** | **Secondary:** | **Secondary:** |
| • To evaluate the pharmacokinetics (PK) of recifercept in children aged ≥2 to <11 years old with achondroplasia. | | 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. |
| • To assess efficacy of recifercept to improve achodroplasia-related complications. | | • Sitting height/standing height ratio.<br>• Arm span to height/length difference.<br>• Knee height:lower segment ratio.<br>• Occipito-frontal circumference. |

| Objectives | Estimands | Endpoints |
|---|---|---|
| | | • Ratio of occipito-frontal distance to occipito-mid-face measurements.<br>• z-score of the above proportionality and skull morphology where achondroplasia reference datasets exist (occipito-frontal circumference, arm span, sitting height).<br>• Fixed flexion angles at elbow.<br>• Polysomnography parameters in those with pre-existing sleep-disordered breathing at the time of enrollment.<br>• Body mass index (BMI).<br>• Waist:chest circumference ratio.<br>• Change from baseline in CHAQ component and index scores, QoLISSY Brief total score. |
| • Assess change in individual safety parameters. | | • Change from baseline in safety labs, vital signs, physical examination.<br>• Rate of anti-drug antibodies. |
| CCI | | |
| | | |

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### 2.1.1. 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 12 months;
- Height Growth = (Observed Change from Baseline 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 12 months adjusted for age and gender.

### 2.1.2. 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 12 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 12 months adjusted for age and gender.

## 2.2. Study Design

This is a phase 2 randomized, 3 arm (3 active doses of Recifercept), parallel group dose-finding study of safety, tolerability, PK and efficacy.

The study will enroll approximately 54 children with achondroplasia aged 2-10 years (inclusive) who will be enrolled and randomized to receive one of three doses of recifercept (1 mg/kg once-weekly, 2 mg/kg twice-weekly or 1.5 mg/kg once-daily, n=18 per dose) such that at least 15 participants per dose are evaluable. CCI [redacted] All participants will receive recifercept for 12 months.

All participants who complete the study and in the opinion of the investigator, continue to have a positive risk:benefit profile, will be offered to enroll into an open-label extension (OLE) study. Participants will continue to receive recifercept at the dose previously received in this phase 2 study or at the therapeutic dose once this is identified.

Enrollment will follow an age and dose-staggered approach (descending age and ascending dose) with review of safety and PK data by the study team before progression to the next enrollment block (see **Figure 1**). If certain pre-defined safety signals occur then a meeting of the eDMC will be convened to make a decision on progression of enrollment. The PK data collected in block A will be used in the PopPK model (developed using healthy adult data) to confirm the dosing for younger children (ie, ≥2 to <6 years and 0-<2 years).

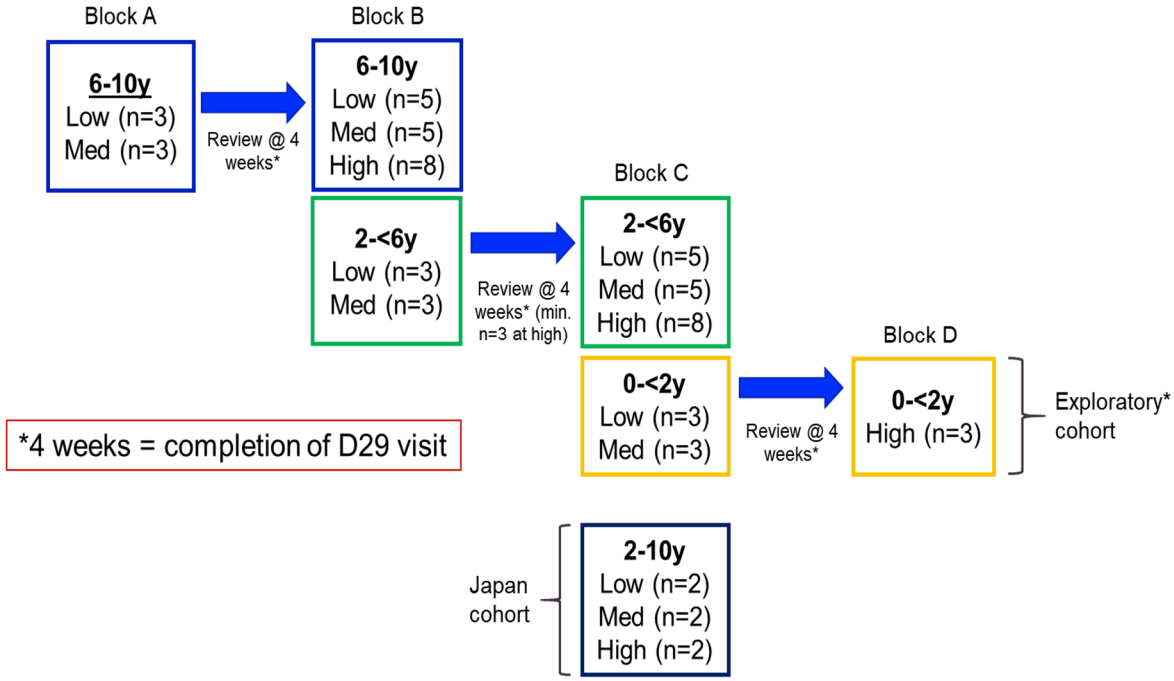
An interim analysis is planned when at least 15 participants per dose aged ≥2 to <11 years have received 6 months of treatment with recifercept. eDMC will review safety, PK and efficacy data to confirm ongoing positive benefit:risk in participants.

Progression to the next enrollment block will be controlled by study team review of safety and PK data in the following manner:

| | |
|---|---|
| **Block A to B** | Review after all block A participants (n=6) have completed D29 |
| **Block B to C** | Review once all 2-6y participants (n=6) and 3 high dose 6-10y participants have completed D29 |
| **Block C to D** | Review once all 0-2y participants (n=6) and 3 high dose 2-6y participants have completed D29 |

The study design schema is described in **Figure 1**.

**Figure 1. Study Design**




Note: This is an example of additional explanatory information for the figure.

## 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

## 3.1. 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].

### 3.1.1. PK Cohort

### Pharmacokinetic

The pharmacokinetic parameters following single dose administration will be derived from the concentration-time profile as follows:

| Parameter | Definition | Method of Determination |
|---|---|---|
| $AUC_{inf}$ | Area under the serum concentration time profile from time 0 extrapolated to infinite time. | $AUC_{last}+(C_{last}*/k_{el})$,<br>Where $C_{last}*$ is the predicted serum concentration at the last quantifiable time point estimated from the loglinear regression analysis. |
| $AUC_{168}$ | Area under the serum concentration-time profile from 0 to 168 hours. | Linear/Log trapezoidal method. |
| $AUC_{360}$ | Area under the serum concentration-time profile from 0 to 360 hours. | Linear/Log trapezoidal method. |
| $C_{max}$ | Maximum serum concentration. | Observed directly from data. |
| $T_{max}$ | Time for $C_{max}$. | Observed directly from data as time of first occurrence. |
| $t_{½}$ | Terminal elimination half-life. | $Log_e(2)/k_{el}$,<br>where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the loglinear concentration time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression. |

Actual PK sampling times will be used in the derivation of PK parameters.

### 3.2. 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.
- Change from baseline in CHAQ component and index scores, QoLISSY Brief total score.

**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.

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### 3.4. Baseline Variables

The following baseline variables will be summarized for each treatment group. Details of summary analyses are described in Section 6.5.1.

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 and/or screening result is missing, baseline data will be defined as the latest result from C4181001 prior to screening, where available.

### 3.5. Safety Endpoints

- laboratory data
- vital signs data
- physical examination

### 3.5.1. 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.

### 3.5.2. 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, or the last available pre-dose collection time point (whichever occurs later).

### 3.5.3. Physical Examination

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

## 4. 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. |
| Per-Protocol Analysis Set (PPAS) | All participants receiving at least one dose of recifercept and have complete data at baseline through month 12 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. |
| PK Concentration set | All participants who received at least one dose of recifercept and have at least one evaluable concentration. |
| PK Study Cohort | All participants who received a dose of the recifercept Phase 2 formulation and a dose of the Phase 3 formulation with at least one evaluable concentration result. |

| Population | Description |
|---|---|
| PK Study Cohort Parameter (PKCP) | All participants in the PK cohort who have at least one PK parameter of interest. |

## 5. 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.

### 5.1. Hypotheses and Decision Rules

The null hypothesis for primary efficacy analysis is that observed height growth 12 months post-baseline for children on recifercept is equal to the expected height growth for the achondroplasia reference population based on Merker (2018). The alternative hypothesis is that observed height growth 12 months post-baseline for children on recifercept is greater than the expected height growth for the achondroplasia reference population based on Merker (2018).

The Bonferroni correction method is used to control the overall familywise error rate of 0.05 for multiple comparisons. The post-baseline estimate will be considered statistically significant at the 1-sided 0.017 level.

### 5.2. 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.

#### 5.2.1. 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.

## 5.3. Methods to Manage Missing Data

In general, for descriptive statistics missing values will not be imputed. In addition, for safety endpoints missing valiues will not be imputed. Other methods for handling missing values are discussed below. Missing data methods for baseline values are discussed in Section 3.4.

### 5.3.1. PK and Biomarker 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.

### 5.3.2. CHAQ

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# 6. ANALYSES AND SUMMARIES

## 6.1. Primary Endpoint(s)

### 6.1.1. Increase in height growth above expected in reference population

#### 6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis set: FAS (Section 4).
- Analysis methodology: Change from baseline relative to Merker (2018) will be analyzed using MMRM including data from Months 3, 6, 9, and 12 with gender (and possibly age) as a covariate, subject (and/or time) as a random effect and an unstructured covariance matrix (Section 5.2.1).
- 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.

#### 6.1.1.2. Sensitivity/Supplementary Analyses

The main analysis will be repeated by using the per-protocol analysis set (PPAS) as defined in Section 6.1.1.1. It will use the same methodology and summary as the main analysis.

### 6.1.2. PK Cohort

Blood samples for PK analysis of Intact and total recifercept wiill be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for intact and total recifercpt from the concentration-time values using standard non-compartmental methods:

**Table 2 Non-compartmental PK Parameters**

| Parameter | Analysis Scale | Recifercept |
|---|---|---|
| $C_{max}$ | ln | D |
| $T_{max}$ | U | D |

| | | |
|---|---|---|
| $t_{1/2}$* | U | D |
| $AUC_{inf}$* | ln | D |
| $AUC_{168}$* | ln | D |
| $AUC_{360}$* | ln | D |

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, U=raw (untransformed), *=if data permits.

To assess the pharmacokinetics of intact and total recifercept, the PKCP parameters detailed above will be listed and summarized for subjects in the PK analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.1. Each PK parameter for intact and total recifercept will be summarized by dose. Each summary will include the set of summary statistics as specified in Table 3.

**Table 3 PK Parameters to be Summarized Descriptively**

| Parameter | Summary Statistics |
|---|---|
| $AUC_{360}$, $AUC_{inf}$, $AUC_{168}$,$C_{max}$ | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%. |
| $T_{max}$ | N, median, minimum, maximum. |
| $t_{1/2}$ | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum. |

There will be a summary table each for Intact and Total Recifercept presenting all PK parameters. Each summary table will be grouped by dose.

To assess the relationship between the PK parameters and dose, dose normalized $AUC_{tau}$ and $C_{max}$ will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose separately. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg/kg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented.

Supporting data from the estimation of t½ and $AUC_{inf}$ will be listed where applicable: terminal phase rate constant ($k_{el}$); goodness of fit statistic from the log-linear regression ($r^2$); the percent of $AUC_{inf}$ based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of $k_{el}$. These data may be included in the clinical study report.

Presentations for intact and total recifercept concentrations will include:

A listing of all concentrations sorted by subject ID, dose, and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

A summary of concentrations by dose, cohort, and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

Median concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by dose and cohort (all doses on the same plot per scale, based on the summary of concentrations by dose, cohort and time post-dose).

Mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by dose and cohort (all doses on the same plot per scale, based on the summary of concentrations by dose, cohort and time post-dose).

Individual concentration time plots by dose and cohort (on both linear and semi-log scale) against actual time post-dose will be produced.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long recifercept concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

## 6.2. Secondary Endpoint(s)

### 6.2.1. Arm span to height/length difference

#### 6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis set: FAS (Section 4).
- Analysis methodology: Change from baseline for Arm span to height/length difference will be analyzed MMRM including data from Months 3, 6, 9, and 12 with gender as a covariate, subject (and/or time) as a random effect and an unstructed covariance matrix (Section 5.2.1).
- 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.

#### 6.2.1.2. Sensitivity/Supplementary Analysis

The main analysis will be repeated by using the per-protocol analysis set (PPAS) as defined in Section 6.2.1.1.

### 6.2.2. Sitting height/standing height ratio

- Analysis set: FAS (Section 4).
- 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.

### 6.2.3. Knee height:lower segment ratio

The analysis set, analysis methodology and intercurrent events and missing data are the same as Section 6.2.2.

### 6.2.4. Occipito-frontal circumference

The analysis set, analysis methodology and intercurrent events and missing data are the same as Section 6.2.2.

### 6.2.5. 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 6.2.2.

### 6.2.6. 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 6.2.2.

### 6.2.7. Fixed flexion angles at elbow

The analysis set, analysis methodology and intercurrent events and missing data are the same as Section 6.2.2.

### 6.2.8. 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 6.2.2.

### 6.2.9. BMI

The analysis set, analysis methodology and intercurrent events and missing data are the same as Section 6.2.2.

### 6.2.10. Waist:chest circumference ratio

The analysis set, analysis methodology and intercurrent events and missing data are the same as Section 6.2.2

### 6.2.11. CHAQ component and index scores; QoLISSY Brief total score

The analysis set, analysis methodology and intercurrent events and missing data are the same as Section 6.2.2.

### 6.2.12. 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 4); 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.

### 6.2.13. 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.

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### 6.4. Subset Analyses

Not applicable.

### 6.5. Baseline and Other Summaries and Analyses

#### 6.5.1. Baseline Summaries

Demographics and baseline disease characteristics defined in Section 3.4 will be summarized by treatment group according to Pfizer standards.

#### 6.5.2. Study Conduct and Participant Disposition

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

#### 6.5.3. 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.

#### 6.5.4. Concomitant Medications and Nondrug Treatments

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

#### 6.5.5. Tanner Stage

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

### 6.6. 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.

#### 6.6.1. Adverse Events

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

#### 6.6.2. 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.

#### 6.6.3. 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 3.4.

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.

#### 6.6.4. 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.

### 6.6.5. 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 3.4.

### 6.6.6. Neurological Examination

Neurological examination will be listed and summarized by treatment. Baseline is as defined in Section 3.4.

## 7. INTERIM ANALYSES

### 7.1. Introduction

There will be an interim analysis will be performed to assess efficacy and safety after at least approximately 45 participants (15 per dose), complete their study participation through 50% of the study (completion of 6 months treatment). Interim analysis results may be used for internal business decisions regarding future study planning, though not stopping for futility, stopping for early success nor conducting a sample size re-estimation.

### 7.2. Interim Analyses and Summaries

*Height Growth & Arn span to height/length difference*

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis set: FAS (Section 4).
- Analysis methodology: Change from baseline relative to Merker (2018) will be analyzed using MMRM including data from Months 3 and 6, with gender as a covariate, subject (and/or time) as a random effect and an unstructed covariance matrix (Section 5.2.1).
- 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 arm span to standing height difference) 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 (and arm span to standing height difference) for all postbaseline visits.

## 8. 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

# 9. 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 12 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. | ANOVA |
| 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. | ANOVA |

## Appendix 2. Data Derivation Details

### Appendix 2.1. Definition and Use of Visit Windows in Reporting

| Visit Label | Target Day | Start Day | End Day |
|---|---|---|---|
| Screening | NA | Day -14 | Day -1 |
| 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 365 | Day 346 | Day 366 |

### Appendix 2.2. Endpoint Derivations

*Height Growth*

The primary efficacy endpoint is *H* defined by the following:

[redacted]



[redacted]

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

where is $Y_{ijkl}$ 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 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

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## 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 differene. 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 | |
| Systolic BP (mm Hg) change from baseline | max, decrease ≤ 30 | max, increase ≤ 30 |
| Diastolic 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 |
| 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 |
| PD | pharmacodynamic(s) |
| 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 |

| | **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 |