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

Study Intervention Number:	PF-07256472
Study Intervention Name:	Recifercept
US IND Number:	[redacted]
EudraCT Number:	2020-001189-13
Protocol Number:	C4181005
Phase:	2b

Short Title: *Phase 2 study of safety, tolerability, PK and efficacy of recifercept in achondroplasia*

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 3	23 March 2022	**The changes in this amendment were made due to eDMC recommendations, regulatory requests from different countries and addition of a PK cohort:** **The following changes were made following recommendation from the eDMC.** **1.2 Schema** Update to expand recruitment of those aged 2-<6y in block C at the high dose (1.5 mg/kg daily) from a total of n=3 to n=8 (ie, move all 5 participants from block D). **6.6.1 Rule for Progression to Next Enrollment Block** Update to a sentinel dosing approach for recruiting those aged 2-<6 years in block C such that n=2 at high dose will be dosed followed by a 2-week delay before further dosing occurs in that age group. **Rationale:** To assess the safety and tolerability in all participants aged 2-6yrs old at the highest dose, prior to dosing 3m-<2yrs old at the highest dose. **1.3 Schedule of Activities** Added footnote for blood chemistry that participants are required to fast for >4 hours prior to blood sampling. **8.2.5 Clinical Safety Laboratory Assessments** Participants are required to fast for ≥4 hours prior to blood sampling.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Rationale: To aid the interpretation of safety blood sample results, specifically Phosphate. **10.2 Appendix 2 – Clinical Laboratory Tests** **In addition, the following changes were made due to regulatory agency request.** **2.2.1 Clinical Overview** Updated clinical safety as of September 2021, to include number of participants per Block and AEs. **The following changes were made to add a PK assessment cohort.** **1.2 Schema** **PK Schema added** **Rationale:** PK analysis following each dose will be conducted to evaluate the two formulations of recifercept. Single dose of 3 mg/kg will be used for the PK study cohort. **1.3 Schedule of Activities** Updated to include PK Cohort SoA table. **4.1 Study Design** Updated to include a PK cohort that will include 12 participants who will randomly receive 1 dose of Phase 2 (process 1c) followed by 1 dose of proposed Phase 3 (process 2) recifercept formulation or vice versa in a cross-over study, at select sites only. PK analysis following each dose will be conducted to evaluate the two formulations. Single dose of 3 mg/kg will be used for the PK study cohort. Dose of the cohort could be changed due to emerging safety and efficacy data in the study.

		4.3 Justification of Dose Updated to include a PK cohort of 12 participants The tentative dose for the PK study cohort is 3 mg/kg. The dose selected for the PK cohort could be changed after evaluating the entirety of the safety, PK and efficacy data collected in the program before initiating the cohort. The dose selected will not exceed the highest dose found to be safe and tolerated. **8.0 Study Assessments and Procedures** Updated to include the PK cohort, as the total blood volume collected for individual participants is approximately 67 mL in this cohort. **8.5 Pharmacokinetics** Updated to include a PK cohort of 12 participants. **9.2 Sample Size Determination** Updated to include PK cohort sample size determination. **9.3 Analysis Sets** Updated to include PK cohort. **9.4 Statistical Analysis** Update to include endpoints for PK cohort. **The following changes made were corrections of errors or minor clarifications to study procedures.** **1.3 Schedule of Activities** Updated Study drug administration row: Removal of arrows from the M12 for the study drug administration and dosing diary completion, as the first dose will be recorded under the C4181008 protocol.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Updated Footnote n: Addition of Japan safety assessment requirements. **Additional updates:** **2.0 Study Introduction** Added that vosoritide is currently the only approved treatment to increase linear growth in children with achondroplasia. **5.2 Exclusion Criteria** Revised criteria from Severe <60 ml to 'Moderate or Severe' per alignment with FDA guidance on renal impairment. **Section 4.1 & 6.6 Dose modifications** Updated data review for progression from block C to D for once ≥3 months -2y participants (n=4) from (n=6). **Rationale:** To allow the initiation of Block D from 4 participants instead of 6. No new safety signals were identified from the 2-11 yrs old participants except injection site reactions. **Section 4.1 & Section 9.5 Interim Analysis** Updated: Interim analyses may be performed to assess efficacy and safety after ~~at least~~ approximately 45 participants (up to 15 per dose) for clarification.
Amendment 2	14 April 2021	**The changes in this amendment were made due to eDMC recommendations and additional regulatory requests from different countries which cumulatively the sponsor classified as substantial:**

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		The following changes were made following recommendation from the eDMC. **1.2 Schema** Block B enrollment of high dose participants was reduced from n=8 to n=3 and enrollment using a sentinel approach. In addition, Block B 2-6yrs old at low & medium doses was expanded from n=3 to n=8 per dose with enrollment also using a sentinel approach. **4.1 Overall Design & 6.6 Dose Modification** Block B to Block C progression rules were revised in line with the sentinel approach from n=3 per dose to n=2 per dose. The number of high dose children included in the safety review will stay the same (n=3). **Appendix 2** Addition of Phosphate to chemistry panel and collection of time since last food intake. **In addition, the following changes was made due to regulatory agency request.** **1.3 Schedule of Activities** Addition of Hematology & Chemistry Labs at Month 9. **2.2.1 Clinical Overview** Final data from study C4181002 added. Summary safety & PK data from Block A added.

		5.2 Exclusion Criteria Criterion No. 6 CrCL GFR formula 'bedside' Schwartz was added. **6.2.1 Preparation & Dispensing** Clarification of what should be considered adequate training for caregivers for home drug administration was added. **6.4.1 Participant Compliance & Home Administration** Clarified instructions for caregivers regarding injection site reactions during home dosing is documented in the caregiver dosing diary. **8.6 Genetics** Confirmation this section is not applicable in Denmark. **8.7.2 Banked Biospecimens for Genetics** Confirmation this section is not applicable in Denmark. **8.7.7. Banked Biospecimens for Biomarkers** Confirmation this section is not applicable in Denmark. **The following changes made were corrections of errors or minor clarifications to study procedures:** **1.3 Schedule of Activities** Minor clarification in the SoA footnotes. **4.3 Justification of Dose** Figure 1 - Erroneously entered multiple times.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		8.3.8 Adverse Events of Special Interest The details of injection site reactions and overall grade have been deleted as they are not being collected in the eCRF. **8.7.2 Banked Biospecimens for Genetics** Clarification the sample is whole blood. **8.7.3 Blood Samples for Biomarker Analysis** Updated blood volume to collect plasma biomarker sample in addition to serum. **Other changes not listed here include general correction of errors such as formatting or minor typographical changes and updates to Appendix where required.**
Amendment 1	09 November 2020	**The following changes were made due to regulatory requests from different countries which the sponsor classified as substantial:** **1.3 Schedule of Activities** Additional ECG at close to C_{max} (Day 4) and additional pharmacokinetic & immunogenicity sample at Month 9 were added. Clarify that monitoring after first 5 doses be done by appropriately trained individuals with access to facilities necessary to manage hypersensitivity MRI at baseline was added and only applicable for those without scan in last 12 months. **4.1 Overall Design** Clarify age range to align with inclusion criteria. **4.2 Scientific Rationale for Study Design**

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Clarify language around baseline MRI. **5.1 Inclusion Criteria** CCI [redacted] **5.2 Exclusion Criteria** Exclude those with evidence of significant renal or hepatic impairment, or with history of hypersensitivity to study intervention or excipients. **6.1.1 Administration** To clarify that only parent/caregiver/healthcare professional should administer the study medication. **6.6 Dose Modification** Clarify age of those in block A. **6.6.1 Rules for Progression to the Next Enrolment Block** There will be a planned eDMC review after block A prior to progressing to block B. Change SUSAR to SAR Clarify that the primary efficacy analysis will be done on treatment naïve participants enrolled to each cohort. **7.1 Discontinuation of Study Intervention** To clarify the role of the investigator in stopping study intervention as a result of adverse events or need for prohibited treatments.

		8.2.4 Electrocardiograms Add D4 ECG. **8.3.1. Time Period and Frequency for Collecting AE and SAE Information** Confirm that investigator should enquire about both AEs and SAEs at follow-up visit. **9.4.2. Primary Endpoint(s)** Clarify the analysis to be performed as ANOVA not ANCOVA. **9.4.2 Primary & 9.4.3. Secondary Endpoint(s)** Clarify the analysis to be performed (removal of stratification). **9.6 Interim Analysis** Describe control of familywise error rate. **10.4.2 Female Participant Reproductive Inclusion Criteria** Confirm that WOCBP cannot enroll in the study since participants must be Tanner stage 1 at enrolment. **10.5 Liver Safety: Suggested Actions and Follow up Assessments Potential Cases of Drug Induced Liver Injury** Clarify that LFTs are measured in routine safety assessments. **The following changes made were corrections of errors or minor clarifications to study procedures:** **1.1. Synopsis** Update synopsis to align with Section 9.1.1 of the main protocol due to typographical error.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		5.2 Exclusion Criteria Move exclusion criteria #5 to correct place. **6.3.2 Other Measures to Minimize Bias & 8.1.1 Anthropometric measurements** To clarify that blinding to treatment should be maintained but that using the same measurer is more important in obtaining accurate data than maintaining blind. **8.1.1 Anthropometric Measurements** Removal of reference to blinding manual from this section since this is a data blinding manual. **8.1.4.2. Quality of Life in Short Stature Youth (QoLISSY) Brief** To provide clearer instructions to the investigator on use of the different QoLISSY scale versions. **8.1.6 – Biological Samples** Section removed as only applicable for vaccine studies. **10.8.1. Telehealth Visits** Incorrect section reference was corrected. **Other changes not listed here include general correction of errors such as formatting or minor typographical changes and updates to Appendix where required.**
Original protocol	22 June 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: *Phase 2 study of safety, tolerability, PK and efficacy of recifercept in achondroplasia*

Rationale

The purpose of the study is to investigate the safety, tolerability, pharmacokinetics (PK) and efficacy of recifercept in children with achondroplasia. Safety has been demonstrated in preclinical studies and in healthy adult volunteers in single and multiple ascending doses.

Recifercept is under development to address the unmet need in children with achondroplasia including the treatment of short stature and cranial, axial and appendicular skeletal complications. Recifercept is a novel class of compound (decoy receptor) that has not been studied before in achondroplasia.

Objectives, Estimands, and Endpoints

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 the IP on a continuous endpoint. Population-level summary: ratio between participants in the trial and a reference population [Merker et al, 2018][30] 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].[30]
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.

Objectives	Estimands	Endpoints
• To assess efficacy of recifercept to improve achondroplasia-related complications.		• 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 (adapted for achondroplasia) component and index scores, QoLISSY Brief total score.
• Assess change in individual safety parameters.		• Change from baseline in safety labs, vital signs, physical examination. • Rate of anti-drug antibodies.
CCI [redacted]	[redacted]	[redacted]
[redacted]		[redacted]

PK Study Cohort:

Multiple changes have been made in the manufacturing process of the drug product (process 2) which will be used in Phase 3. These changes include, but are not limited to, host cell line change, manufacturing process optimization, scale up and manufacturing site changes. Therefore, an additional PK cohort (at selected sites only) has been added, to evaluate the PK of Phase 2 formulation (process 1c) and Phase 3 formulation (process 2).

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate the PK of single subcutaneous doses of 2 formulations (process 1c and process 2) of recifercept in children aged ≥2 to <11 years old with achondroplasia.	N/A	PK endpoints after single dose recifercept: C_{max}, T_{max}, AUC_{168}, AUC_{360}, AUC_{inf} and $t_{½}$.
Secondary:	**Secondary:**	**Secondary:**
• To assess the safety and tolerability of single SC doses of 2 formulations (process 1c and process 2) of recifercept in children aged ≥2 to <11 years old with achondroplasia.		Adverse event monitoring, injection/infusion site assessment.

Overall Design

The study is a phase 2, randomized, dose-finding study of safety, tolerability, pharmacokinetics, and efficacy. Approximately 63 participants will be randomized to one of three doses (1mg/kg once weekly, 2 mg/kg twice-weekly, 1.5 mg/kg once-daily) for 12 months. Participants will be children diagnosed with achondroplasia aged ≥3 months to <11 years; enrollment will progress in an age and dose staggered manner (descending age and ascending dose). Progression to the next enrollment block will be after review of safety and PK data, including review by an external data monitoring committee (eDMC) if safety signals are identified. In order to minimize bias in measurement of the primary efficacy endpoint (height), the anthropometrist will be blinded to dose assignment. There will be no additional blinding.

An interim analysis will be performed when approximately 45 participants (up to 15 participants per dose) aged ≥2 to <11 years have received 6 months of treatment with recifercept.

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.

PK Study Cohort:

At selected sites only, an additional PK cohort has been added to evaluate the PK of two recifercept formulations (process 1c and process 2). A total of 12 children with achondroplasia aged 2- <11 years will be enrolled in the PK cohort (6 in each treatment sequence). Each participant will receive 2 treatments (3 mg/kg Phase 2 formulation [process 1c] and 3 mg/kg Phase 3 formulation [process 2]) in a randomized manner according to one of two sequences.

Number of Participants

Approximately 54 participants aged 2-10 inclusive at the time of informed consent will be randomly assigned to study intervention enrolled such that approximately 45 evaluable participants complete the study. In addition, 9 participants aged ≥3 months - 2y at the time of informed consent will be enrolled in CCI cohort.

PK Study Cohort:

A PK cohort will include 12 participants who will randomly receive a single dose of 3 mg/kg of Phase 2 study (process 1c) formulation and a single dose of 3 mg/kg of the proposed Phase 3 (process 2) study formulation in a cross over study. Dose of the cohort could be changed due to emerging safety and efficacy data in the study.

Note: "Enrolled" means a participant's legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

63 participants will receive recifercept for 12 months and will be randomized to one of the following three doses of recifercept: 1 mg/kg once-weekly, 2 mg/kg twice-weekly or 1.5 mg/kg once-daily. All doses are given by subcutaneous injection. There are no prospectively planned dose changes, however the dose may be changed based on review of safety and PK data. Dose will be adjusted according to weight every 3 months.

PK Study Cohort:

In PK study cohort only, participants will randomly receive a single dose of Phase 2 (process 1c) followed by a single dose of Phase 3 (process 2) recifercept formulation or vice versa in a cross over study. A single dose of 3 mg/kg will be used for the PK study cohort. Dose of the cohort could be changed due to emerging safety and efficacy data in the study.

Data Monitoring Committee or Other Independent Oversight Committee:

An external data monitoring committee will assess the safety and, where relevant, PK data on a regular basis and additionally, if certain pre-defined criteria are met, at enrollment block progression review. A patient advocate will also be included on the eDMC if an appropriately qualified individual can be identified as agreed upon by the eDMC chairperson.

Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

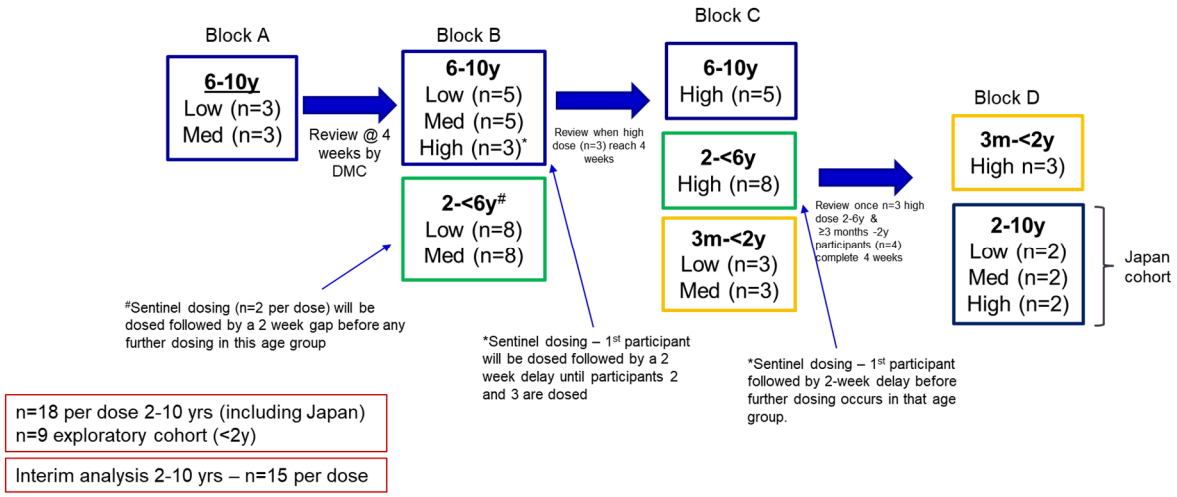
The primary efficacy estimand will be the population treatment effect of the mean change-from-baseline of a continuous response (ie, height growth) at month 12 irrespective of IP compliance. Increase in height growth above expected growth in reference population, a co-primary endpoint, is defined as the height growth in the achondroplasia reference population +50%. Intercurrent event for the efficacy estimand: withdrawal and all events leading missing data will be excluded from efficacy analysis and will not have their data imputed. The population-based treatment effect will be the mean change-from-baseline at month 12.

Sample size determination is based on the co-primary endpoint of height growth, defined as change from baseline of height at 12 months for participants on drug versus change from baseline of height at 12 months for a reference achondroplasia population. A total of 18 participants each randomized to three doses in order to obtain 15 participants per dose, assuming a one-sided family-wise error rate of 0.05 with a Bonferroni correction (0.017 after Bonferroni adjustment for 3 comparisons), and inter-participant variability. of .15 (estimated from C4181001), there is over 90% power to detect at least one dose providing 50% height growth above reference. No statistical comparison will be made between recifercept doses.

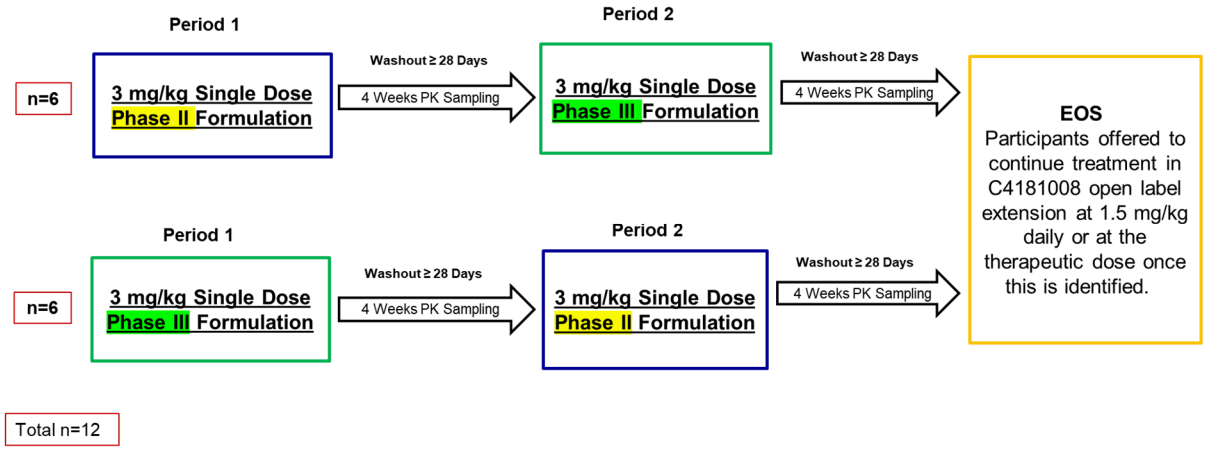
PK Study Cohort:

No formal sample size calculation was performed and 12 participants were selected empirically to characterize PK, safety, and tolerability after single 3 mg/kg dose administration of two formulations.

1.2. Schema for Blocks A-D



Study schema for PK Study cohort



* Dose of the cohort could be changed due to emerging safety and efficacy data in the study.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the wellbeing of the participant.

Abbreviations used in this table may be found in Appendix 9.

	Screening	M1					M2	M3	M4[a]	M5[a]	M6	M7[n]	M8[n]	M9	M10[n]	M11[n]	M12	Early Termination/ Discontinuation	Follow-up[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Days Relative to Day 1[c]	**Day -14 to -1**	**D1**	**D4**	**D8**	**D15**	**D29**	**D61**	**D91**	**D121**	**D152**	**D183**	**D213**	**D243**	**D273**	**D303**	**D333**	**D365**		**D396**
Visit Window (Days)		**0**	**0**	**0**	**0**	**+1**	**±3**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	14		**±7**
Informed consent/assent	X																		
Demography[d]	X																		
Medical history	X																		
Physical examination[e]	X	X	X	X	X	X	X	X			X			X			X	X	
Neurological examination	X					X		X			X						X	X	
Weight	X							X			X			X			X	X	
Vital signs	X	X	X	X	X	X	X	X			X			X			X	X	
Laboratory																			
Hematology	X			X	X	X	X	X			X			X			X	X	
Blood chemistry[p]	X			X	X	X	X	X			X			X			X	X	
Pregnancy test[f]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	
Contraception check[f]	X					X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X		X																

	Screening	M1					M2	M3	M4[a]	M5[a]	M6	M7[n]	M8[n]	M9	M10[n]	M11[n]	M12	Early Termination/ Discontinuation	Follow-up[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Days Relative to Day 1[c]	**Day -14 to -1**	**D1**	**D4**	**D8**	**D15**	**D29**	**D61**	**D91**	**D121**	**D152**	**D183**	**D213**	**D243**	**D273**	**D303**	**D333**	**D365**		**D396**
Visit Window (Days)		**0**	**0**	**0**	**0**	**+1**	**±3**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	14		**±7**
Study intervention																			
Randomization[c]		X																	
Study Intervention Dispensing		X				X	X	X	X	X	X	X	X	X	X	X			
Study intervention administration[g]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Dosing diary		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Assessments																			
Anthropometry		X						X			X			X			X	X	
Polysomnography[h]	X																X	X	
Tanner staging	X							X			X			X			X	X	
Cranial MRI[i]	X																X		
Clinical Outcome Assessments																			
CHAQ (adapted for achondroplasia)		X						X			X			X			X	X	
QoLISSY Brief		X						X			X			X			X	X	
Acceptability and Tolerability Questionnaire				X	X	X	X	X	X	X	X			X			X	X	
EuroQol 5D		X						X			X			X			X	X	
PGIS anchor items		X						X			X			X			X	X	
PGIC anchor items								X			X			X			X	X	
Additional blood sampling																			
PK sampling[j]			X	X	X	X	X[k]	X[l]			X			X			X	X	X[o]
Immunogenicity sampling[j]	X				X	X	X	X			X			X			X	X	X[o]
Biomarker blood sampling[j]	X		X	X	X	X	X	X			X						X	X	

	Screening	M1					M2	M3	M4[a]	M5[a]	M6	M7[n]	M8[n]	M9	M10[n]	M11[n]	M12	Early Termination/ Discontinuation	Follow-up[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Days Relative to Day 1[c]	**Day -14 to -1**	**D1**	**D4**	**D8**	**D15**	**D29**	**D61**	**D91**	**D121**	**D152**	**D183**	**D213**	**D243**	**D273**	**D303**	**D333**	**D365**		**D396**
Visit Window (Days)		**0**	**0**	**0**	**0**	**+1**	**±3**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	14		**±7**
Biobanked blood samples[m]	X										X						X		
Concomitant treatment(s)	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

a. M4 and M5: Telephone contact only, drug dispensing through IRT.

b. Follow-up visit only applicable to those participants not continuing in the open label extension study. Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.

c. Day relative to start of study intervention (Day 1). If required, dose assignment may be allocated in the Interactive Response Technology (IRT) system prior to Day 1

d. Data collected to reflect local regulatory requirements on date of birth, race and ethnicity.

e. Examination of cardiovascular, respiratory, gastrointestinal systems and skin.

f. Pregnancy testing is Only for WOCBP, urine pregnancy test with sensitivity of at least 25 mIU/ml acceptable. Contraception check is applicable to both WOCBP and sexually active male participants.

g. Participants must have dosing performed at site with clinical observation for a minimum of 4 hours post-dose for first 5 doses (**Once daily dosing; Days 1-5, Twice-weekly dosing; Days 1, 4, 8, 11, 15, Once-weekly dosing; Days 1, 8, 15, 22, 29).** Staff administering the dose should be trained in management of acute hypersensitivity with access to appropriate facilities to treat such events. Following appropriate training, dosing will then be performed at home. First dose at home to be observed by home nursing. Dosing may be performed in the clinic at any time if investigator determines that home dosing is not feasible or appropriate.

h. Sleep study to be performed only in participants with a documented diagnosis of sleep-disordered breathing prior to enrollment. Baseline PSG data can be within 6 months prior to enrollment. Final PSG to be ±1 months of M12 visit.

[redacted]

j. Samples to be drawn pre-dose unless otherwise specified.

k. Day 61 sample to be taken pre-dose and between 20 – 28 h post-dose for participants receiving once- or twice-weekly dosing (2 samples in total). Once-daily dosing participants will have only the pre-dose sample (1 sample in total).

l. Day 91 sample to be taken pre-dose and between 40-56h post-dose for participants receiving once- or twice-weekly dosing (2 samples in total). Once-daily dosing participants will have only the pre-dose sample (1 sample in total).

m. Prep-D1.5 can be collected at any blood draw during the study, prep B1.5 to be collected at specified time points.

n. M4 & M5 are telephone contact only and for dispensing medication using the Interactive Response Technology (IRT) system, except Japan safety assessment (at least but not limited to: AE/SAE, concomitant treatment) should be confirmed via physical site visit or telehealth before dispensing. M7, M8, M10 & M11 are for dispensing medication using the IRT system. No on-site visit is scheduled for M7, M8, M10 & M11, except Japan safety assessment (at least but not limited to: AE/SAE, concomitant treatment) should be confirmed via physical site visit or telehealth before dispensing. Drug may be shipped to the participants home after dispensing. Site personnel can register the visits anywhere in the SoA window and schedule pick up and delivery. Site personnel should not register multiple visits at once, except under special circumstances, eg, the patient is traveling out of the country for a long duration.

o. Participants attend site for PK/ADA sampling at follow up visit only if ADA positive at M12.

p. Participants are required to fast for >4 hours prior to blood sampling.

PK Study Cohort – Period 1

	Screening											
Visit Identifier	**1**	**2**	**2**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**
Days Relative to Day 1[a]	**Day -14 to -1**	**D1 0h**	**D1 2h**	**D1 6h**	**D1 12h**	**D2 24h**	**D3 48h**	**D4 72h**	**D6 120h**	**D8 168h**	**D12 264h**	**D18 408h**
Visit Window (Hours)		**0**	**0**	**0**	**0**	**±2**	**±6**	**±6**	**±12**	**±12**	**±24**	**±48**
Informed consent/assent	X											
Demography[b]	X											
Medical history	X											
Physical examination[c]	X	X								X		
Weight	X											
Vital signs	X	X								X		
Hematology	X									X		
Blood chemistry[d]	X									X		
Pregnancy test[e]	X											
Contraception check[e]	X									X		
12-Lead ECG	X							X				
Randomization		X										
Study intervention administration[f]		X										
PK sampling[g]		X[g]	X[h]	X[h]	X[h]	X	X	X	X	X	X	X
Immunogenicity sampling[g]		X[g]										
Concomitant treatment(s)	X	→	→	→	→	→	→	→	→	→	→	→
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→

a. Day relative to start of study intervention (Day 1).

b. Data collected to reflect local regulatory requirements on date of birth, race, and ethnicity.

c. Examination of cardiovascular, respiratory, gastrointestinal systems, and skin.

d. Participants are required to fast for >4 hours prior to blood sampling.

e. Urine pregnancy test with sensitivity of at least 25 mIU/ml acceptable. Contraception check is applicable to both WOCBP and sexually active male participants.

f. Participants will receive 1 dose of the recifercept Phase 2 (process 1c) formulation on D1 and 1 dose of the proposed Phase 3 (process 2) recifercept formulation on Day 29 or vice versa.

g. Samples to be drawn pre-dose unless otherwise specified.

h. For PK collection window, see Section 8.5.

PK Study Cohort – Period 2

Visit Identifier	12	12	12	12	13	14	15	16	17	18	19	20
Days Relative to Day 1[a]	**D29 0h**	**D29 2h**	**D29 6h**	**D29 12h**	**D30 24h**	**D31 48h**	**D32 72h**	**D34 120h**	**D36 168h**	**D40 264h**	**D46 408h**	**D57/EOS[b] 672h**
Visit Window (Hours)		**0**	**0**	**0**	**±2**	**±6**	**±6**	**±12**	**±12**	**±24**	**±48**	**±24**
Physical examination[c]	X								X			X
Weight	X											
Vital signs	X								X			X
Hematology	X								X			X
Blood chemistry[d]	X								X			X
Pregnancy test[e]	X											
Contraception check[e]	X								X			X
Study intervention administration[f]	X											
PK sampling[g]	X[g]	X[h]	X[h]	X[h]	X	X	X	X	X	X	X	X
Immunogenicity sampling[g]	X[g]											X
Concomitant treatment(s)	→	→	→	→	→	→	→	→	→	→	→	→
Serious and non-serious adverse event monitoring	→	→	→	→	→	→	→	→	→	→	→	→

a. Day relative to start of study intervention (Day 29 for Period 2).

b. End of Study visit with option to enroll in the open label study C4181008.

c. Data collected to reflect local regulatory requirements on date of birth, race and ethnicity.

d. Participants are required to fast for >4 hours prior to blood sampling.

e. Urine pregnancy test with sensitivity of at least 25 mIU/ml acceptable. Contraception check is applicable to both WOCBP and sexually active male participants.

f. Participants will receive 1 dose of the recifercept Phase 2 formulation (process 1c) on D1 and 1 dose of the proposed Phase 3 (process 2) recifercept formulation on Day 29 or vice versa.

g. Samples to be drawn pre-dose unless otherwise specified.

h. For PK collection window, see Section 8.5.

2. INTRODUCTION

Achondroplasia is the commonest skeletal dysplasia in humans with a prevalence of around 4 per 100,000 (Waller et al., 2008)[2] and results from mutations in the gene for the FGFR3 receptor. Almost all cases of achondroplasia result from p.Gly380Arg mutations that are gain-of-function. Whilst achondroplasia is inherited in an autosomal dominant fashion, approximately 80% of cases are due to de novo mutations.

Achondroplasia results in short stature and a range of severe complications due to abnormal ossification centres in the cranial base, facial bones, vertebrae, rib cage, and joints. There is shortening of the limbs, with the proximal segments disproportionately affected (rhizomelia), as well as large head with frontal bossing, midface hypoplasia, narrowed skull base foramina, spinal stenosis, kyphosis/lordosis, tibial bowing and respiratory tract complications. Short stature impacts quality of life, social functioning and self-esteem (Gollust et al., 2003).[13] Significant morbidity and functional impairment arise from abnormal proportionality, tibial bowing, joint hypermobility, excessive lumbar lordosis, fixed hip contractures and flexion deformities of knees/elbows (Kopits, 1988; Kitoh et al., 2002; Ireland et al., 2011; Ireland, Donaghey, et al., 2012).[17,18,4,19] There is associated neurodevelopment and psychosocial morbidity [Ireland et al, 2011;[4] Wigg et al, 2016],[5] with increased mortality throughout life that is most pronounced in early childhood [Hecht et al, 1987; Hecht et al, 1988; Horton et al, 2007; Simmons et al, 2014; Hashmi et al, 2018].[6-10]

Thoracolumbar kyphosis is observed soon after birth and remains at least until the child is able to stand independently, when lumbar hyper-lordosis begins to develop. Kyphosis may require bracing if severe/persistent and severe kyphosis associated with vertebral wedging at age 5 requires surgical intervention (Misra and Morgan, 2003; Ireland et al., 2014).[24,12] There is also associated overall developmental motor delay and inter-vertebral disc abnormality can be present even very early in life (Karikari et al., 2012).[25]

Vosoritide is currently the only approved treatment to increase linear growth in children with achondroplasia. Other available treatments are either aimed at limb lengthening with surgery or are interventions to treat the complications of achondroplasia. Limb length can be significantly increased (an average of 20 cm) by limb lengthening surgery, however, complications, including fractures, early consolidation, failed union, malalignment, joint stiffness, paralysis, equinus, and severe infections [Shirley and Ain, 2009; Aldegheri and Dall'Orca, 2001][27,26] occur in up to 70% of patients [Donaldson et al, 2015].[28]

Recifercept is a modified soluble recombinant human FGFR3 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.

2.1. Study Rationale

The purpose of the study is to investigate the safety, tolerability, pharmacokinetics (PK) and efficacy of recifercept in children with achondroplasia. In addition, one PK study cohort of 12 participants has been added in the study to evaluate the PK of single subcutaneous doses of 2 formulations (Phase 2 [process 1c] and proposed Phase 3 [process 2]) of recifercept before initiating Phase 3 study. Safety has been demonstrated in preclinical studies and in healthy adult volunteers in single and multiple ascending doses – more details can be found in the IB.

2.2. Background

Recifercept is under development to address the unmet need in children with achondroplasia including the treatment of short stature and cranial, axial and appendicular skeletal complications. Recifercept is a novel class of compound (decoy receptor) that has not been studied before in achondroplasia.

In preclinical studies, recifercept was active in restoring growth to long bones and normalising cranial anatomy and skull morphology with maintenance and restauration of patency of synchondroses in the cranial base in Fgfr3ach/+ mice, as well as significantly reducing the complications that lead to mortality in these mice. Based on these studies, the minimally effective SC dose in the mouse is approximately 3 mg/kg twice weekly, and the optimally effective dose is 10 mg/kg twice weekly. These in vivo studies strongly support further development of recifercept as a treatment for achondroplasia. Further details of the preclinical safety studies can be found in the IB.

2.2.1. Clinical Overview

As of September 2021, a total of 32 participants were enrolled from 2 to 10 years old. 14 participants were randomized to 1 mg/kg once weekly (QW) arm and 15 participants were randomized to 2 mg/kg twice weekly (BIW) dosing arm and 3 participants were randomized to 1.5 mg/kg daily (QD). A total of 36 treatment related AEs were reported from 13 out of 32 participants; 3 at low dose, 8 at medium dose and 2 at high dose. The most frequently reported AEs were ISRs such as redness/rash/erythema/pruritis at the injection site. All AEs were mild or moderate in severity and there were no serious adverse events. There were no other clinically significant laboratory abnormalities or physical examination/vital sign changes. Following, administration of study drug, observed serum recifercept concentrations at all three doses were in the range of the predicted exposures in 2 to <10 year old children with achondroplasia using the population PK (PopPK) model.

In the recifercept Phase 1 study (C4181002), healthy participants were administered single (n=30) and multiple (n=24) SC doses of recifercept. In addition, 18 participants received placebo in the study. The dose-range studied in single ascending dose (SAD) part of the study was 0.3 – 20 mg/kg and in the multiple ascending dose (MAD) part was 1 mg/kg and 3 mg/kg twice weekly and 3 and 10 mg/kg once weekly for four weeks. Signs and symptoms of an injection site/infusion site reaction, including erythema, swelling, pain, inflammation, and pruritis, were the most frequently reported adverse events in the SAD and MAD part of

the study. There were no clinically significant changes in laboratory tests, vital signs or ECG. No systemic allergic reactions or serious adverse events occurred during the study.

In the SAD portion of the study, all participants were ADA negative (ADA-) prior to treatment with recifercept. A confirmed ADA positive (ADA+) response was observed in 8 participants receiving recifercept and 1 placebo participant at the end of the study (Day 29). In the MAD portion of the study, 2 participants were ADA+ prior to treatment with recifercept. The majority of the participants who received multiple doses of recifercept were ADA+ (21/24) and 2 placebo participants during the observation period.

Results from C4181002 suggest that the PK of recifercept after single SC administration is approximately dose proportional in the dose range 0.3-3 mg/kg and more than proportional in the range 3-20 mg/kg. Median time of maximum concentration (T_{max}) increases with increasing dose. The mean terminal half-life ($t_{1/2}$) ranged from about 47.8 hours to 92.1 hours across a dose range from 1 to 20 mg/kg recifercept dose groups, respectively.

In the MAD portion; following multiple SC dose of recifercept BIW at 1 mg/kg and 3 mg/kg, median T_{max} was 30.0 and 60.0 hours post dose, respectively, after administration on Day 1, and 12.0 and 18.0 hours post dose, respectively, after administration on Day 25. The mean $t_{1/2}$ was 96.1 and 71.3 hours after administration of 1 mg/kg and 3 mg/kg, respectively, on Day 25. After both 1 mg/kg and 3 mg/kg BIW administration, mean trough concentrations on Day 11, Day 15 and beyond suggest that steady state was achieved after the third dose for both the doses. The geometric mean accumulation ratio (Rac) for TA-46 was 4.90 for the 1 mg/kg treatment and 3.51 for the 3 mg/kg treatment.

Following multiple SC dose administration of recifercept once weekly at 3 mg/kg and 10 mg/kg, median T_{max} was 72.0 and 36.04 hours post dose, respectively, after administration on Day 1, and 60.01 and 48.0 hours post dose, respectively, after administration on Day 22. The mean $t_{1/2}$ was 93.5 and 97.4 hours after administration of 3 mg/kg and 10 mg/kg, respectively, on Day 22. After 3 mg/kg and 10 mg/kg QW administration, mean trough concentrations on Day 15 and Day 22 suggest that steady state was achieved after the third dose for both the doses. The Rac for TA-46 was 1.47 for the 3 mg/kg treatment and 1.16 for the 10 mg/kg treatment. More than proportional increase in exposures were observed between 3 mg/kg and 10 mg/kg QW dosing regimen on Day 1 and Day 22.

Further details of the phase 1 study can be found in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of recifercept may be found in the IB which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [Recifercept]		
Risk of injection site reactions (ISR).	ISRs seen in the phase 1 study in healthy volunteers.	Monitoring of ISRs as AESI.
Hypersensitivity to study intervention.	Risk of hypersensitivity to early doses of study intervention. No cases seen in phase 1 study.	At a minimum, the first 5 doses must be administered at site with post-dose monitoring. Caregivers will be trained to administer the study intervention during these dose administrations.
Study Procedures		
Blood sampling.	Younger children may require multiple/large volumes of blood to be taken.	Limits on sampling volumes and prioritization of samples (see Section 8).
General anaesthetic administered to perform MRI scanning.	Children undergoing MRI scans may require a general anaesthetic to undertake scanning.	Allowing collection of data at baseline from a "standard of care" MRI scan to reduce the number of scans within the trial to a single scan at the end of the trial. MRIs will only be performed at centres experienced in the procedure in young children.

2.3.2. Benefit Assessment

Potential benefits of participating in the trial include:

- Potential benefit of recifercept on growth and associated complications of achondroplasia;
- Contribution to the development of medicines for the treatment of achondroplasia and its complications.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with recifercept are justified by the anticipated benefits that may be afforded to participants with achondroplasia.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

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 the IP on a continuous endpoint. Population-level summary: ratio between participants in the trial and a reference population [Merker et al, 2018][30] 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].[30]
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 achondroplasia-related complications.		• Sitting height/standing height ratio. • Arm span to height/length difference.

Objectives	Estimands	Endpoints
		• 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 (adapted for achondroplasia) component and index scores, QoLISSY Brief total score.
• Assess change in individual safety parameters.		• Change from baseline in safety labs, vital signs, physical examination. • Rate of anti-drug antibodies.
CCI [redacted]	[redacted]	[redacted]
[redacted]		[redacted]

PK Study Cohort

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate the PK of single subcutaneous doses of 2 formulations (process 1c and process 2) of recifercept in children aged ≥2 to <11 years old with achondroplasia.	N/A	PK endpoints after single dose recifercept: C_{max}, T_{max}, AUC_{168}, AUC_{360}, AUC_{inf} and $t_{½}$.
Secondary:	**Secondary:**	**Secondary:**
• To assess the safety and tolerability of single SC doses of 2 formulations (process 1c and process 2) of recifercept in children aged ≥2 to <11 years old with achondroplasia.		Adverse event monitoring, injection/infusion site assessment.

4. STUDY DESIGN

4.1. Overall 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 approximately 45 paticpants are evaluable (up to 15 participants per dose). Additionally, CCI cohort of approximately 9 children with achondroplasia, ages 3 months to 2 years, will be enrolled later in the study (n=3 per dose). All 63 participants in this part of the study will receive recifercept for 12 months.

PK Study Cohort:

At selected sites only, an additional PK cohort has been added to evaluate the PK of two recifercept formulations. A total of 12 children with achondroplasia aged 2- <11 years will be enrolled in the PK cohort (6 in each treatment sequence). Each participant will receive 2 treatments (3 mg/kg Phase 2 formulation [process 1c] and 3 mg/kg Phase 3 formulation [process 2]) in a randomized manner according to one of two sequences as outlined in Table 1 below. Dose of the cohort could be changed due to emerging safety and efficacy data in the study.

PK samples collected following each dose will be analyzed to evaluate the exposures of two formulations.

Table 1. Treatment Sequence

Sequence	Period 1	Period 2
1 (n = 6)	Phase 2 study (process 1c) Formulation	Phase 3 study (process 2) Formulation
2 (n = 6)	Phase 3 study (process 2) Formulation	Phase 2 study (process 1c) Formulation

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 Section 1.2). If certain pre-defined safety signals occur (see Section 6.6.1) 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 ≥3 months to <2 years).

An interim analysis is planned when approximately 45 participants (up to 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, all aged 6-10y) have completed D29
Block B to C	Review once 2-6y participants (n=4) and 3 high dose 6-10y participants have completed D29
Block C to D	Review once all ≥3m-2y participants (n=4) and 3 high dose 2-6y participants have completed D29

4.2. Scientific Rationale for Study Design

Achondroplasia is a disease of abnormal endochondral ossification at growth plates, therefore the ability to affect this process only exists whilst these growth plates are open. Fusion of growth plates varies across anatomical sites occurring very early in life for some cranial and spinal ossification centres (Dimeglio and Canavese, 2012, Calandrelli et al., 2017),[40,41] but persisting until adolescence in the long bones (Hoover-Fong, Del Pino, Merker).[11,16,30]

Treatment with recifercept is only of potential benefit to those with open growth plates, thus this trial will only include children that are still growing in height. The effect of pubertal growth spurt is not clear in achondroplasia, therefore this phase 2 study will only enroll those aged ≥3months to <11y and Tanner stage 1.

Enrollment will progress in an age- and dose-staggered fashion to confirm the safety profile of recifercept before increasing exposure or progressing to younger participants. This approach also allows confirmation of the predicted exposures using PopPK modelling in older (heavier) participants before progression to younger (lighter) participants.

Human reproductive safety data are not available for recifercept, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4). Given the age of the participants in the study, abstinence is the only acceptable form on contraception.

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

CCI [redacted] Complications at the craniocervical junction are amongst the most serious complications seen in achondroplasia and are particularly prevalent in those under 2 years. MRI scanning in very young children with achondroplasia is being widely adopted and standard of care [Kubota et al, Clin Pediatr Endocrinol. 2020; 29(1): 25–42.].[45] In order to minimize risk from general anaesthetic, data can be collected at baseline from a prior "standard of care" MRI scan and an additional scan taken at the end of this study.

PK Study Cohort:

Multiple changes have been made in the manufacturing process of the drug product (process 2) which will be used in Phase 3. These changes include, but are not limited to, host cell line change, manufacturing process optimization, scale up and manufacturing site changes. Therefore, an additional PK cohort (at selected sites only) has been added, to evaluate the PK of Phase 2 formulation (process 1c) and Phase 3 formulation (process 2).

Serum & Plasma biomarker samples will be taken during the study as indicated in the SoA. Further details can be found in Section 8.7.

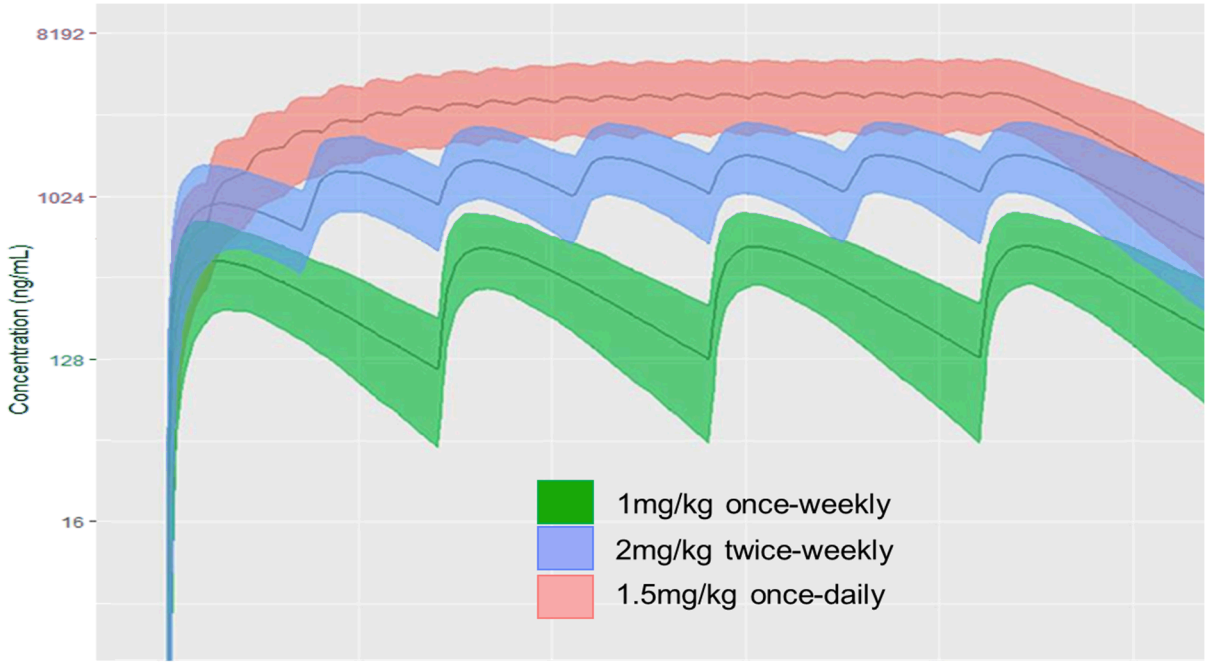
4.2.1. Participant Input Into Design

Patient advocacy groups and patient experts assisted with review of the protocol, including attending the final medical advisory board meeting on phase 2 design.

4.3. Justification for Dose

PK data from the FIH study is discussed in Section 2.2.1. The proposed doses for this study are 1 mg/kg once-weekly, 2 mg/kg twice-weekly and 1.5 mg/kg once-daily in achondroplasia participants aged ≥2 to <11 years old. The 3 doses and dosing regimen selected in this study are widest feasible dose range with minimal exposure overlap (Figure 1) to evaluate dose/exposure response relationship for clinically relevant efficacy, biomarker and safety event in children with achondroplasia.

Figure 1. Predicted Concentration vs Time Profile for a 20kg Child at Low, Medium and High Doses Using the PopPK Model from the C4181002 Phase 1 Study



Based upon the proposed mechanism, it is presumed that efficacy of recifercept will be related to the degree of ligand trapping and the prevention of native FGFR3 receptor dimerization. Recifercept has demonstrated efficacy in restoring normal growth in a mouse model of achondroplasia. However, the relationship between exposure and biomarker/efficacy cannot be established in adults (due to closed growth plates) and, therefore, high uncertainty remains around target exposure in children with achondroplasia which could be efficacious.

Exposure ratios at the NOAEL in monkey ranged from ~8.5-20 fold higher than that predicted by the PopPK modelling of steady-state recifercept concentrations ($AUC_{0\text{-}168}$) at 1.5 mg/kg once daily dosing (10.5 mg/kg weekly dose) in children with achondroplasia age 6–10 year old (Table 2). This along with the safety data from the FIH study provides an acceptable safety and tolerability profile to study the proposed three doses in children with achondroplasia.

Table 2. Monkey Exposure Margins Based on Steady State Serum Recifercept Concentrations Compared to the NOAELs

Study	Dose (mg/kg)	AUC (µg·h/mL)	Exposure Margins at NOAEL
Monkey 4-week GLP toxicity	100	12600	-
Monkey 26-week GLP toxicity	100	5350	-
C4181002 phase 1 study	10	1118.5	4.8 – 11.3
Population PK model	1.5 once-daily (10.5 total weekly)	629.9	**8.5 - 20**

PopPK modelling was developed using the data from C4181002 single and multiple ascending dose cohorts. For prediction of recifercept exposures in the pediatric patient population it was assumed that the PK parameters scale with body weight with the theoretical allometric exponents (Figure 1). For this age group no maturation effects on PK were assumed since recifercept is a protein therapeutic. The theoretical values of allometric exponents (0.75 for clearance and 1.0 for volume of distribution) are considered to have physiological basis and often provide adequate explanation for body weight relationships in paediatric patients thus exposures were likely to decrease for lower bodyweights, this increases the exposure margins and supports the proposed phase 2 design. The PopPK model will be updated in the step-wise cohort enrollment approach. However, even if exposures lie at the upper limits of the prediction model, exposure remains within safe margins.

The PK and safety data from the phase 1 study, as described in the IB and above, support once-weekly, twice-weekly and daily dosing.

PK will be assessed on an ongoing basis using sparse sampling approach to inform and update the PopPK model. The PopPK model could be used to predict exposure in the younger children and before progression to the next enrollment block (≥2 to <6 years and ≥3 months to <2 years). Dose may be amended based on this PK assessment.

PK Study Cohort:

The tentative dose for the PK study cohort is 3 mg/kg. The dose selected for the PK cohort could be changed after evaluating the entirety of the safety, PK, and efficacy data collected in the program before initiating the cohort. The dose selected will not exceed the highest dose found to be safe and tolerated. Weight limits for this study (Section 5.2) are based on technical feasibility of dosing with the current study intervention formulation such that injection volumes will be between 0.2 ml and 1 ml.

4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study, including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Main cohort: Aged ≥2 years to <11 years (up to the day before 11th birthday inclusive) at time of enrollment; CCI [redacted]

Type of Participant and Disease Characteristics

2. Documented, confirmed genetic diagnosis of achondroplasia from historical medical records prior to entry into this trial (test must have been performed at a laboratory fully accredited for genetic testing under local regulations).

3. Completed the C4181001 natural history study with at least 2 valid height/length measurements (at least 3 months apart) prior to enrollment in this study. One of these measurement timepoints must be within the 3 months prior to enrollment in C4181005.

4. Tanner stage 1 based on investigator assessment during physical examination (must include assessment of breast development for females, testicular stage for males).

5. Able to stand independently for height measurements (if ≥2 years of age at enrollment).

6. If aged <2 years at enrollment, has a documented historical MRI brain/cervical spine performed in the previous 12 months.

Informed Consent:

7. Capable of giving signed informed consent/assent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

8. Following receipt of oral and written information about the trial, the child (depending on local institutional review board/independent ethics committee requirements) must provide assent, and one or both (according to local regulations) parents or guardians of the child must provide signed informed consent before any trial-related activity is carried out.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Presence of co-morbid conditions or circumstances that, in the opinion of the investigator, would affect interpretation of growth data or ability to complete the trial procedures.

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

3. Presence of severe obesity (BMI >95th percentile on Hoover-Fong BMI charts) [Hoover-Fong et al, 2008].[14]

4. Known closure of long bone growth plates (cessation of height growth).

5. Body weight <7 kg or >30 kg.

6. Moderate or severe renal impairment CrCL GFR <60 mL/min/1.73m^2 (Calculated GFR based on updated "bedside" Schwartz formula for pediatric patients (CrCL (mL/min/1.73 m^2) = 0.413 * Height (cms)/ Serum cr (mg/dL) or hepatic impairment (AST/ALT >1.5 ULN).

7. History of hypersensitivity to study intervention or any excipients.

Prior/Concomitant Therapy:

8. History of any prior treatment with human growth hormone or related products (including insulin-like growth factor 1 [IGF-1]).

9. History of receipt of any treatment that are known to potentially affect growth (including oral steroids >5 days in the last 6 months, high dose inhaled corticosteroids (>800 mcg/day beclametasone equivalent) and medication for attention deficit hyperactivity disorder).

10. History of limb lengthening surgery (defined as distraction osteogenesis/Ilizarov/callostasis technique following submetaphyseal osteotomy to extend bone length).

11. Any limb lengthening/corrective orthopaedic surgery planned at any point during the trial period.

12. Less than 6 months since fracture or surgical procedure of any bone determined from the screening visit date.

13. Presence of any internal guided growth plates/devices.

14. History of removal of internal guided growth plates/devices within less than 6 months.

15. History of receipt of any investigational product for achondroplasia or that may affect growth/interpretation of growth parameters.

16. History of receipt of an investigational product (not for achondroplasia/growth affecting) within the last 30 days or 5 half-lives (whichever is longer).

Other Exclusions

17. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

Should a participant become a WOCBP (defined as reaching menarche) during the course of the study then the investigator or his or her designee, in consultation with the participant and their guardian, will confirm that the participant has been informed of the potential risks of pregnancy whilst receiving study intervention and advised of the need for continuing total abstinence from sexual activity. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use continue total abstinence from sexual activity and document the conversation and the participants affirmation in the participants' chart. This also applies to males should they become sexually active. In addition, the investigator or designee will instruct the participant or guardian to call immediately if total abstinence from sexual activity is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to recifercept (PF-07256472) provided as lyophilized powder for solution for injection/infusion, 50 mg/vial.

Further details for the sections below can be found in the Investigational Product Manual (IP Manual) and/or dosing diary.

6.1. Study Intervention(s) Administered

Intervention Name	PF07256472 (Recifercept).
ARM Name (group of patients receiving a specific treatment (or no treatment)	Refer to the study schema provided in the STUDY DESIGN section.
Type	Biologic.
Dose Formulation	Lyophilized powder for solution for injection.
Unit Dose Strength(s)	50 mg/vial.
Dosage Level(s)	Refer to the study schema provided in the STUDY DESIGN section.
Route of Administration	Subcutaneous injection.
Use	Experimental.
IMP or NIMP	IMP.
Sourcing	Provided centrally by the sponsor. Refer to the IP Manual for further information.
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. The IP will be provided as open label, as the only personnel required to be blinded are anthropometrists. Vials are single-use only.
Current/Former Name(s) or Alias(es)	TA-46.

6.1.1. Administration

Administer study intervention according to the Subcutaneous Dosing Instructions (see Appendix 10). Study intervention should not be self-administered by the participant.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply study intervention. Authorized site staff and caregivers, who have demonstrated their proficiency, may prepare and administer study intervention.
- All study interventions stored at the clinical site must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.
- Site staff will instruct caregivers on the proper storage requirements for take home study intervention.
- All study interventions stored at participants' homes must be stored according to the labeled storage conditions.
- Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken.
    - The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP Manual.
    - Pfizer cannot analyze the acceptability of any excursion that occurs once the study intervention leaves the clinical site. If an excursion occurs at the participants' homes, the caregivers must quarantine the study intervention until it can be returned to the clinical site for accountability. Further instructions are provided in the dosing diary.
- Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

- Study interventions should be stored in their original containers.
- See the IP manual for storage conditions of the study intervention once reconstituted.
- Details of the transport to and storage of study intervention at the participants' homes can be found in the dosing diary.
- Used and unused vials stored at the participants' homes must be returned to site.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent and dosing diary. All study interventions will be accounted for using a study intervention accountability form/record.
- Further guidance and information for the final disposition of unused study interventions are provided in the IP Manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery, as described in the IP Manual.

6.2.1. Preparation and Dispensing

Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. Site staff will reference the IP Manual for instructions on how to prepare the study intervention for administration. A second staff member will verify the preparation of the dose. All persons who are responsible for dose preparation and dispensing of IP must be listed on the Delegation of Authority log.

Caregivers will reference the Dosing Instructions Diary for instructions on how to prepare and administer the study intervention at home, following demonstration of their proficiency at the site.

Adequate caregiver competency for home-dosing may include, but not be limited to the following criterion:

- Caregivers demonstrate adequate adherence to storage & preparation routine including sterile technique.
- Caregivers understand which sites can be used for injection and the need to rotate these sites.

- Caregivers demonstrate correct techniques to reconstitute & draw up solution into syringe for administration.

- Caregivers demonstrate correct injection technique including preparation of skin prior to injection.

- Caregivers show knowledge of adequate disposal of used medication supplies and completion of dosing diary.

The caregiver should be instructed to maintain the study intervention in the vials and cartons provided, throughout the course of dosing, and return the vials, in the cartons provided, to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

In order to minimize bias in measurement of the primary efficacy endpoint (height), the anthropometrist will be blinded to dose assignment. There will be no additional blinding.

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including, but not limited, to the user's ID and password, the protocol number and the participant number. The site personnel will then be provided with a treatment assignment, randomization number and Dispensable Unit (DU) or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number and DU or container number assigned. The confirmation report must be stored in the site's files.

This is a partially blinded study with open-label supplies. Potential bias will be reduced by the following: central randomization, and an otherwise uninvolved third party will be responsible for conducting assessments related to primary efficacy endpoint and anthropometric secondary endpoints. Study intervention will be dispensed at the study visits summarized in the SoA.

The study -specific IRT reference manual and IP Manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Other Measures to Minimize Bias

Anthropometric data will only be collected by appropriately trained individuals at the trial site and in accordance with the anthropometric measurement manual. All sites will follow a consistent, structured and documented training program. This will occur prior to trial start, through regular refresher training and at targeted retraining based on analysis of measurement data consistency at the site. Training and assessment of competency will be performed by dedicated anthropometric training staff contracted by the sponsor.

Sites will be required to make all efforts to have the same anthropometrist at each visit for each participant (longitudinal consistency) and between participants (cross-sectional consistency). As well as following the specific procedures for measurement laid out in the measurement manual, sites will be provided with the same (or exactly equivalent) equipment across all sites and will follow the specific calibration procedures. The anthropometrist should remain blinded to dose assignment.

If the anthropometrist becomes unintentionally unblinded then they should continue to act as the anthropometrist for that participant since a change in anthropometrist is known to be a significant source of variability in measurement data. If any measures are taken following unblinding of the anthropometrists, this will be recorded in the eCRF. All blinded & unblinded measurements collected will be analysed, with further details available in the SAP.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator, a designee (under medical supervision) or from the caregiver under supervision of site staff. The date, time, injection site and volume of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The same data will be collected in the dosing diary when administered at home. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IP Manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

When participants are dosed at home, compliance will be monitored by completion of a dosing diary by the caregiver which will record date, time, injection site and volume of dose administration. This diary will be reviewed by the site staff. Where home nursing have supported home dosing then this will be recorded.

If poor compliance is identified by site staff then additional training and support will be provided to the caregivers.

6.4.1. Participant Compliance and Home Administration

Caregivers will be permitted to administer recifercept once they have demonstrated an understanding of the preparation and administration process at the site. Confirmation of a caregiver’s ability to perform preparation and administration must be documented in the site file. For administration of recifercept at home, compliance and any injection site reactions will be captured and completed by the caregiver by completing the dosing diary. Caregivers should contact the site immediately in the event of any potential injection site reactions.

Caregivers will administer treatment from the point of which they have demonstrated the capability to do so (as stated above) until the end of dosing. Prior to administration at home, sites must ensure caregivers are trained on IP administration and storage per the dosing diary. Dosing between planned clinic visits may be administered by investigational site staff until the respective caregiver has been properly trained in administration. Sites should follow -up (eg, via phone call) to ensure compliance with administration instructions, where necessary. Clinic administration of study intervention can be readministered at any time where home dosing is deemed not feasible or inappropriate. Caregivers will be supported to reinstitute home dosing where appropriate.

6.5. Concomitant Therapy

6.5.1. Prohibited During the Study

Participants may not receive any medication or procedure that may affect the growth of the long bones. This includes human growth hormone (or related medicines such as IGF-1) and surgical/interventional procedures such as limb lengthening.

Participants cannot undergo surgical procedures of the bone during the course of the trial. This includes limb lengthening, guided growth (eg, 8 plates), tibial osteotomies, spinal surgery, neurosurgical procedures or ear, nose, and throat (ENT) bone procedures.

6.5.2. Prohibited Prior Treatments

Participants who have received prior human growth hormone or related products will not be eligible to participate.

Any participant that has previously received an investigational medicinal product for the treatment of achondroplasia is not eligible to participate.

Past receipt of any investigational medicinal product that could affect growth may not participate.

Receipt of any other investigational medicinal product (not covered above) in the last 30 days or 5 half-lives (whichever is longer) is prohibited.

Participants may not have previously undergone any limb-lengthening surgery.

6.6. Dose Modification

The decision to proceed to the next enrollment block of recifercept will be made by the study team based on safety, tolerability, and preliminary PK data obtained in at least 3 participants at each new dose and age bracket. The PK data from Block A participants aged ≥6 to <11 years will be integrated into the PopPK model developed using healthy adult PK data, to then confirm the dosing recommendations in younger age sub-cohorts (≥2 to <6 years and ≥3 months to <2 years). It is anticipated that the relationship between body weight and PK will be well characterized at this stage and no further dosing adjustment may be required for the youngest age group (≥3 months to <2 years). However, to minimize the uncertainty in

children aged ≥3 months to <2 years, PK data collected in the ≥2 to <6 -years cohort will be used to evaluate consistency with the predicted dose-concentration relationship. This review will be performed at the following times:

Block A to B	Review after all block A participants (n=6, all aged 6-10y) have completed D29
Block B to C	Review once 2-6y participants (n=4) and 3 high dose 6-10y participants have completed D29
Block C to D	Review once all ≥3 months -2y participants (n=4) and 3 high dose 2-6y participants have completed D29

6.6.1. Rules for Progression to Next Enrollment Block

The eDMC will meet after block A participants have received 4 weeks of study intervention (completed D29) to review safety and PK data. They will make recommendations on dose levels and progression to block B.

Progression to blocks C and D, will occur without eDMC review if NONE of the following criteria are met:

- Serious Adverse Reaction (IMP-related SAR);
- ≥2 participants affected by the same moderate/severe study intervention-related AE;
- ≥2 participants affected by an AE of hypersensitivity to study intervention;
- ≥2 participants with severe ISRs;
- ≥2 participants with ISR leading to withdrawal of study intervention.

If any of these criteria are met then the eDMC must be convened to make a decision on progression to the next enrollment block. In addition, no further participants will be enrolled at that dose (or higher) until eDMC recommendation has been issued.

A sentinel approach will be used in recruiting those aged 2-<6 years in block C such that n=2 at high dose will be dosed followed by a 2-week delay before further dosing occurs in that age group.

The dosing schedule may also be adjusted by the eDMC to expand a dosing cohort to further evaluate safety and/or PK findings at a given dose level or to amend the doses to be studied in each enrollment block. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts.

In addition, following evaluation of the overall benefit:risk assessment at the interim analysis, the dose levels may be adjusted. If a new dose level is introduced then this will form a new cohort (minimum n=15) of treatment naïve participants. Previously treated subjects at a discontinued dose will be moved to the next lowest continuing dose.

Any dose modifications will not exceed the current maximum dose (1.5mg/kg once-daily) without submission and approval of a protocol amendment.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study, however participants will be offered to roll over into an open-label extension study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Non-compliance with study intervention;
- Pregnancy;
- Withdrawal of consent by parent/guardian;
- Investigator decision to withdraw;
- Death.

The decision to withdraw the participant from the study ultimately lies with the investigator. For example occurrence of any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal. Additionally if a subject experiences a serious or intolerable AE that prevents them from continuing with study participation such as severe injection site reaction or hypersensitivity, this would be expected to lead to withdrawal.

Study intervention will be discontinued if the investigator considers that it is in the participants best interest to initiate any of the prohibited treatments described in Section 6.5.1.

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

ECG Changes

ECG will be collected at baseline and at Day 4, then only repeated if, in the opinion of the investigator, they are clinically indicated. If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE. Further details of potentially significant ECG changes can be found in Appendix 6.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted. See the SoA for assessments to be collected at the time of early termination and follow-up and for any further evaluations that need to be completed.

The early termination visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants and/or their parent/guardian should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit or refuses attendance of the home nurse:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any -study specific procedures including assent as per local regulations.

The date of birth will be collected to critically evaluate the effect on growth by age. At a minimum the recorded date of birth must include the participant's month and year of birth.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or within 24 hours following awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol -specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol -required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test specified in this protocol. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol -required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 130 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer. For the PK cohort, the total blood sampling value for individual participants is approximately 67 mL.

Sampling volumes will not exceed 1% of total blood volume in any single blood draw or 3% blood volume within a 28 day period. [Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Revision 1. 18 September 2017.].

If sampling will exceed these limits then the samples should be prioritized as follows:

1. Clinical Safety Laboratory Samples.
2. PK.
3. Immunogenicity.
4. Biomarker samples.
5. Biobanked samples.

Further details, such as minimum volumes required for each type of sample, can be found in the laboratory manual.

8.1. Efficacy Assessments

8.1.1. Anthropometric Measurements

Anthropometric measurements for height and proportionality will be performed and reported in the eCRF. Anthropometric measurements will be performed according to a trial-specific Anthropometric Measurement Manual, which will be provided to the investigational sites. This manual will contain a detailed description on the following:

1. Which measurements to perform.
2. The tools/instruments to be used.
3. Standard procedure for performing these measurements.

The measurements to be taken on a 3-monthly basis are:

- Standing height (length for participants <2y);
- Sitting height (crown-rump length for participants <2y);
- Knee height;
- Head circumference;
- Arm span;
- Body weight;
- Elbow extension angle;
- Cranial dimensions (occipito-frontal, occipito-nasal distances).

Waist and chest circumference will be measured at baseline and at final visit.

Anthropometric data will only be collected by appropriately trained individuals at the trial site and in accordance with the anthropometric measurement manual. All sites will follow a consistent, structured and documented training programme. This will occur prior to trial start, through regular refresher training and at targeted retraining based on analysis of measurement data consistency at the site.

Sites will be required to make all efforts to have the same anthropometrist at each visit for each participant (longitudinal consistency) and between participants (cross-sectional consistency). As well as following the specific procedures for measurement laid out in the measurement manual, sites will be provided with the same (or exactly equivalent) equipment across all sites and will follow the specific calibration procedures.

Anthropomotrists should remain blinded to dose assignment in order to minimize bias.

8.1.2. Polysomnography/Sleep Study

In participants with a documented current diagnosis of sleep disordered breathing at enrollment, baseline sleep study data will be collected. This sleep study should be within 6 months of enrollment (this can be at site or a home study). The following data will be collected where available:

- Clinical summary of findings (including reported diagnosis);
- Whether study was performed in room air/oxygen/on continuous positive airway pressure;
- Apnea-hypopnea index (obstructive and total);
- Desaturation index (number of desaturations per hour >3% from baseline);
- Percentage time spent <90% oxygen saturation (SaO2);
- Percentage time spent with end-tidal carbon dioxide >50 mmHg;
- SaO2 nadir.

The sleep study will be repeated at the end of the study.

8.1.3. MRI

MRI scans of the brain will be assessed in the CCI cohort of those aged under 2 years at enrollment. A historical scan collected within the 12 months prior to enrollment can be used as baseline data. The scan will be repeated at the end of this study. The scan will be read and reported locally with the following data entered into the eCRF.

- Whether the participant has had prior foramen magnum surgery.
- History of other cranial surgery.
- CSF signal loss.
- Presence of posterior effacement ± associated anterior effacement.
- Whether there is increased intramedullary signal on T2-weighted sequences.
- Were any other intracranial abnormalities identified?
    - Reduced cisterna magna;
    - Enlarged ventricles;
    - Increased CSF spaces (non-ventricular);
    - Increased tentorial angle;
    - Other (specified).
- Does the participant have document central apnoea (this should also be recorded under the polysomnography)?
- Are the scan findings associated with any abnormalities on neurological examination?
- Did this scan prompt foramen magnum decompression surgery to take place?

8.1.4. Patient-Reported (PRO)/Observer-Reported (ObsRO) Outcome Assessments

COAs implemented in this study are the Childhood Health Assessment Questionnaire (adapted for achondroplasia, [CHAQ]), Quality of Life in Short Stature Youth (QoLISSY) Brief, and Acceptability and Tolerability Questionnaire-Achondroplasia. These measures were chosen to be included in the phase 2 study based on: 1) concept mapping to the conceptual model, and 2) guidance provided to the team based on regulatory feedback provided to date.

The COA measures are completed in accordance with the SoA during the scheduled site visits. At each relevant visit, the measures are administered before dosing, treatment, or conversation between health care team and participants about their health condition.

8.1.4.1. Childhood Health Assessment Questionnaire (adapted for achondroplasia, [CHAQ])

The Childhood Health Assessment Questionnaire (adapted for achondroplasia, [CHAQ]) is a 36-item measure of health status and physical function. Participants aged 1 year of age and older at enrollment will have the CHAQ (adapted for achondroplasia) completed at designated study visits. The parent-report version will be completed for all participants. Participants will start on the age appropriate version and continue with that version throughout the study.

Participants or their caregivers will be asked to provide responses to questions designed to assess function in 8 components/domains in addition to: 2 scales (pain and well-being), 2 questions that ask about the use of aids and devices, and 2 questions that ask about the requirement for help with the functional areas. The 8 functional components are: Dressing and Grooming (4 items); Getting Up (2 items); Eating (3 items); Walking (2 items); Hygiene (5 items); Reach (4 items); Grip (5 items); and Activities (5 items). Both a disability and discomfort index can be calculated. The CHAQ (adapted for achondroplasia) has a recall period of 'over the past week'. A 5-point Likert Scale is utilized ranging from 'without any difficulty' to 'unable to do' and a 'not applicable option'. Lower component and index scores indicate better health status/functioning.

8.1.4.2. Quality of Life in Short Stature Youth (QoLISSY) Brief

For participants aged 4 years of age and above at enrollment, the parent will complete the Quality of Life Short Stature Youth Brief (QoLISSY Brief) tool. QoLISSY Brief measures health-related quality of life (HRQoL) in children 4-18 years old from the participant and caregiver perspectives. The assessment assignments will start with the age appropriate version at baseline and continue with that the same version assignment throughout the study. The 9 items on the QoLISSY Brief were selected from the full QoLISSY physical, social and emotional HRQoL dimensions. The QoLISSY Brief questions ask the participant or caregiver about their status currently. Intended for children or caregivers of children, the instrument uses a 5-point Likert Scale ranging from 'not at all/never' to 'extremely/always'. The QoLISSY Brief total score is the 0-100 transformed sum of the 9 item scores, with higher scores representing better quality of life.

The assessment version assignments will start with the age appropriate version at baseline and continue with the same version throughout the study.

8.1.4.3. Acceptability and Tolerability Questionnaire - Achondroplasia

The Acceptability and Tolerability Questionnaire – Achondroplasia will be used to measure the acceptability and tolerability of the subcutaneous injection being received as part of the achondroplasia treatment. There are 10 items with a recall period of 'past 7 days' that ask about pain, satisfaction with treatment, acceptability and tolerability of the injection. The caregiver completes the questionnaire throughout the study.

8.1.4.4. EuroQol 5 Dimensions – Youth (EQ-5D-Y) and Youth Proxy Version 1 (EQ-5D-Y Proxy Version 1)

The EQ-5D-Y is a newly developed generic instrument measuring health-related quality of life in children and adolescents 8 years and older. The EQ-5D-Y Proxy measures the health status of children 4 to 7 years of age. EQ-5D-Y was adapted from the EQ-5D original questionnaire (http://www.euroqol.org/about-eq-5d.html). It consists of a descriptive system (EQ-5D) of health-related quality of life states, consisting of five dimensions including mobility (walking about), self-care (looking after myself), usual activities (doing usual activities), pain/discomfort (having pain or discomfort), and anxiety/depression (feeling worried, sad or unhappy) each of which can take one of three responses. The responses record three levels of severity (no problems, some problems, or a lot of problems) within a particular ED-5D dimension. Additionally, the EQ-5D consists of a standard vertical 20 cm visual analogue scale (EQ VAS) for recording an individual's rating of their current health-related quality of life state on a scale from 0 to 100 with 0 representing the worst and 100 the best health state he or she can imagine. All items refer to the health state "today". For younger ages, the caregiver completes the EQ-5D-Y Proxy Version 1 and continues to complete throughout the study; the children can also complete the EQ-5D-Y self-report version when they are old enough.

8.1.4.5. Patient Global Impression of Severity and Patient Global Impression of Change Anchor Items

Additionally, 4 anchor items have been developed to assess change over time on the CHAQ (adapted for achondroplasia) and QoLISSY Brief: two global impression of severity items (PGIS) and 2 global impression of change items (PGIC); all four anchor items are completed by the caregiver. The 2 PGIS single item assessments will be completed at each clinic visit when the CHAQ (adapted for achondroplasia) and QoLISSY Brief are assessed. The 2 PGIC single item assessments will be also completed at each clinic visit when the CHAQ (adapted for achondroplasia) and QoLISSY Brief are assessed, but not at the baseline visit.

The PGIS-Physical Activities-Caregiver is a single item assessment completed by the caregiver rating the impact of achondroplasia on their child's ability to do physical activities over the past 7 days. The response scale is a 4-point categorical rating scale ranging from "none" to "severe".

The PGIS-Emotional and Social Well-Being-Caregiver is a single item assessment completed by the caregiver rating the impact of achondroplasia on their child's overall emotional and social well-being over the past 7 days. The response scale is a 4-point categorical rating scale ranging from "none" to "severe".

The PGIC-Physical Activities-Caregiver is a single item assessment completed by the caregiver rating the change in their child's ability to do physical activities since they started taking the study medication. The response scale is a 5-point categorical rating centered around "no change" with 2 grades of improvement and 2 grades of worsening.

The PGIC-Emotional and Social Well-Being-Caregiver is a single item assessment completed by the caregiver rating the change in their child's overall emotional and social well-being since they started taking the study medication. The response scale is a 5-point categorical rating centered around "no change" with 2 grades of improvement and 2 grades of worsening.

8.1.5. Tanner Staging

In order to evaluate the effects of early puberty on growth trajectory, Tanner stage of puberty will be assessed. For children 7 years and older, at the timing indicated in the SoA, the Tanner Stage of puberty will be recorded in the eCRF as stage I-V. Children under 7 years of age do not require this assessment, providing the investigator confirms there is no suspicion of a diagnosis of precocious puberty.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examination

A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal systems and skin. Height and weight will also be measured and recorded as per the anthropometric measurements manual.

Investigators should pay special attention to clinical signs related to medical history.

8.2.2. Neurological Examination

Neurological examination will be performed at visits indicated in the SoA. This will include examination of cranial nerves (excluding fundoscopy) and examination of upper and lower limbs to include tone, power, reflexes and sensation. This should be performed by an investigator, or designee, experienced in such examinations in children who can suitably adapt to the age range in this study.

8.2.3. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure measurement must use an appropriate size cuff for the age and weight of the participant.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones) where possible (with consideration of the age of the child).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 1 blood pressure measurement. If the BP reading is abnormal then this should be repeated after 1 minute. The blood pressure reading will be recorded on the eCRF.

8.2.4. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at screening and at Day 4 using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position (where possible).

ECGs in this study are conducted at screening to document baseline ECG characteristics prior to dosing.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 6. However, these should be considered in light of age-specific norms.

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Participants are required to fast for ≥4hr prior to blood sampling. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 1 week after the last dose of study intervention should be repeated according to the judgement of the investigator until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a non-leading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian/legally authorized representative provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including the follow up visit. At the final follow up (final contact), the participant/parent(s)/legal guardian/legally authorized representative will be contacted by telephone to inquire about AEs and SAEs, including hospitalizations and NDCMCs, since visit Month 12.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the parent(s)/legal guardian/legally authorized representative withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow--up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to -follow-up (as defined in Section 7.3).

In general, -follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on -follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if: A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 4 weeks after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Injection site reactions will be considered an adverse event of special interest (AESI). Injection site reactions may include but are not limited to erythema, induration, ecchymosis, pain and pruritis. The size and severity of these symptoms or reactions will be assessed and documented. The following details will be collected:

- Date of onset and resolution of the ISR;
- Presence of the following features on a mild/moderate/severe grading scale:
  - Erythema;
  - Induration;
  - Pain;
  - Swelling;
  - Pruritis.
- Did the ISR lead to any missed or delayed doses?
- Did the ISR lead to withdrawal of the participant from the study?

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

Not applicable.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of recifercept equivalent to greater than 5mg/kg within a 48-hour time period or greater than 20mg/kg within a 7 day period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of recifercept (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples of approximately 2 mL, to provide approximately 1 mL serum, will be collected for measurement of serum concentrations of recifercept as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. Collection of samples up to and including 12 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted. The actual date and time (24-hour clock time) of each sample will be recorded.

Serum samples for population pharmacokinetic (PK) and non-compartmental (for PK study cohort only) analysis of recifercept will be collected as per the time points specified in SoA. In general, every effort should be made to collect blood samples for PK analysis within specified time windows. At all times, it is essential to accurately record the date and time study treatment is administered and PK samples are collected. Samples will be used to evaluate the Population PK of recifercept. Each serum sample will be divided into 2 aliquot(s) (1 each for Intact recifercept and Total [intact + clipped] recifercept analysis). Samples collected for analyses of recifercept serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal CCI purposes.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Samples collected for measurement of serum concentrations of recifercept will be analyzed using a validated analytical method in compliance with applicable SOPs. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

Genetics (specified analyses) are not evaluated in this study. CCI [redacted]

This section is not applicable in Denmark.

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA.

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

CCI [redacted]

8.7.3. Blood Samples for Biomarker Analysis

A 6 mL sample will be collected at timepoints outlined in the Schedule of assessments and described in the laboratory manual. However, should the blood volumes to be taken exceed maximum guidelines then the clinical safety laboratory assessments, PK sampling and immunogenicity samples will be prioritized.

- Detailed collection, processing, storage, and shipment instructions will be provided in the central laboratory manual.
- Samples will be analyzed using analytical methods in compliance with Pfizer standard operating procedures.

The following biomarkers may be analysed using immunoassays:

CCI

CCI [redacted]

8.7.4. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.7.5. Specified Protein Research

Specified protein research is not included in this study.

8.7.6. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

CCI [redacted]

8.8. Immunogenicity Assessments

Blood samples of approximately 2 mL, to provide a minimum of 1 mL serum volume, will be collected for determination of ADA and NAb as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

CCI [redacted]

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

Height Growth Endpoint

Null hypothesis for height growth in this study is that height 12 months post-baseline for children on recifercept is equal to the expected height growth for the achondroplasia reference population based on Merker (2018).[30] The alternative hypothesis is that height growth for recifercept-treated participant is greater than the expected growth for achondroplasia reference population based on Merker (2018).[30]

9.1.1. Estimands

The primary efficacy estimand will be the population treatment effect of the mean change-from-baseline of a continuous response (ie, height growth) at month 12 irrespective of IP compliance. Increase in height growth above expected growth in reference population, a co-primary endpoint, is defined as the height growth in the achondroplasia reference population +50%. Intercurrent event for the efficacy estimand: withdrawal and all events leading missing data will be excluded from efficacy analysis and will not have their data imputed. The population-based treatment effect will be the mean change-from-baseline at 12 months.

The secondary estimand will be the population treatment effect of the mean change from baseline of a continuous response, defined as the decline in the difference of arm span to standing height. Intercurrent event for the efficacy estimand: withdrawal and all events leading missing data will be excluded from efficacy analysis and will not have their data imputed.

9.2. Sample Size Determination

Sample size determination is based on the co-primary endpoint of height growth, defined as change from baseline of height at 12 months for participants on drug versus change from baseline of height at 12 months for a reference achondroplasia population. A total of 54 participants randomized to three dose levels in order to obtain 15 participants per dose, assuming a one-sided family-wise error rate of 0.05 with a Bonferroni correction (0.017 after Bonferroni adjustment for 3 comparisons), and inter-participant variability of .15 (estimated from C4181001), there is over 90% power to detect at least one dose providing 50% height growth above reference. No statistical comparison will be made between recifercept doses.

PK Study Cohort:

No formal sample size calculation was performed and 12 participants will be selected empirically to characterize PK, safety and tolerability after single 3 mg/kg dose administration of two formulations.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	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 their randomized dose.
PK Concentration set	All participants who received at least one dose of recifercept and have at least one evaluable concentration result.
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.
PK Study Cohort Parameter (PKCP)	All participants in the PK cohort who have at least one PK parameter of interest.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

Data presented in tables will be summarized by recifercept dose (defined in Section 4.1) and total. If needed summary presentations may also be grouped by gender. In addition, separate summaries will be completed for participants aged 3 months to<2 years (by dose, though not stratified by gender).

9.4.2. Primary Endpoint(s)

Efficacy

The primary efficacy endpoint of change from baseline of height at 12 months will be analyzed using an analysis of variance (ANOVA) model comprising terms for recifercept dose groups. Change from baseline estimates for height and their corresponding 95% confidence intervals will be provided via least-square means. A Bonferroni adjustment will be applied to the 95% confidence intervals. The population for the primary analysis will be based on the FAS, while the PPAS is the population that will be used for sensitivity analysis.

Safety

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- TEAEs and SAEs;
- Withdrawals from treatment due to AEs.

Change from baseline in laboratory data and vital signs will be additionally summarized. Participant listings will also be produced for these safety endpoints.

PK Study Cohort:

The pharmacokinetic parameters following single dose administration in the PK cohort 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.	$AUC_{last}+(C_{last}*/k_{el})$, 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.	$Log_e(2)/k_{el}$, 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.

The serum PK parameters for recifercept will be summarized descriptively by formulation. Serum concentrations will be listed and summarized descriptively by formulation and nominal PK sampling time. Individual participant summary profiles (mean and median plots) of the serum-concentration time data will be plotted by formulation and PK sampling time. For summary statistics and summary plots, the nominal PK sampling time will be used. For individual participant plots, the actual PK sampling time will be used, whilst the pre-dose will be set to zero. Summary plots will be presented on both linear-linear and log-linear scales.

9.4.3. Secondary Endpoint(s)

The secondary efficacy endpoint of change from baseline of the difference of arm span to height difference at 12 months will be analyzed using an analysis of variance (ANOVA) model comprising terms for recifercept dose groups. Change from baseline estimates for height and their corresponding 80% confidence intervals will be provided via least-square means. The population for the primary analysis will be based on the FAS, while the PPAS is the population that will be used for sensitivity analysis.

Additional safety endpoints (laboratory values, physical examination, vital signs and immunogenicity) will be analyzed as change from baseline by dose group.

PK Study Cohort:

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations.

CCI [redacted]

9.4.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

9.4.6. Other Analyse(s)

Patient-reported/observer-reported outcome assessments will be summarized by dose. Additional analysis of these assessments will be detailed in the SAP or in a separate analysis plan.

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4.7. Pharmacokinetic Data

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. PK will be assessed on an ongoing basis using a sparse sampling approach to inform and update the PopPK model. The PK data from Block A participants aged ≥6 to <11 years will be integrated into the PopPK model developed using healthy adult PK data, to confirm the dosing recommendations in younger age sub-cohorts (≥2 to <6 years and ≥3 months -<2 years).

PK Study Cohort:

Non-compartmental analysis will be conducted to evaluate the PK of the two formulations administered in the PK study cohort.

9.5. Interim Analyses

Interim analyses may be performed to assess efficacy and safety after approximately 45 participants (up to15 per dose), complete their study participation through 50% of the study (completion of 6 months treatment). Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in a charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

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. No statistical comparisons will be performed between treatment arms.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an eDMC. The eDMC is independent of the study team and includes only external members. The eDMC charter describes the role of the eDMC in more detail.

The eDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charters. The recommendations made by the eDMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data to regulatory authorities, as appropriate.

The study team will meet to assess progression to the next enrollment block (Section 1.2) based on the available safety and PK data. If safety signals are identified at this review (see Section 6.1) then a meeting of the eDMC will be convened to decide next steps.

The eDMC will meet regularly to assess all available safety and PK data to ensure ongoing safety of all trial participants. The eDMC will review unblinded safety data in order to fully assess the impact of dose/exposure on safety signals. A patient advocate will also be included on the eDMC if an appropriately qualified individual can be identified as agreed upon by the eDMC chairperson.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative defined as parent or legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study -related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD. Additionally, assent of the participant must be obtained as per local regulations.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant -specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant -specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for -Pfizer sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for -Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for -Pfizer sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, -risk based initiatives in operations and quality such as risk management and mitigation strategies and analytical -risk based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the clinical monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 3. Protocol--Required Safety Laboratory Assessments

Hematology	Chemistry (>4 h fast)[b]	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Phosphate	• Pregnancy test (β-hCG)[a]

a. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.

b. Time since last food intake should be entered on the laboratory requisition form.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, -Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/-self harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately -life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.	All AEs/SAEs associated with exposure during pregnancy or breastfeeding. Occupational exposure is not recorded.	All (and EDP supplemental form for EDP). Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 21 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) ***plus*** an additional 90 days (a spermatogenesis cycle):

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

10.4.2. Female Participant Reproductive Inclusion Criteria

The requirement for participants to be Tanner stage 1 at enrolment will preclude WOCBP from enrolling, however it is possible participants may become WOCBP later in the study.

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and agrees to total abstinence until 21 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator, or his or her designee, in consultation with the participant and the participant's legally authorized representative, will confirm that the participant has been informed of the potential risks of pregnancy whilst receiving study intervention and advised of the need for continuing total abstinence from sexual activity.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy;

- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

10.4.4. Contraception Methods

Sexual abstinence:

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events
• New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events
• QTcF prolongation >500 msec.
ECG Findings That Qualify as Serious Adverse Events
• Change in pattern suggestive of new myocardial infarction. • Sustained ventricular tachyarrhythmias (>30 seconds' duration). • Second- or third-degree AV block requiring pacemaker placement. • Asystolic pauses requiring pacemaker placement. • Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion. • Ventricular fibrillation/flutter. • At the discretion of the Investigator, any arrhythmia classified as an adverse experience.
The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.7. Appendix 7: Genetics

Use/Analysis of DNA collected as part of the banked biospecimens

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to recifercept or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic locally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.8.2.1 of this appendix regarding pregnancy tests.
- If PRO/ObsROs can be administered by telehealth then these should be performed.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.8.2. Alternative Facilities for Safety Assessments

10.8.2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- See table of safety labs in Appendix 2.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.8.2.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.8.3. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Recifercept may be shipped by an appropriate third-party courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for recifercept. Pfizer does not permit the shipment of recifercept by mail. The tracking record of shipments and the chain of custody of recifercept must be kept in the participant's source documents/medical records.

Study intervention can continue to be administered at home in accordance with the protocol.

10.8.4. Home Health Visits

A home health care service will be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Support of home dosing in accordance with the protocol;
- Blood draws.

10.8.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.8.6. Efficacy Assessments

Anthropometric measurements cannot be undertaken in the participant's home. Administration of PRO/ObsRO and blood draws may be undertaken by home health teams.

10.8.7. Independent Oversight Committees

The eDMC will continue to meet via teleconference in accordance with the eDMC charter.

10.9. Appendix 9: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	absolute
ADA	anti-drug antibodies
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-168}	area under the concentration-time curve from time 0 to 168 hours
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval t
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BIW	twice weekly
BMI	body mass index
BP	lood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CHAQ	Childhood Health Assessment Questionnaire
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance of drug from eg, plasma
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COA	Clinical Outcome Assessment
CCI [redacted]	[redacted]
CONSORT	Consolidated Standards of Reporting Trials
CCI [redacted]	[redacted]
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CCI [redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Term
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eDMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
ENT	Ear nose and throat
EQ-5D	EuroQol- 5 dimensions
EQ-VAS	EuroQoL- visual analogue score
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR3	Fibroblast growth factor receptor 3
FIH	first-in-huma
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good laboratory practice
HIPAA	Health Insurance Portability and Accountability Act
HRQL	health-related quality of life
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IGF-1	Insulin-like growth factor 1
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IPM	investigationalp manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	injection site reaction
LFT	liver function test
MAD	multiple ascending dose

Abbreviation	Term
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NDCMC	newly diagnosed chronic medical condition
Msec	millisecond
N/A	not applicable
Nab	neutralizing antibodies
CCI	[redacted]
NDCMC	Newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NPRB	Natriuretic peptide receptor B
ObsRo	Observer report outcome
OLE	Open-label extension
CCI	[redacted]
PBMC	peripheral blood mononuclear cell
PCRU	Pfizer clinical research unit
PD	pharmacodynamic(s)
PFS	prefilled syringe
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PI	principal investigator
PK	pharmacokinetic(s)
PKCP	PK study cohort parameter
PopPK	Population pharmacokinetics
PRO	Patient-Reported Outcome
CCI	[redacted]
PSG	polysomnography
PT	prothrombin time
QoLISSY Brief	Quality of Life in Short Stature Youth Brief
QTc	corrected QT
QTcF	QTc corrected using Fridericia's formula
QW	Once Weekly
R_{AC}	accumulation ratio based on AUC (observed)
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAD	single ascending dose
SaO2	oxygen saturation
SAP	statistical analysis plan
SAR	Serious Adverse Reaction
SC	subcutaneous

Abbreviation	Term
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	terminal phase half-life
TA-46	Previous name for recifercept
TBili	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman/women of childbearing potential

10.10. Appendix 10: Subcutaneous Dosing Instructions

SUBCUTANEOUS DOSING INSTRUCTIONS

GENERAL INSTRUCTIONS

- Allow prepared syringes with the medication to reach room temperature for 15 minutes prior to administration (they should not be cold to touch);
- Never reuse needles or syringes;
- Dispose of all used materials in the appropriate sharps container and return used vials into the cartons to be checked by a study monitor.

Gather your supplies:

- Alcohol pads;
- Prepared syringe with medication;
- Puncture resistant sharps container.

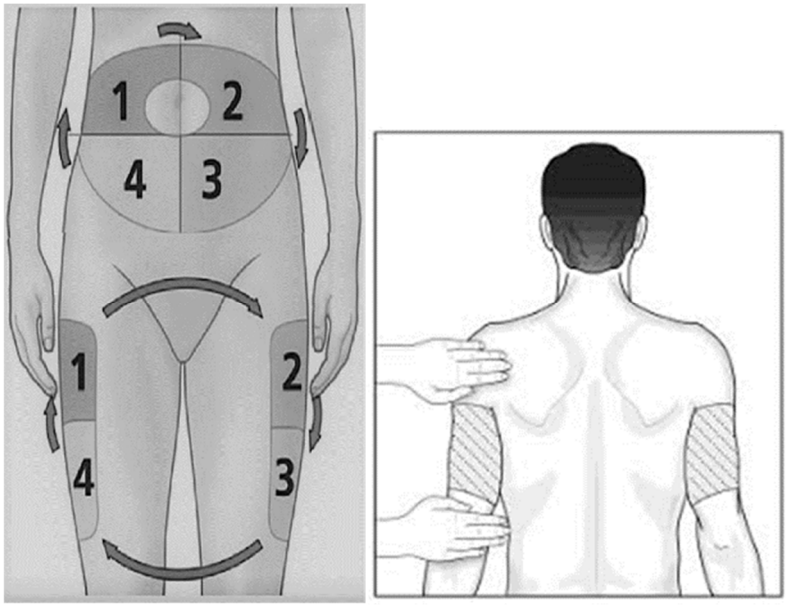
Choose one of the recommended injection sites described below:

The injection(s) should be given when participant is sitting or lying down into the **abdomen or outer thighs. The back of the arms may be used as an alternative injection site (Figure 2).**

Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars, moles and avoid the area 1 inch from the naval.

- Injections should start in either the abdomen or outer thighs at number one and proceed in a clockwise manner from site number 1 through to number 4.
- If injections are given in the back of the arms, alternate between the left and right arms.
- For each injection given (including if two injections are needed for one dose), a new injection site must be chosen. Inject at least 2 inches from the previous site.

Figure 2. Injection Site Rotation



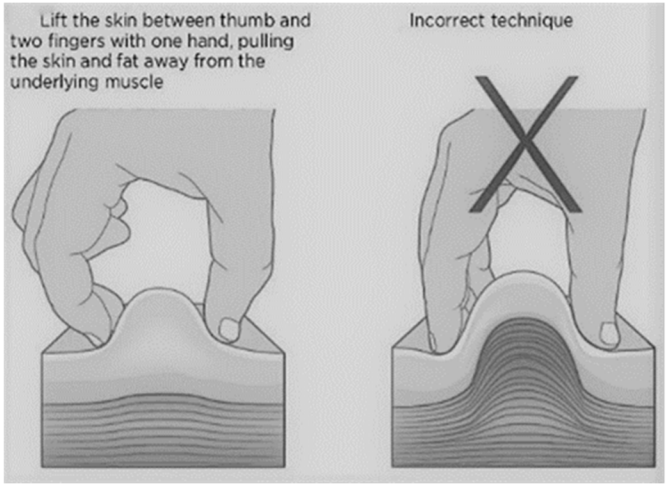
Preparing the subcutaneous injection site and injecting Recifercept

1. Wash hands thoroughly with soap and water prior to any injections.

2. Choose the site from Figure 2 and clean the site where Recifercept is to be injected with a new alcohol swab, using a circular motion, starting from the inside and working to the outside of the chosen injection site. Allow the area to dry thoroughly, do not blow the area dry. DO NOT touch this area again before giving the injection.

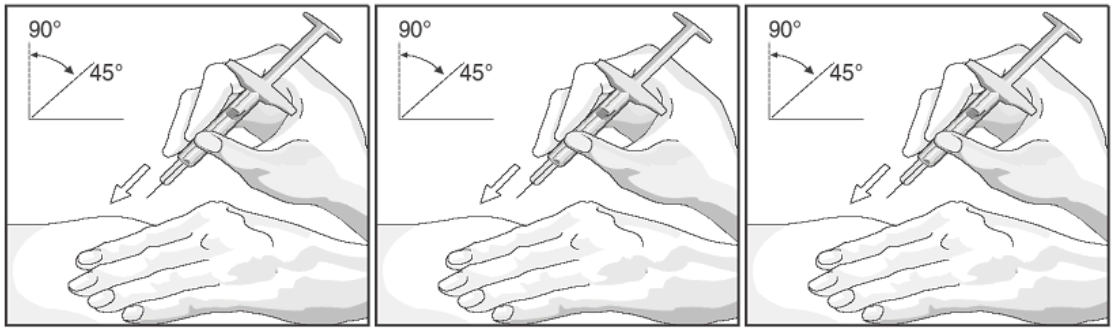
3. Using the thumb and forefinger, lift up a fold of skin with one hand (Figure 3).

Figure 3. Technique for Holding Skin Prior to Injection



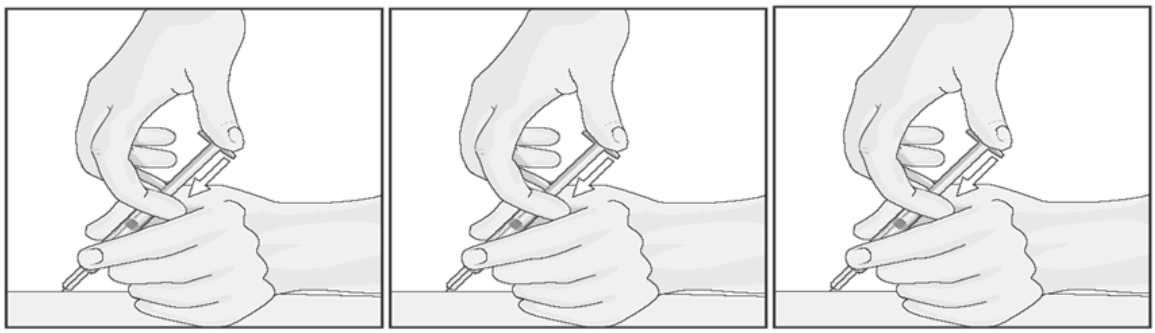
1. With the other hand, hold the syringe like a pencil with the bevel up. With a quick, short motion, push the needle into the skin at an angle of 45° (Figure 4).

Figure 4. Injection Angle



1. Once the needle has been pushed into the skin, release the pinched skin while still holding the needle in place. With your free hand, push the plunger all the way down at a slow, steady rate to deliver the entire contents of the syringe Figure 5).

Figure 5. Technique for Injecting Study Intervention



1. When the syringe is empty, remove the needle from the skin; be careful to keep it at the same angle it was when it was inserted into the skin. Place the syringe/needle in the sharps container provided.

2. Repeat steps 1 through 5 if a second syringe is required for the total dose.

3. Slight bleeding may occur. Cover with a sterile gauze pad if needed. DO NOT rub the injection site. You may place a band aid over the injection site.

11. REFERENCES

1. Banholzer ML, Wandel C, Barrow P, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partner: update. Clin Transl Med 2016;5(1):23-37.

2. Waller, D. K., Correa, A., Vo, T. M., et al. (2008). The population-based prevalence of achondroplasia and thanatophoric dysplasia in selected regions of the US. American Journal of Medical Genetics Part A, 146A(18), 2385–2389.

3. Ornitz, D. M., & Legeai-Mallet, L. (2017). Achondroplasia: development, pathogenesis, and therapy. Developmental Dynamics, 246(4), 291–309.

4. Ireland, P. J., McGill, J., Zankl, A., et al. (2011). Functional performance in young Australian children with achondroplasia. Developmental Medicine and Child Neurology, 53(10), 944–950.

5. Wigg, K., Tofts, L., Benson, S., & Porter, M. (2016). The neuropsychological function of children with achondroplasia. American Journal of Medical Genetics Part A, 170(11), 2882–2888.

6. Hecht, J. T., Francomano, C. A., Horton, W. A., & Annegers, J. F. (1987). Mortality in achondroplasia. American Journal of Human Genetics, 41(3), 454–464.

7. Hecht, J. T., Horton, W. A., Reid, C. S., Pyeritz, R. E., & Chakraborty, R. (1989). Growth of the foramen magnum in achondroplasia. American Journal of Medical Genetics, 32(4), 528–535.

8. Horton, W. A., Hall, J. G., & Hecht, J. T. (2007). Achondroplasia. Lancet, 370(9582), 162–172.

9. Simmons, K., Hashmi, S. S., Scheuerle, A., Canfield, M., & Hecht, J. T. (2014). Mortality in babies with achondroplasia: revisited. Birth Defects Research. Part A, Clinical and Molecular Teratology, 100(4), 247–249.

10. Hashmi, S. S., Gamble, C., Hoover-Fong, J., et al. (2018). Multicenter study of mortality in achondroplasia. American Journal of Medical Genetics Part A, 176(11), 2359-2364.

11. Hoover-Fong J., Bober M., Hashmi S., et al. (2018). Achondroplasia natural history: a large, ongoing multi-center cohort study. Journal of Bone and Mineral Research, 32 (Suppl 1), 121–122.

12. Ireland, P. J., Pacey, V., Zankl, A., Edwards, P., Johnson, L. M., & Savarirayan, R. (2014). Optimal management of complications associated with achondroplasia. Application of Clinical Genetics, 7, 117-125.

13. Gollust, S. E., Thompson, R. E., Gooding, H. C., & Biesecker, B. B. (2003). Living with achondroplasia in an average-sized world: an assessment of quality of life. American Journal of Medical Genetics Part A, 120A(4), 447–458.

14. Hoover-Fong, J. E., Schulze, K. J., McGready, J., Barnes, H., & Scott, C. I. (2008). Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height. American Journal of Clinical Nutrition, 88(2), 364–371.

15. Hoover-Fong, J., McGready, J., Schulze, K., Alade, A. Y., & Scott, C. I. (2017). A height-for-age growth reference for children with achondroplasia: expanded applications and comparison with original reference data. American Journal of Medical Genetics Part A, 173(5), 1226–1230.

16. del Pino, M., Fano, V., & Adamo, P. (2018). Growth velocity and biological variables during puberty in achondroplasia. Journal of Pediatric Endocrinology and Metabolism, 31(4), 421–428.

17. Kopits, S. E. (1988). Orthopedic aspects of achondroplasia in children. Basic Life Sciences, 48, 189–197.

18. Kitoh, H., Kitakoji, T., Kurita, K., Katoh, M., & Takamine, Y. (2002). Deformities of the elbow in achondroplasia. Journal of Bone and Joint Surgery. British Volume, 84(5), 680–683.

19. Ireland, P. J., Donaghey, S., Mcgill, J., et al. (2012). Development in children with achondroplasia: a prospective clinical cohort study. Developmental Medicine and Child Neurology, 54(6), 532–537.

20. Galasso, C., Siracusano, M., El Malhany, N., Cerminara, C., Pitzianti, M., & Terribili, M. (2016). Cognitive phenotype and language skills in children with achondroplasia. Minerva Pediatrica. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26899672.

21. Hunter, A. G., Bankier, A., Rogers, J. G., Sillence, D., & Scott, C. I. Jr. (1998). Medical complications of achondroplasia: a multicentre patient review. Journal of Medical Genetics, 35(9), 705–712.

22. Lee, S. T., Song, H. R., Mahajan, R., Makwana, V., Suh, S. W., & Lee, S. H. (2007). Development of genu varum in achondroplasia. The Journal of Bone and Joint Surgery. British Volume, 89–B(1), 57–61.

23. Kaissi, A. A., Farr, S., Ganger, R., Hofstaetter, J. G., Klaushofer, K., & Grill, F. (2013). Treatment of varus deformities of the lower limbs in patients with achondroplasia and hypochondroplasia. The Open Orthopaedics Journal, 7, 33–39.

24. Misra, S. N., & Morgan, H. W. (2003). Thoracolumbar spinal deformity in achondroplasia. Neurosurgical Focus, 14(1), e4.

25. Karikari, I. O., Mehta, A. I., Solakoglu, C., Bagley, C. A., Ain, M. C., & Gottfried, O. N. (2012). Sagittal spinopelvic parameters in children with achondroplasia: identification of 2 distinct groups. Journal of Neurosurgery: Spine, 17(1), 57–60.

26. Aldegheri, R., & Dall'Oca, C. (2001). Limb lengthening in short stature patients. Journal of Pediatric Orthopedics Part B, 10(3), 238–247.

27. Shirley, E. D., & Ain, M. C. (2009). Achondroplasia: manifestations and treatment. The Journal of the American Academy of Orthopaedic Surgeons, 17(4), 231–241.

28. Donaldson, J., Aftab, S., & Bradish, C. (2015). Achondroplasia and limb lengthening: Results in a UK cohort and review of the literature. Journal of Orthopaedics, 12(1), 31-34.

29. Stamoyannou, L., Karachaliou, F., Neou, P., Papataxiarchou, K., Pistevos, G., & Bartsocas, C. S. (1997). Growth and growth hormone therapy in children with achondroplasia: a two-year experience. American Journal of Medical Genetics, 72(1), 71–76.

30. Merker, A., Neumeyer, L., Hertel, N. T., et al. (2018). Growth in achondroplasia: development of height, weight, head circumference, and body mass index in a European cohort. American Journal of Medical Genetics Part A, 176(8), 1723–1734.

31. Horton, W. A., Rotter, J. I., Rimoin, D. L., Scott, C. I., & Hall, J. G. (1978). Standard growth curves for achondroplasia. Journal of Pediatrics, 93(3), 435–438.

32. Coste, J., Pouchot, J., & Carel, J.-C. (2012). Height and health-related quality of life: a nationwide population study. Journal of Clinical Endocrinology and Metabolism, 97(9), 3231–3239.

33. Christensen, T. L., Djurhuus, C. B., Clayton, P., & Christiansen, J. S. (2007). An evaluation of the relationship between adult height and health-related quality of life in the general UK population. Clinical Endocrinology (Oxf), 67(3), 407–412.

34. Silva, N., Bullinger, M., Sommer, R., Rohenkohl, A., Witt, S., & Quitmann, J. (2018). Children's psychosocial functioning and parents' quality of life in paediatric short stature: the mediating role of caregiving stress. Clinical Psychology and Psychotherapy, 25(1), e107–e118.

35. Ayyar, V. S. (2011). History of growth hormone therapy. Indian Journal of Endocrinology and Metabolism, 15(Suppl 3), S162-165.

36. Kim, S.-J., Balce, G. C., Agashe, M. V., Song, S.-H., & Song, H.-R. (2012). Is bilateral lower limb lengthening appropriate for achondroplasia?: midterm analysis of the complications and quality of life. Clinical Orthopaedics and Related Research, 470(2), 616–621.

37. Kleiber, M. (1932). Body size and metabolism. Hilgardia, 6(11), 315–353.

38. Mahmood, I. (2014). Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. Clinical Pharmacokinetics, 53(4), 327–346.

39. Germovsek, E., Barker, C. I., Sharland, M., & Standing, J. F. (2017). Scaling clearance in paediatric pharmacokinetics: all models are wrong, which are useful? British Journal of Clinical Pharmacology, 83(4), 777–790.

40. Dimeglio, A., & Canavese, F. (2012). The growing spine: how spinal deformities influence normal spine and thoracic cage growth. European Spine Journal, 21(1), 64−70.

41. Calandrelli, R., Panfili, M., D'Apolito, G., Zampino, G., Pedicelli, A., Pilato, F., & Colosimo, C. (2017). Quantitative approach to the posterior cranial fossa and craniocervical junction in asymptomatic children with achondroplasia. Neuroradiology, 59(10), 1031–1041.

42. del Pino, M., Fano, V., & Lejarraga, H. (2011). Growth references for height, weight, and head circumference for Argentine children with achondroplasia. European Journal of Pediatrics, 170(4), 453–459.

43. del Pino, M., Fano, V., & Adamo, P. (2019). Height growth velocity during infancy and childhood in achondroplasia. American Journal of Medical Genetics Part A, 179(6), 1001-1009.

44. WHO Multicentre Growth Reference Study Group. (2006). WHO child growth standards based on length/height, weight and age. Acta Paediatrica Supplement, 450, 76–85.

45. Kubota T, Adachi M, Kitaoka T, et al. Clinical Practice Guidelines for Achondroplasia. Clin Pediatr Endocrinol. 2020;29(1):25-42. doi:10.1297/cpe.29.25.

46. Olney RC, Permuy JW, Prickett TC, Han JC, Espiner EA. Amino-terminal propeptide of C-type natriuretic peptide (NTproCNP) predicts height velocity in healthy children. *Clin Endocrinol (Oxf)*. 2012;77(3):416-422. doi:10.1111/j.1365-2265.2012.04392.x.

47. R. F. Coghlan, J. A. Oberdorf, S. Sienko, M. D. Aiona, B. A. Boston, K. J. Connelly, C. Bahney, J. LaRouche, S. M. Almubarak, D. T. Coleman, I. Girkontaite, K. von der Mark, G. P. Lunstrum, W. A. Horton, A degradation fragment of type X collagen is a real-time marker for bone growth velocity. *Sci. Transl. Med.* 9, eaan4669 (2017).