Study information

Title	A pilot project to evaluate the feasibility of constructing a concurrent external control for recifercept
Protocol number	C4181010
Protocol version identifier	v 1.1
Date	November 09, 2023
EU Post Authorization Study (PAS) register number	N/A
Active substance	Recifercept
Medicinal product	N/A
Research question and objectives	There are two research questions: 1) Can a concurrent external control for the recifercept phase 2 clinical trial be constructed using achondroplasia patients from a prospective observational natural history study? 2) What are differences in height growth, achondroplasia-related complications, patient functional status, and quality of life between patients enrolled in the recifercept phase 2 clinical trial and those in the concurrent external control? Objectives: 1. To construct a concurrent external control arm for recifercept phase 2 clinical trial using achondroplasia patients from a prospective observational 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 clinical trial and those in the concurrent external control:

	• Height growth • 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, and spinal stenosis), and other achondroplasia-related complications (including apnea, otitis media, and hydrocephalus) • Differences in functional status and health-related quality of life
Author	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AOM	Acute otitis media
BMI	Body mass index
CCI	[redacted]
CKD	Chronic kidney disease
COM	Chronic otitis media
CRF	Case report form
CSA	Clinical study agreement
DCT	Data collection tool
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FGFR3	Fibroblast growth factor receptor 3
GPP	Good Pharmacoepidemiology Practices
ICH	International Council for Harmonisation
IPW	Inverse probability weight
MRI	Magnetic resonance imaging
NPR-B	Natriuretic peptide receptor type B
PK	Pharmacokinetics
PS	Propensity score
CCI	[redacted]
SAP	Statistical analysis plan

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD			

4. ABSTRACT

Title: A pilot project to evaluate the feasibility of constructing a concurrent external control for recifercept

Version and Date: v1.1, November 09, 2023

Author: PPD

Rationale and background

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 25,000-30,000 or approximately 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 European Medicines Agency (EMA) (for achondroplasia patients aged 2 years and older with open growth plates) and U.S. Food and Drug Administration (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, achondroplasia-related symptoms, tests, and treatments among children with achondroplasia. A total of 300 achondroplasia patients aged 0 to 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.

Objectives of this project are to evaluate the feasibility of constructing a concurrent external control for the recifercept phase 2 clinical trial (Study C4181005) using achondroplasia patients from the ongoing prospective natural history study (Study C4181001) and to compare selected outcomes of interest such as height growth, achondroplasia-related complications, patient functional status, and quality of life between achondroplasia patients in Study C4181005 and those in the concurrent external control. Ultimately, this project will assess the feasibility of leveraging the ongoing Study 4181001 to construct a concurrent external control for the recifercept pivotal trial.

Research question and objectives

There are two research questions:

1) Can a concurrent external control for the recifercept phase 2 clinical trial be constructed using achondroplasia patients from a prospective observational natural history study?

2) What are differences in height growth, achondroplasia-related complications, patient functional status, and quality of life between patients enrolled in the recifercept phase 2 clinical trial and those in the concurrent external control?

Objectives of this pilot project will be:

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:

    - Height growth

    - 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

Study design

This is a retrospective cohort study using existing data from two ongoing studies: C4181001 and C4181005. Study C4181005 includes 63 achondroplasia patients in total, approximately 54 patients aged 2 to 10 years (inclusive) and 9 patients aged 3 months to 2 years, 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, n=21 per dose) subcutaneously for 12 months. Study C4181001 includes approximately 300 children with achondroplasia aged 0-15 years who are recruited from global sites. Patient data will be collected at baseline and at every 3-month interval visit, for a maximum of 5 years.

Study population

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 enrollment

Data sources

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 longitudinal anthropometric and disease-related complication data in children with achondroplasia. It will include approximately 300 achondroplasia patients aged 0-15 years with Tanner Stage 1 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 Table3.

Study size

The determination of study size of this protocol is exclusively limited to addressing the second objective of examining the differences between patients enrolled in the recifercept phase 2 clinical trial and those enrolled in the concurrent external control. For the purposeof consistency with the analysis of the primary endpoint Study C4181005, consideration of study size for this protocol is further limited to a comparison of height growth, defined as the

ratio of change from baseline of standing height at 6 months or 12 months of a patient taking recifercept to a matched subject in the concurrent external control. The null hypothesis is the median value (ie, 50 percentile) of the aforementioned ratio is equal to 1.

A table and figure presented below displays the number of pairs required to detect the median ratio (denoted as φ) under the alternative hypothesis.

Table 1. Sample size and power calculation

Type I error	Power	Number of Pairs to detect φ					
		φ = 1.5	φ = 2	φ = 2.5	φ = 3	φ = 3.5	φ = 4
.05	.8	88	22	10	6	4	3
.05	.9	115	29	13	8	5	4
.1	.8	71	18	8	5	3	2
.1	.9	96	24	11	6	4	3
.2	.8	55	14	7	4	3	2
.2	.9	77	20	9	5	4	3

Data analysis

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. 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. height growth). 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.

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 CCI outcomes of interest and 95% confidence intervals will be computed.

Hazard ratios and associated 95% confidence intervals of dichotomous outcomes (including height growth in the achondroplasia reference population +50%, and occurrence of selected achondroplasia-related complications) in PS-matched groups will be estimated by multivariable cox proportional hazards regression models. The effect of recifercept on continuous outcomes (including height growth, anthropometric measures, CCI in PS-matched groups will be estimated by linear mixed models.

To maximize the number of patients in the trial cohort and the concurrent external control cohort included in this pilot project, additional methods will be explored. Coarsened weighting and full matching may be explored. Other than matching, inverse probability weight (IPW) and/or the fine stratification weighting may also be used to balance the key covariates between patients in the concurrent external control cohort (patients in C4181001 who meet the inclusion and exclusion criteria of Study C4181005) and patients in Study C4181005 (details of these methods will be outlined in the SAP).

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.1	Nov 09, 2023	Milestones	Realigned end of data collection date; Updated CSR approval date to be 11 months after end of data collection, and BR tables to be 12 months after end of data collection.	Recifercept discontinued, never reached POC; hence not a Pfizer authorized product, not subject to Article 46, and CSR approval deadline should be 11 months after end of data collection date not 6 months; BR tables deadline should be 12 months after end of data collection. Team agreed, Kofi suggested to do protocol administrative amendment.

6. MILESTONES

Milestone	Timeline
Study Protocol	May 2022
Statistical analysis plan	June 2022
Start of data collection	October 2022
End of data collection	May 2023
Data analysis and internal study report	April 2024
Basic Results tables for CT.gov	May 2024

7. RATIONALE AND BACKGROUND

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.

Objectives of this project are to evaluate the feasibility of constructing a concurrent external control for the recifercept phase 2 clinical trial (Study C4181005) using achondroplasia patients from the ongoing prospective natural history study (Study C4181001) and to compare selected outcomes of interest such as height growth, achondroplasia-related complications, and quality of life between achondroplasia patients in Study C4181005 and those in the concurrent external control. Ultimately, this project will assess the feasibility of leveraging the ongoing Study 4181001 as a concurrent external control arm for the recifercept pivotal trial.

8. RESEARCH QUESTION AND OBJECTIVES

There are two research questions:

1) Can a concurrent external control for the recifercept phase 2 clinical trial be constructed using achondroplasia patients from a prospective observational natural history study?

2) What are differences in height growth, achondroplasia-related complications, patient functional status, and quality of life between patients enrolled in the recifercept phase 2 clinical trial and those in the concurrent external control?

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:

- Height growth
- 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

9. RESEARCH METHODS

9.1. 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.

9.2. Setting

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.

Table 2. 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	- Complications collected every 3 months
	- Anthropometric measurements every 3 months	- Anthropometric measures every 3 months
	- Biomarkers baseline, D1, D4, D8, D15, D29, M2, M3, M6, M9, M12	- Biomarkers sample taken once annually
	CCI [redacted]	CCI [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	- Collection of longitudinal anthropometric and disease-related complication data in children with achondroplasia

	- Assess efficacy of recifercept to increase height growth 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 - To assess change in individual safety parameters	- Investigation of potential serum biomarkers in children with achondroplasia
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]		

9.2.1. 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, patients from Study C4181001 will need to meet the following inclusion criteria from Study C4181005 to be eligible for inclusion:

- 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 the observational natural history study.
- Havecompleted at least 2 valid height/length measurements (at least 3 months apart)
- Assessed for Tanner stage 1 during physical examination before or at enrollment (must include assessment of breast development for females, 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 the natural history study

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- 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 enrollment

9.3. Variables

Table 3. Listing of all variables of importance

Variable	Role	Phase II Recifercept Clinical Trial (C4181005)	Natural History Study (C4181001)	Operational definition
Achondroplasia treatment	Exposure	Recifercept dosage and duration: Recifercept dosage: 1mg/kg once-weekly 2mg/kg twice-weekly 1.5mg/kg once-daily	Achondroplasia-related treatment and duration Collected every 3 months	
Height Growth	Primary outcome	Collected every 3 months until end of study participation	Collected every 3 months until end of study participation	Defined as increase in height growth above expected growth in reference population, defined as the height growth in the achondroplasia reference population +50%
Anthropometric Measurements	Secondary outcome	- 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 - Collected at 1m, 3m, 6m, 9m, 1y	- 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 -collected at baseline, every 3m, and end of study visit	Length of the legs will be calculated as the difference between standing and sitting height
Achondroplasia-related orthopaedic complications	Secondary outcome	Baseline collection - foramen magnum decompression - cranial surgery Occurrence during follow-ups	- Lordosis - Kyphoscoliosis - Small foramen magnum - Spinal stenosis - collected at 6m, 1y, 2y, 3y, and 4y Collected every 3 months until end of study participation	

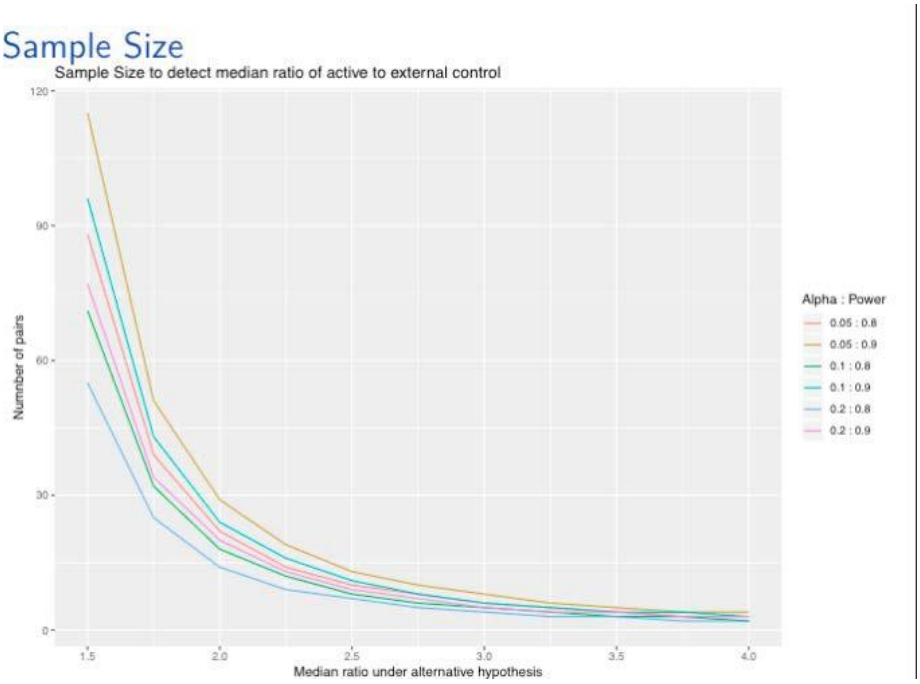
Other achondroplasia-related complications	Secondary outcome	- Sleep disordered breathing - Acute Otitis Media (AOM) - Hydrocephalus	- Sleep disordered breathing - Acute Otitis Media (AOM) - Hydrocephalus	
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Demographics	Covariate	- Age - Gender - Race and ethnicity Collected at baseline	- Age - Gender - Race and ethnicity Collected at baseline	
Puberty	Covariate	Tanner stage Collected at baseline	Tanner stage Collected at baseline	
Weight	Covariate	Body weight Collected every 3 months until end of study participation	Body weight Collected every 3 months until end of study participation	
History of achondroplasia-related medical conditions	Covariate	Sleep-disordered breathing Chronic otitis media Lordosis Kyphosis Spinal stenosis Hydrocephalus Assessed at baseline	Sleep-disordered breathing Chronic otitis media Lordosis Kyphosis Spinal stenosis Hydrocephalus	

9.4. Study size

The determination of study size of this protocol is exclusively limited to addressing the second objective of examining the differences between patients enrolled in the recifercept phase 2 clinical trial and those enrolled in the concurrent external control. For the purposeof consistency with the analysis of the primary endpoint Study C4181005, consideration of study size for this protocol is further limited to a comparison of height growth, defined as the ratio of change from baseline of standing height at 6 months or 12 months of a patient taking recifercept to a matched subject in the concurrent external control. The null hypothesis is the median value (ie, 50 percentile) of the aforementioned ratio is equal to 1.

A table and figure presented below displays the number of pairs required to detect the median ratio (denoted as φ) under the alternative hypothesis (Table 1).

Figure 1. Sample Size



9.5. Data management

All data for the described analysis will be obtained from Study C4181001 and Study C4181005 databases. Data management procedures including data collection, retrieval, preparation and retention are described in those protocols.

In summary, for study C4181001 data management involved the completion of a CRFfor each study participant. The investigator was responsible for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents). Additionally, all study data was required to be verifiable by source

documents. Study records were retained by the investigator in accordance with International Council for Harmonisation (ICH), local guidelines, or clinical study agreement (CSA). Records were required to be kept for a minimum of 25 years after study completion or discontinuation of the study or for longer if required by applicable local regulations.

For study C4181005, all participant data relating to the study was recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator was responsible for verifying that data entries were accurate and correct, maintaining accurate documentation of source data that supports the CRF, and ensuring that CRF were securely stored in electronic form. Sponsors or designees were responsible for data management and quality checking the data. Study monitors also performed ongoing source data verification to confirm that entered into the CRF were accurate, complete, and verifiable from source documents. Records and documents pertaining to study conduct were required to be maintained for at least 15 years, unless local policies or institutional regulations required a longer retention period.

9.6. Data analysis

A single pooled dataset will be released for analysis. The release will occur when for selected, targeted data (in Table 3): a) review and documentation of relevant CRF and non-CRF data; and b) all open queries are resolved. There will be two releases of data. The first release coincides with approximately 30 pairs of patients – that is, a patient from C4181001 matched to a patient from C4181005 – having 6 months of growth data. The second release will take place at the beginning of the interim analysis for C4181005. There may be an additional release of data from both studies that coincides with the completion of C4181005.

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. 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. height growth). 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.

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.

Hazard ratios and associated 95% confidence intervals of dichotomous outcomes (including height growth in the achondroplasia reference population +50%, and occurrence of selected achondroplasia-related complications) in PS-matched groups will be estimated by multivariable cox proportional hazards regression models. The effect of recifercept on continuous outcomes (including height growth, anthropometric measures, CCI [redacted] in PS-matched groups will be estimated by linear mixed models.

To maximize the number of patients in the trial cohort and the concurrent external control cohort included in this pilot project, additional methods will be explored. Coarsened weighting and full matching may be explored. Other than matching, inverse probability weight (IPW) and/or the fine stratification weighting may also be used to balance the key covariates between patients in the concurrent external control cohort (patients in C4181001 who meet the inclusion and exclusion criteria of Study C4181005) and patients in Study C4181005 (details of these methods will be outlined in the SAP).

9.7. Data sources

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. Further details on data sources are presented in Table 2.

9.8. Quality control

Quality control procedures are described in the protocols of Study C4181001 and Study C4181005. No additional quality control will be performed in this study.

9.9. Limitations of the research methods

There are several limitations to this study. Externally controlled studies do not rely on randomization, resulting in inherent bias and a potential lack of comparability between treated and untreated groups (Tjiete & Brouder, 2010)(6). We will apply the same inclusion and exclusion criteria to select patients in the external control arm and use propensity score methodology to adjust for the differences between patients included in the Study C4181005 and patients as external controls. However, depending on the extent of data collection in Study C4181001 and Study C4181005, the propensity score modeling may not adjust for all potential confounders. Additionally, even though Study C4181001 is a multi-country study, patients included in Study C4181001 and Study C4181005 may not represent the entire achondroplasia patient population, and generalizability of study results may be limited.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

Not applicable.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices

described in Guidelines for Good Pharmacoepidemiology Practices (GPP), The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (7–9).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

18. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.