Non-Interventional Study Protocol
C4181010

A PILOT PROJECT TO EVALUATE THE FEASIBILITY OF CONSTRUCTING A CONCURRENT EXTERNAL CONTROL FOR RECIFERCEPT

Statistical Analysis Plan
(SAP)

Version: 2

Author: PPD

Date: 15-Mar-2024

TABLE OF CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

This amendment to the version 1 for the SAP will take place after last subject, last visit. Changes to the SAP include:

1. Height Growth will be excluded as a study objective (Section 2.3): Height Growth was specified as the primary endpoint in concordance with the primary endpoints from C4181005; however the definition of height growth is inappropriate as an endpoint for this protocol. For C4181005, there are no placebo/comparator arms as part of that trial. In C4181010 there is an arm considered as placebo. Height growth is a ratio of observed versus expected change from baseline for anthropometric endpoints using historical controls. In this setting that would necessitate formulation of a Cauchy random variable.
2. Section 2.1 revised to reflect binary treatment group
3. Safety Endpoints are removed (Sections 5.2): All safety endpoints for this study can be reviewed by perusing the original CSRs for C4181005 (for treated patients) and C4181001 (for untreated patients).
4. Achondroplasia & PRO endpoints are removed (Section 5.3)
5. Statistical Hypothesis uses Height Z-score instead for Height Growth (Section 3.1)
6. Age and gender are removed as covariates (Section 5.4)
7. Height Z-Score replaces Height growth (section 7.2.2)
8. AGV is removed from Appendix
9. Height Z-Score replaces Height growth (section 7.2.4)
10. All Bayesian method exploration are removed (section 7.2.1)
11. Safety analyses removed (section 7.2.3)
12. “Proportion of patients reaching Height Growth Threshold ≥ 1.5” analysis is removed (section 7.2.4)
13. SAS Code for Statistical Analysis added to section 10.3
14. Analyses of Achondroplasia-Related Complications and PRO endpoints for Objective 2 are removed.

2 INTRODUCTION

- Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

- *Achondroplasia is a heritable autosomal dominant disorder and is the most common form of skeletal dysplasia in humans, with a global birth prevalence of 1 in 25-30,000 or ~250,000 individuals worldwide (1–3). Achondroplasia is caused by a single-point gain-of-function mutation in the gene encoding the fibroblast growth factor receptor 3 (FGFR3) (2,4). FGFR is a key inhibitory regulator of endochondrial ossification and its over-activiation interferes with normal chondrocyte maturation and causes shorter long bones and changes in flat bones such as the occipital bone and vertebrae.*

- *Achondroplasia results in short stature and a range of severe complications due to abnormal ossification centers in the cranial base, facial bones, vertebrae, rib cage, and joints. Lordosis, kyphosis, small foramen magnum, and spinal stenosis are the most common achondroplasia-related orthopaedic complications. Other achondroplasia related complications include sleep-disordered breathing, otitis media, and hydrocephalus. Medical complications associated with achondroplasia greatly impact physical and psychosocial functioning, self-esteem, and patient quality of life (3,5).*

- *Currently, vosoritide is the only treatment approved by EMA (for achondroplasia patients aged 2 years and older with open growth plates) and FDA (for achondroplasia patients aged 5 years and older with open growth plates) to increase linear growth. It is an analog of C-type natriuretic peptide and works by binding to a receptor called natriuretic peptide receptor type B (NPR-B), which reduces the activity of FGFR3. Other available treatments are either aimed at limb lengthening with surgery or are interventions to treat the complications associated with achondroplasia. Recifercept is a modified soluble recombinant human FSFR3 under development for the treatment of achondroplasia. Recifercept is designed to be a decoy protein, competing for ligands of the FGFR3-G380R receptor responsible for achondroplasia and by forming inactive heterodimers with FGFR3 monomers. By binding free FGFR3-activating ligands and forming inactive dimers, recifercept reduces activation of the receptor, allowing chondrocyte proliferation and differentiation to proceed.*

- *A recifercept phase 2 clinical study (Study C4181005) is ongoing to investigate the safety, tolerability, pharmacokinetics (PK) and efficacy of recifercept in children aged 3 months to 10 years with achondroplasia. Fifty-four eligible participants aged 2-10 years and 9 patients aged 3 months to 2 years will be enrolled and randomized to receive one of three doses of recifercept subcutaneously (1mg/kg once-weekly, 2mg/kg twice weekly, or 1.5mg/kg once-daily, n=21 per dose). Once participants complete the phase 2 trial, they will be offered enrollment into an open-label extension study at the dose previously received in the phase 2 trial or at the therapeutic dose once it is identified. A separate multi-country prospective observational natural history study (Study C4181001) is ongoing to examine the anthropometric characteristics, and achondroplasia-related symptoms, tests, and treatments among children with achondroplasia. A total of 300 achondroplasia patients aged 0 and 15 years of age will be recruited and followed up for a duration of 5 years. All patients participating in Study C4181005 were or will be recruited from Study C4181001.*

2.1 STUDY DESIGN

- *This is a retrospective cohort study using existing data from two ongoing studies: C4181001 and C4181005. The study population will include two independent study*

cohorts: a) patients from Study C4181005 who have completed Visits 1 through 11 (at D183); b) patients from Study C4181001 who meet the eligibility criteria for Study C4181005 and have at least 6 months follow-up data. Eligible patients from Study C4181001 will be included as potential external controls for patients in Study C4181005, using propensity score methodology.

This pilot study has the potential to demonstrate the feasibility of Study C4181001 as concurrent external controls and provide viable study design options for the recifercept pivotal trial. It will also provide information on the efficacy of recifercept compared to clinical practices in the real world. Having an external control arm in the trial allows for increased efficiency and decreased product development time.

Study population

This retrospective cohort study will include achondroplasia patients from Study C4181005 and those from Study C4181001 who meet the inclusion and exclusion criteria of Study C4181005. Study C4181005 is a single-arm trial to evaluate the safety and tolerability of recifercept doses and dosing regimen, and efficacy to increase height growth in achondroplasia patients. Study C4181005 will include approximately 63 children with achondroplasia aged 3 months to 10 years (inclusive) with Tanner Stage 1, who are enrolled and randomized to receive one of three doses of recifercept (1mg/kg once-weekly, 2mg/kg twice-weekly, or 1.5mg/kg once-daily) subcutaneously for 12 months. Demographics, medical history, anthropometric measurements, and patient-reported outcomes in functional status and quality of life are collected approximately every 3 months. Study C4181001 is a prospective natural history study to collect the longitudinal anthropometric and disease-related complication data in children with achondroplais. It will include approximately 300 achondroplasia patients aged 0-15 years with Tanner Stage I recruited from global sites. Patient data will be collected at baseline and at every 3-month interval visits, for a maximum of 5 years. Further details on data sources are presented in Table 1.

Data source

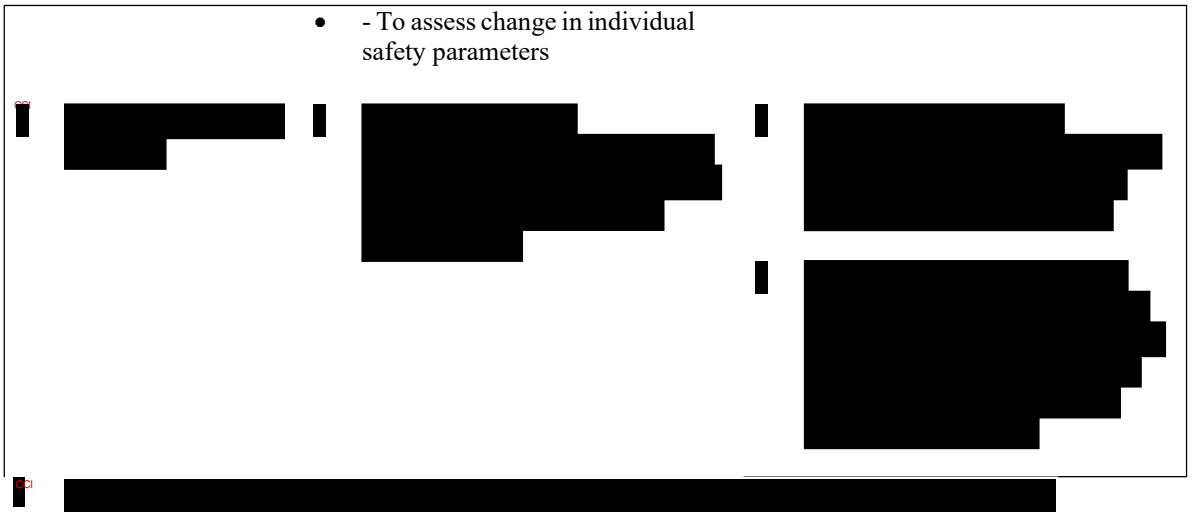
- *For this pilot study, the data in Table 9.3 from C4181001 and C4181005 will be pooled to create a single dataset. With respect to patients the component datasets will be mutually exclusive – that is, there are no patients common to both studies.*

This retrospective cohort external control arm study will include achondroplasia patients from Study C4181005 and those from Study C4181001 who meet the inclusion and exclusion criteria of Study C4181005. Study C4181005 is a single-arm trial to evaluate the safety and tolerability of recifercept doses and dosing regimen, and efficacy to increase height growth in achondroplasia patients. Study C4181005 will include approximately 63 children with achondroplasia aged 3 months to 10 years (inclusive) with Tanner Stage 1, who are enrolled and randomized to receive one of three doses of recifercept (1mg/kg once-weekly, 2mg/kg twice-weekly, or 1.5mg/kg once-daily)

subcutaneously for 12 months. Demographics, medical history, anthropometric measurements, and patient-reported outcomes in functional status and quality of life are collected approximately every 3 months. Study C4181001 is a prospective natural history study to collect the longitudinal anthropometric and disease-related complication data in children with achondroplais. It will include approximately 300 achondroplasia patients aged 0-15 years with Tanner Stage I recruited from global sites. Patient data will be collected at baseline and at every 3-month interval visits, for a maximum of 5 years.

Table 1. Data sources*

	Recifercept phase 2 Clinical Trial (Study C4181005)	Natural History Study (Study C4181001)
Study population	3m-10y, Tanner Stage 1	0-10y, Tanner Stage 1
Study duration	12 months	Up to 5 years
Visit interval	- Medical history collected at baseline - Anthropometric measurements every 3 months - Biomarkers baseline, D1, D4, D8, D15, D29, M2, M3, M6, M9, M12 [redacted]	- Complications collected every 3 months - Anthropometric measures every 3 months - Biomarkers sample taken once annually [redacted]
Sample size	63 patients	300 patients anticipated
Primary objective	- Evaluate the safety and tolerability of recifercept doses and dosing regimens in participants aged ≥ 2 to <11 years with achondroplasia - Assess efficacy of recifercept to increase height growth in children with achondroplasia	- Collection of longitudinal anthropometric and disease-related complication data in children with achondroplasia
Secondary outcomes	- To evaluate the pharmacokinetics of recifercept in participants aged ≥ 2 to <11 years with achondroplasia - To assess efficacy of recifercept to improve ahondroplasia-related complications	- Investigation of potential serum biomarkers in children with achondroplasia



Treatment/cohort labels

Treatment are determined which protocol each participant is in and will be reported as such.

Protocol	Treatment	Label
C4181001	Not treated	
C4181005	Treated	Recifercept

2.2 STUDY OBJECTIVES

Objectives of this pilot project include:
1. Construct a concurrent external control arm for recifercept phase 2 clincial trial using achondroplasia patients from a prospective observal natural history study
2. If objective #1 is met, the following will be compared to examine differences between patients enrolled in the recifercept phase 2 clincial trial and those in the concurrent external control:

- *Selected anthropometric measurements, including but not limited to: standing height, sitting height, knee height, arm span, length of the legs, sitting height/standing height ratio, arm span to height/length difference, knee height/lower segment ratio*

- *Achondroplasia-related orthopaedic complications (including lordosis, kyphosis, small foramen magnum, spinal stenosis), and other achondroplasia-related complications (including apnea, AOM, and hydrocephalus)*

- *Differences in functional status and health-related quality of life*

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

This study includes an CCI element and specific hypotheses to be tested. That null hypothesis is limited to a comparison of height Z-Score. The null hypothesis for that objective is as follows:

> Null: Mean Change from Baseline of Height Z-Score up to 12 months is no different between patients on treatment and patients in the natural history study.

3.2 STATISTICAL DECISION RULES

The alpha level will be 0.05, 2-sided. No adjustments for multiple comparisons will be made.

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

The Full Analysis set includes all patients who met the inclusion & exclusion criteria listed below.

Inclusion criteria

All patients from Study C4181005 who have completed Visits 1 through 11 (at D183) will be included in this project.

To construct a concurrent external control from Study C4181001, patients from Study C4181001 will need to meet the following eligibility criteria from Study C4181005:

- *Documented, confirmed genetic diagnosis of achondroplasia from historical medical records (test must have been performed at a laboratory fully accredited for genetic testing under local regulations)*
- *Aged ≥ 3 months to <11 years (up to the day before 11th birthday inclusive) at time of enrollment into Study C4181001*
- *Have completed at least 2 valid height/length measurements (at least 3 months apart)*
- *Assessed for Tanner stage 1 during physical examination before or at enrollment into Study C4181001 (must include assessment of breast development for females, or testicular stage for males)*
- *Able to stand independently for height measurements (if ≥ 2 years of age at enrollment); If aged <2 years at enrollment, has a documented historical MRI brain/cervical spine performed in the previous 12 months.*

- *Have at least 6 months of available follow-up data after enrollment into Study C4181001*

Exclusion criteria

- *Presence of severe obesity (BMI > 95% percentile on Hoover-Fong BMI charts)*
- *Body weight <7kg or >30kg*
- *History of chronic kidney disease (CKD) or renal impairment*
- *History of receipt of any treatment that are known to potentially affect growth (including oral steroids > 5 days in the last 6 months before enrollment, high dose inhaled corticosteroids (>800 mcg/day beclametasone equivalent) and medication for attention deficient hyperactivity disorder)*
- *Less than 6 months since fracture or surgical procedure of any bone determined from the baseline visit date.*
- *Presence of any internal guided growth plates/devices*
- *History of removal of internal guided growth plates/devices within 6 months prior to enrolment*

4.2 SAFETY ANALYSIS SET
Safety analysis set is the same as the full analysis set.

4.3 OTHER ANALYSIS SET
There are no other analysis sets to be used in this study

4.4 SUBGROUPS
Subgroup analysis will not be performed.

5 ENDPOINTS AND COVARIATES
For the untreated group, baseline value is defined as the value recorded at the date of informed consent, whereas for the treated group the baseline value is the value taken at Day 1.

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)
For objective #2, these are the following endpoints:

Anthropometric endpoints	• Z-score of standing height • Arm span to height/length difference.

5.2 SAFETY ENDPOINTS
Not applicable.

5.3 OTHER ENDPOINTS
Not applicable.

5.4 COVARIATES
Not applicable.

6 HANDLING OF MISSING VALUES

No imputation for missing values will be performed.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS
Descriptive statistics will be tabulated on patient demographic and baseline clinical characteristics between achondroplasia patients from Study C4181005 and patients from Study C4181001 who meet all the inclusion and exclusion criteria of Study C4181005.

7.2 STATISTICAL ANALYSES
To evaluate objective 2, 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.) There will be random effects for both slopes (i.e. visit as a continuous variable) and intercept, clustered by subject nested within a propensity-score matched set or clustered by subject weighted by Inverse Probability Weights (see section 10.3). Random effects for slopes will be removed in the above models do not converge. Unstructured covariance matrix will be assumed for the model errors.

7.2.1 <u>Objective 1</u>

To construct a concurrent external control for Study C4181005, a propensity score (PS) will be created to achieve balance across covariates between achondroplasia patients from Study C4181005 and patients from Study C4181001 who meet all the eligibility criteria of Study C4181005. The PS will be estimated using standard logistic regression approaches with the "outcome" variable being the data source (whether patients were included in Study C4181005 and exposure to recifercept treatment) and the predictors being the variables associated with both the exposure (recifercept treatment) and the outcomes of interest (i.e. standing height & arm-span-to-height difference). This model will provide the predicted probability of being in the trial cohort relative to the concurrent external control cohort as a function of the covariates (the propensity score of being included in Study C4181005). The potential covariates may include demographics (e.g. age, gender, race and ethnicity), clinical characteristics (e.g. presence of achondraplasia-related complications, Tanner stage, and other non-achondroplasia-

related conditions of medical significance). The distribution of the PS will be reviewed and patients with a PS in the areas of nonoverlap and/or with extreme PS values might be excluded to improve validity (PS trimming). Each patient in the PS trimmed receifercept group will be matched on a ratio of 1:1 with patients in the PS trimmed concurrent external control using optimal nearest neighbour matching with a maximum caliper of 1%. Pre- and post-matching balance will be assessed using standardized differences between these two PS-matched groups. A negative control outcome may also be identified to evaluate the pre- and post-matching balance. There are different options that will be considered while modelling via PS. These include:

1. Calipers: range from [.01,.25]
2. Statistic (used to match treated to control subject): logit of PS, minimizing difference of PS, Mahalanobis distance
3. Ratio match (treatment-to-untreated): 1-to-1, 1-to-m

Exact matching can be included within the PS model. Exact matching will be done by gender. A binary variable will be created to specify race. The variable will have the value of "Yes" for "White" and "No" for all other values.

Standardized mean differences of the matched variables are the main criteria used to determine whether objective 1 is met. An external control dataset is confirmed (i.e., objective 1 is met) when all of the standard mean differences for the matched variables are less than 0.1.

After the concurrent external control is constructed by PS matching, descriptive statistics will be tabulated on patient demographic and baseline clinical characteristics between achondroplasia patients from PS-matched recifercept phase 2 trial cohort and those from PS-matched concurrent external control. Two-sample T-tests will be used for continuous variables, and chi-square tests for categorical variables assuming the distribution is normal. Frequency of primary, secondary and exploretary outcomes of interest and 95% confidence intervals will be computed.

Another method to construct an external control for C4181005 for the purpose of estimating the Average Treatment Effect (ATE) of recifercept is Inverse Probability Weights (IPW). IPW will use PS to weight the observations prior to the analysis of height growth. Weights are calculated for each subject as 1/PS for Recifercept and 1/(1-PS) for the untreated group. Standardized differences between the untreated and Recifercept groups will be assessed both before and after weighting. Standardized mean differences of <10% may be considered a negligible difference.

7.2.2 Objective 2

Achondroplasia disease measures including height growth, anthropometric measurements, difference in functional status and health-related of life will be summarized using descriptive statistics.

Analyses of Height Z-Score and Arm-Span-to-Height Difference

If objective 1 is met, either a matched dataset – exclusively with a ratio of treated to untreated of 1:1 – via PS or a dataset augmented by IPW will be used to analyze height Z-Score. Baseline summaries of Height Z-score and Arm-Span to Height-difference and change from baseline a months 3, 6, 9, and 12 will be presented.

7.2.3 Safety Analyses

Not applicable.

7.2.4 Summary of Analyses

The list below is not an exhaustive list of statistical analyses that will be performed for objective 1.

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroup	Statistical Method	Covariates/Strata	Missing Data
External Control dataset	Full analysis set	1	None	Propensity score matching or IPW via Logistic regression	Demographic and clinical characteristics, including baseline comorbidities.	Excluded
Height Z-Score (and other Anthropometric endpoints)	Full analysis set	2	None	Mixed model repeated measures model, Propensity Score Matched or IPW	Propensity Score Matched, or data augmented by IPW, by Demographic and clinical characteristics.	Excluded

8 LIST OF TABLES AND TABLE SHELLS

9 REFERENCES

Example

1. Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. Am J Epidemiol. 2006;163(12):1149-56
2. Capistrano ESM, Moodie EEM, Schmidt AM. Bayesian estimation of the average treatment effect on the treated using inverse weighting. Statistics in Medicine. 2019;38:2447–2466.

10 APPENDICES

10.1 APPENDIX 1: DATA DERIVATION DETAILS

A1.1 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

A1.2 Further definition of endpoints

Height Z-score, as well as standing height and arm-span were measured in triplicate. For each subject the result at a given visit is an average of the triplicate results.

10.2 APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

A2.1 Further Details of the Statistical Methods

10.3 APPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED IN THE STUDY

Propensity Score Matching

```
proc psmatch data = adsl ;
        class SEX DRUG WHITE ;
        psmodel DRUG (treated = 'Recifercept') = SEX AAGE WHITE ;
        match method = varratio (kmax = 4) distance = lps exact = (SEX WHITE) ;
        assess lps allcov / weight = none plots = (barchart boxplot) ;
        output out(obs = match) = outasa lps = _Lps matchid = _MatchID ;
run ;
```

MMRM with Propensity Score Matching clusters

```
proc mixed data = ps_match_mmrm ;
        by paramcd ;
        class _MatchID usubjid sex drug (ref = 'Not Treated') ;
        model chg = month drug / s ; /*** s = Solution for Fixed Effects ***/
        random int month / subject = usubjid(_MatchId) ;
run ;
```

Inverse Probability Weighting

```
proc psmatch data = adsl region = allobs ;
        class SEX DRUG WHITE ;
        psmodel DRUG (treated = 'Recifercept') = SEX AAGE WHITE ;
        assess lps var = (SEX AAGE WHITE) / weight = atewgt plots = (barchart boxplot) ;
        output out(obs = all) = ipw_ate ATEWGT = _ATE_ ;
run ;
```

MMRM with Inverse Probability Weights

```
PROC GLIMMIX DATA = ate_ipw METHOD = quadrature (qpoints = 27) EMPIRICAL =
classical NOREML ;
        NLOPTIONS GCONV = 1E-10 TECHNIQUE = TRUREG ;
        where PARAMCD APSBLFL = "Y" ;
        CLASS DRUG (REF = "Not Treated") USUBJID ;
        MODEL CHG = DRUG MONTH / SOLUTION ;
        RANDOM INT MONTH / subject = USUBJID WEIGHT = _ATE_ ;
RUN ;
```