# A PHASE 2 OPEN LABEL EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF RECIFERCEPT IN CHILDREN WITH ACHONDROPLASIA

| | |
|---|---|
| **Study Intervention Number:** | PF-07256472 |
| **Study Intervention Name:** | Recifercept |
| CCI [redacted] | [redacted] |
| **EudraCT Number:** | 2021-003149-39 |
| **Protocol Number:** | C4181008 |
| **Phase:** | Phase 2 |

**Brief Title:** *Phase 2 study of long-term safety, tolerability, PK and efficacy of recifercept in achondroplasia*

## Document History

| Document | Version Date |
|---|---|
| Amendment 1 | 17 May 2022 |
| Original protocol | 02 August 2021 |

## Amendment 1 - 17 May 2022

## Overall Rationale for the Amendment:

Country Specific Amendment.

| Section # and Name | Description of Change | Brief Rationale | Substantial or Nonsubstantial |
|---|---|---|---|
| Section 10.6.1 Italy | Addition of Exclusion Criteria for Liver & Renal Failure.<br>Tanner Stage V added as an additional discontinuation criteria.<br>Addition of eDMC review.<br>Additional contraception options added as per the CTFG Recommendations related to contraception and pregnancy testing in clinical trials, Version 1.1. | Request by Italian Medicine Agency (AIFA) | Substantial |
| Section 10.6.2 Denmark | Additional details added to preparation & dispensing and participant home health nursing procedures in line with Danish Medicine Agency's Guidance on the Implementation of Decentralised Elements in Clinical Trials with Medicinal Products, Version 2.0, September 2021. | Request by Danish Medicine Agency (DKMA) | Substantial |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Brief Title:** *Phase 2 study of long-term safety, tolerability, PK and efficacy of recifercept in achondroplasia*

### Rationale

The purpose of the study is to investigate the long-term safety, tolerability, PK and efficacy of recifercept in children with achondroplasia. Safety has been demonstrated in preclinical studies, in healthy adult volunteers and an ongoing Phase 2 study in children with Achondroplasia up to a dose of 1.5 mg/kg QD.

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, Endpoints, and Estimands

| Objectives | Estimands | Endpoints |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| • Evaluate the long-term safety and tolerability of recifercept doses and dosing regimes in participants aged ≥15 m to <12 years with achondroplasia. | N/A. | Long-term Safety and tolerability of recifercept as assessed through frequency and severity of AEs/SAEs. |
| • To assess long-term 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.<br><br>Population-level summary: ratio between participants in the trial and a reference population [Merker et al, 2018][23] in growth of height at 24 month; ratio between treated and reference population is observed change-from-baseline of treated participants standardized by reference participant given age and gender. | • Increase in height growth above expected in reference population [Merker et al, 2018].[23] |
| **Secondary:** | **Secondary:** | **Secondary:** |
| • To evaluate the PK of recifercept in children aged ≥15m to ≤12 years old with achondroplasia. | | Population PK characterization in children aged ≥15m to <12years old with achondroplasia. 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.<br>• Arm span to height/length difference.<br>• Knee height:lower segment ratio.<br>• Occipito-frontal circumference.<br>• Ratio of occipito-frontal distance to occipito-mid-face measurements.<br>• z-score of the above proportionality and skull morphology where achondroplasia reference datasets exist (occipito-frontal circumference, arm span, sitting height).<br>• Fixed flexion angles at elbow.<br>• Polysomnography parameters in those with pre-existing sleep-disordered breathing at the time of enrollment.<br>• BMI.<br>• Waist:chest circumference ratio. |
| • Assess change in individual safety parameters. | | • Change from baseline in safety labs, vital signs, physical examination.<br>• Rate of ADAs. |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] |

## Overall Design

## Brief Summary

This is a Phase 2 open label extension study to assess long-term safety, tolerability, PK, and efficacy of recifercept. The study will be offered to approximately 63 participants from the Phase 2 C4181005 study will be offered to participate who, in the opinion of the investigator, continue to have a positive risk: benefit profile. All enrolled participants will continue treatment with recifercept on 1 of 3 doses (1mg/kg QW, 2 mg/kg BIW, 1.5 mg/kg QD) for up to 24 months. Participants will be children diagnosed with achondroplasia aged ≥15 months to ≤12 years (inclusive); who have completed the C4181005 Phase 2 protocol.

Participants will continue to receive recifercept at the dose previously received in the Phase 2 study or at the therapeutic dose once this is identified.

**Number of Participants**

Approximately 63 participants will be enrolled to study intervention.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity.

**Intervention Groups and Duration**

All participants will continue to receive recifercept at 1 of the following 3 doses of recifercept: 1 mg/kg QW, 2 mg/kg BIW or 1.5 mg/kg QD until a therapeutic dose is identified. All doses are given by SC injection. Dose will be adjusted according to weight every 3 months.

**Data Monitoring Committee or Other Independent Oversight Committee: Yes**

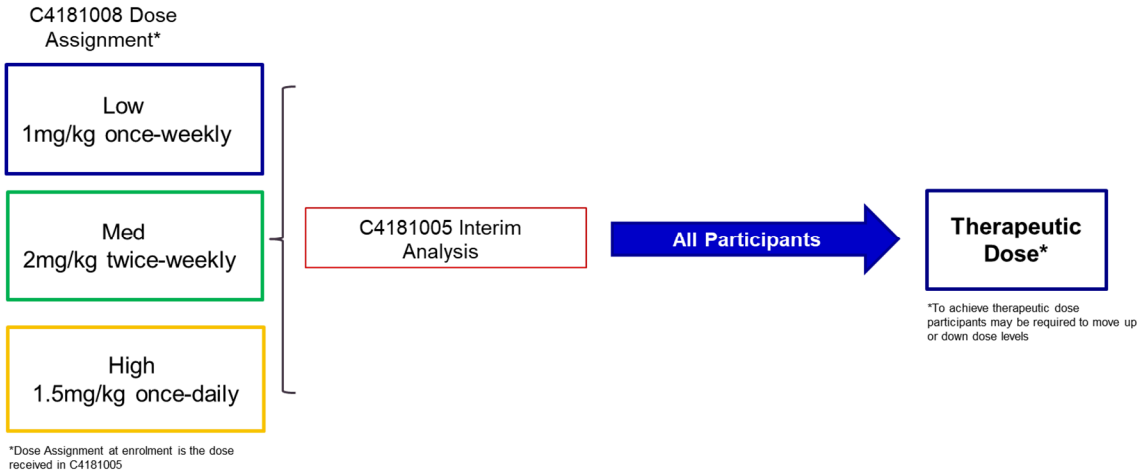
An internal review committee will assess the safety and, where relevant, PK data on a regular basis.

**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 24 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 24.

## 1.2. Schema


C4181008 Dose Assignment*
Low 1mg/kg once-weekly
Med 2mg/kg twice-weekly
High 1.5mg/kg once-daily
*Dose Assignment at enrolment is the dose received in C4181005
C4181005 Interim Analysis
All Participants
Therapeutic Dose*
*To achieve therapeutic dose participants may be required to move up or down dose levels

## 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 well-being of the participant.

| | Enrollment | M1[b] | M2[b] | M3 | M4[b] | M5[b] | M6 | M7[b] | M8[b] | M9 | M10[b] | M11[b] | M12 | M13[b] | M14[b] | M15 | M16[b] | M17[b] | M18 | M19[b] | M20[b] | M21 | M22[b] | M23[b] | M24 | Early Term/ Discon. | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Identifier** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** |
| **Days Relative to Day 1[a]** | **1** | **29** | **61** | **91** | **121** | **151** | **181** | **211** | **241** | **271** | **301** | **331** | **361** | **391** | **421** | **451** | **481** | **511** | **541** | **571** | **601** | **631** | **661** | **691** | **721** | | |
| **Visit Window (Days)** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** |
| Informed consent/assent | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demography[c] | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Contraception check[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Inclusion/Exclusion Check | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomisation | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination[d] | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| Neurological examination | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| Weight | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| Vital signs | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| Hematology | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| Blood chemistry | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| Study intervention dispensing | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Study intervention administration | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | | |
| Dosing diary | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | | |
| Anthropometry | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |

| | Enrollment | M1[b] | M2[b] | M3 | M4[b] | M5[b] | M6 | M7[b] | M8[b] | M9 | M10[b] | M11[b] | M12 | M13[b] | M14[b] | M15 | M16[b] | M17[b] | M18 | M19[b] | M20[b] | M21 | M22[b] | M23[b] | M24 | Early Term/ Discon. | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Identifier** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** |
| **Days Relative to Day 1[a]** | **1** | **29** | **61** | **91** | **121** | **151** | **181** | **211** | **241** | **271** | **301** | **331** | **361** | **391** | **421** | **451** | **481** | **511** | **541** | **571** | **601** | **631** | **661** | **691** | **721** | | |
| **Visit Window (Days)** | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 |
| Polysomnography[f] | | | | | | | | | | | | | X | | | | | | | | | | | | X | X | |
| Tanner staging | | | | | | | [redacted] | | | | | | [redacted] | | | | | | [redacted] | | | | | | [redacted] | [redacted] | |
| [redacted] | | | | | | | | | | | | | X | | | | | | | | | | | | X | | |
| [redacted] | | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | [redacted] | |
| | | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | [redacted] | |
| Acceptability and Tolerability Questionnaire | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| EQ-5D | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| PK sampling[g] (pre-dose) | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | |
| Immunogenicity sampling[g] (pre-dose) | | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X | X[i] |
| [redacted] | | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | | | [redacted] | [redacted] | |
| Concomitant treatment(s) | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → |
| Serious and non-serious adverse event monitoring | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → |

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

b. Remote telephone visit to caregiver to confirm receipt of drug shipment (if required), dosing diary completion, AEs/concomitant medications and contraception check.

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

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

e. Urine pregnancy testing is required at screening and then only for those participants who are assessed as WOCBP, urine pregnancy test with sensitivity of at least 25 mIU/ml acceptable at each month. A serum pregnancy test will be analysed from the chemistry sample taken every 3 months. Contraception check is applicable to both WOCBP and sexually active male participants.

f. Sleep study to be performed only in participants with a documented current diagnosis of sleep-disordered breathing prior to enrollment. Baseline PSG data can be within 6 months prior to enrollment.

g. CCI

i. Follow up visit conducted by phone. If required for ADA positive participants, additional immunogenicity sampling may be required.

## 2. INTRODUCTION

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.

Achondroplasia is the most common skeletal dysplasia in humans with a prevalence of around 4 per 100,000[1] 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 centers 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.[2] 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.[3-6] There is associated neurodevelopment and psychosocial morbidity[6,7] with increased mortality throughout life that is most pronounced in early childhood.[8-12]

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.[12,13] There is also associated overall developmental motor delay and inter-vertebral disc abnormality which can be present even very early in life.[15]

At present, there is no approved cure or specific pharmacologic treatment for achondroplasia. 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[16,17] occur in up to 70% of patients.[18]

### 2.1. Study Rationale

The purpose of the study is to investigate the long-term safety, tolerability, PK and efficacy of recifercept in children with achondroplasia. Safety has been demonstrated in preclinical studies, in healthy adult volunteers and an ongoing Phase 2 study in children with Achondroplasia up to a dose of 1.5 mg/kg daily (QD); 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 restoration 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 BIW, and the optimally effective dose is 10 mg/kg BIW. 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 March 2021, the Phase 2 study enrolled a total of 6 participants from 6 to 10 years old. There were 3 participants randomized to 1 mg/kg QW arm and 3 participants randomized to 2 mg/kg BIW dosing arm. A total of 16 adverse events were reported, of which 9 were assessed as related to study drug - ISRs. ISRs were reported as erythema/pruritis at the injection site. All AEs were mild severity and there were no SAEs. There were no other clinically significant laboratory abnormalities or physical examination/vital sign changes. Following, 1 mg/kg QW and 2 mg/kg BIW SC administration, observed serum recifercept concentrations were lower than the predicted exposures for a 20 kg child with achondroplasia using the PopPK model. ADA samples are being collected and characterized throughout the study. In addition, assay development is ongoing for the assessment of ADAs for detection of NAbs.

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 SAD part of the study was 0.3–20 mg/kg and in the MAD part was 1 mg/kg and 3 mg/kg BIW and 3 and 10 mg/kg QW for 4 weeks. Signs and symptoms of an injection site/infusion site reaction, including erythema, swelling, pain, inflammation, and pruritis, were the most frequently reported AEs 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 SAEs occurred during the study.

In the SAD portion of the study, all participants were ADA- prior to treatment with recifercept. A confirmed 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 $T_{max}$ increases with increasing dose. The mean $t_{1/2}$ 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 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 QW 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 ISRs. | 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. | 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.<br><br>The potential use of conscious sedation as an alternative to general anaesthetic is generally acceptable if the site is trained and experienced in using this technique for obtaining MRIs<br><br>MRIs will only be performed at centers 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 to minimize risk to study participants, the potential risks identified in association with recifercept are justified by the anticipated benefits that may be afforded to participants with achondroplasia.

## 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| • Evaluate the long-term safety and tolerability of recifercept doses and dosing regimes in participants aged ≥15m to ≤12 years with achondroplasia. | • N/A. | Long-term safety and tolerability of recifercept as assessed through frequency and severity of AEs/SAEs. |
| • To assess long-term 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.<br>• Population-level summary: ratio between participants in the trial and a reference population [Merker et al, 2018][23] in growth of height at 24 month; ratio between treated and reference population is observed change-from-baseline of treated participants standardized by reference participant given age and gender. | • Increase in height growth above expected in reference population [Merker et al, 2018].[23] |
| **Secondary:** | **Secondary:** | **Secondary:** |
| • To evaluate the PK of recifercept in children aged ≥15m to ≤12 years old with . | | • Population PK characterization in children aged ≥15m to ≤12 years old with achondroplasia. 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.<br>• Arm span to height/length difference.<br>• Knee height:lower segment ratio.<br>• Occipito-frontal circumference.<br>• Ratio of occipito-frontal distance to occipito-mid-face measurements.<br>• z-score of the above proportionality and skull morphology where achondroplasia reference datasets exist (occipito-frontal circumference, arm span, sitting height).<br>• Fixed flexion angles at elbow.<br>• Polysomnography parameters in those with pre-existing sleep-disordered breathing at the time of enrollment.<br>• BMI.<br>• Waist:chest circumference ratio. |
| • Assess change in individual safety parameters. | | • Change from baseline in safety labs, vital signs, physical examination.<br>• Rate of ADAs. |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] |

## 4. STUDY DESIGN

### 4.1. Overall Design

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

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

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

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

### 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 centers,[19,20] but persisting until adolescence in the long bones.[21-23] 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.

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 of contraception.

Participants aged less than 3 years at enrollment will continue to undergo MRI scanning of the brain and cervical spinal cord every 12 months up to the age of 5 years.[24] 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.[25]

Serum and CCI [redacted] samples will be taken during the study as indicated in the SoA. Further details can be found in Section 8.6.

#### 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. The assessments conducted in this protocol are the same as the C4181005 Phase 2 study.

### 4.2.2. Diversity of Study Population

Reasonable attempts will be made to retain participants to ensure the study population is representative of the patient population that will use recifercept in clinical practice.

### 4.2.3. Adjudication Committee

Not Applicable.

### 4.2.4. Choice of Contraception/Barrier Requirements

Studies to evaluate the development toxicity of recifercept have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

## 4.3. Justification for Dose

All participants will continue to receive 1 of 3doses of recifercept (1 mg/kg QW, 2 mg/kg BIW or 1.5 mg/kg QD) as assigned in C4181005 study or at the therapeutic dose once this is identified. Dose will be adjusted according to weight every 3 months.

PK will be assessed on an ongoing basis using sparse sampling approach to inform and update the PopPK model.

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

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.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

- The participant has reached end of puberty (Tanner Stage V);
- The participant is enrolled in any other interventional study;
- The participant is to receive any growth hormone, IGF-1, anabolic steroids, or any other drug expected to affect growth velocity.

# 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 nonmedical 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. Male and female participants between the ages of ≥15 months to ≤12 years inclusive, at Visit 1 (Screen 1).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

**Type of Participant and Disease Characteristics:**

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests lifestyle considerations and other study procedures.

3. Completed the C4181005 Phase 2 study.

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

**Informed Consent:**

5. 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.

6. Following receipt of oral and written information about the trial, the child (depending on local IRB/independent EC requirements) must provide assent, and 1 or both (according to local regulations) parent(s) or legal 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 >95$^{th}$ percentile on Hoover-Fong BMI charts) [Hoover-Fong et al, 2008].[26]

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

5. Body weight ≥45 kg.

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

**Prior/Concomitant Therapy:**

7. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8 Concomitant Therapy.

8. History of any prior treatment with human growth hormone or related products (including 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 µg/day beclomethasone 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.

**Prior/Concurrent Clinical Study Experience:**

15. History of receipt of any other (except recifercept) IP for achondroplasia or that may affect growth/interpretation of growth parameters.

16. Previous administration with an investigational drug (not for achondroplasia/growth affecting) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (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

Participants that become a WOCBP (defined as reaching menarche) during the course of the study, the investigator or his or her designee, in consultation with the participant, 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 (see Appendix 4 Section 10.4.4). 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 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.

### 5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not Applicable.

## 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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 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)** | Recifercept |
| **Type** | Biologic. |
| **Dose Formulation** | Lyophilized powder for solution for injection. |
| **Unit Dose Strength(s)** | 50 mg/vial. |
| **Dosage Level(s)** | 1mg/kg - QW<br>2mg/kg – BIW<br>1.5mg/kg - QD |
| **Route of Administration** | SC injection. |
| **Use** | Experimental. |
| **IMP or NIMP** | IMP. |
| **Sourcing** | Provided centrally by the sponsor.<br><br>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 supplies.<br>Vials are single-use only. |
| **Current/Former Name(s) or Alias(es)** | TA-46. |

### 6.1.1. Administration

Administer study intervention according to the SC Dosing Instructions (see Appendix 8). Study intervention should not be self-administered by the participant.

### 6.1.2. Medical Devices

Not Applicable.

## 6.2. Preparation, Handling, Storage, and Accountability

1. 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.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply. All study interventions 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.

3. 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.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. See the IP manual for storage conditions of the study intervention once reconstituted and/or diluted.

8. 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. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

9. 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

See the IP manual for instructions on how to prepare the study intervention for administration. 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. A second staff member will verify the dispensing. All persons who are responsible for dose preparation and dispensing of IP must be listed on the Delegation of Authority log.

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.

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 and 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 and 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

There is no blinding requirement in this open label study.

### 6.3.1. Allocation to Study Intervention

This is an open-label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

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. Breaking the Blind

Not applicable.

## 6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. 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 has supported home dosing then this will be recorded in the dosing diary. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of vials dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

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.

A home health care service may be utilized to facilitate certain activities per the Schedule of Activities, or when additional caregivers are trained. Any requests for home health support should be submitted to the sponsor for approval.

## 6.5. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose will not exceed 1.5 mg/kg QD.

In case a dose reduction is necessary, the study intervention will be administered as follows:

| | |
|---|---|
| **High Dose (1.5 mg/kg QD)** | Participants experiencing continued tolerability issues such as injection site reactions may be reduced to 2 mg/kg BIW and then if required to 1 mg/kg QW. |
| **Medium Dose (2 mg/kg BIW)** | Participants experiencing continued tolerability issues such as injection site reactions may be reduced to 1 mg/kg QW, if persistent then participant should be discontinued. |
| **Low (1 mg/kg QW)** | Participants experiencing continued tolerability issues such as ISRs should be discontinued from the study. |

Participants that have been switched to any lower dose must stay on that dose for the remainder of the study.

### 6.6. Continued Access to Study Intervention After the End of the Study

No intervention will be provided to study participants at the end of their study participation.

### 6.7. Treatment of Overdose

For this study, any dose of recifercept greater than 20 mg/kg within a 7-day period will be considered an overdose.

There is no 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 5 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 Pfizer 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.

### 6.8. Concomitant Therapy

#### 6.8.1. 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 ENT bone procedures.

#### 6.8.2. 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.

### 6.8.3. Permitted During the Study;

Participants who experience injection site reactions may be treated with topical corticosteroids as needed. The type of treatment, dose and duration must be recorded in the eCRF.

### 6.8.4. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with recifercept, standard medical supportive care must be provided to manage the AEs.

## 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

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

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to complete the final follow-up visit. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

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 participant withdrawal. Additionally, if a participant

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 6.8.

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.

### 7.1.1. Liver and Renal Injury

Participants who develop hepatic or renal impairment during the study may be required to discontinue the study intervention. Isolated elevations should be followed up with a repeat blood sample 7 days later.

#### 7.1.1.1. Renal Impairment

- eGFR of <60 mL/min.

(eGFR is to be calculated using the serum creatinine based on updated "bedside" Schwartz formula for pediatric patients (CrCL (mL/min/1.73 m2) = 0.413 * Height (cms)/ Serum cr (mg/dL).

#### 7.1.1.2. Hepatic Impairment

- AST ≥1.5 x ULN;
- ALT ≥1.5 x ULN.

### 7.1.2. ECG Changes

Not applicable.

### 7.1.3. Pregnancy

Any participant who becomes pregnant during the study will be immediately discontinued and followed up according to Section 8.3.3.

### 7.1.4. Lack of Efficacy

Not applicable.

### 7.1.5. Temporary Discontinuation

Not applicable.

### 7.1.6. Rechallenge

Not applicable.

## 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 study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

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

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

The participant will be permanently discontinued from the study intervention and the study at that time.

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.

### 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/attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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 or equivalent 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.

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 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. 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 105 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer.

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. CCI [redacted].

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:

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

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

- Standing height (length for participants <2 years of age);
- Sitting height (crown-rump length for participants <2 years of age);
- 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 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.

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.

### 8.1.2. Polysomnography/Sleep Study

In participants with a documented current diagnosis of sleep disordered breathing prior to enrollment, baseline sleep study data will be collected. Baseline PSG data can be within 6 months prior to 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 12 months and at the end of the study.

CCI

- CCI

CCI [redacted]

### 8.1.7. Acceptability and Tolerability Questionnaire - Achondroplasia

The Acceptability and Tolerability Questionnaire – Achondroplasia will be used to measure the acceptability and tolerability of the SC 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.

### 8.1.8. EQ-5D-Yand - (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 HRQoL states, consisting of 5 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 3 levels of severity (no problems, some problems, or a lot of problems) within a particular EQ-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.

### 8.1.9. 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 of age 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 Examinations

A complete 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 part of the anthropometric measurements collected.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.1.2.

### 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

Oral, axillary, skin or temporal artery temperature, PR, respiratory rate, and BP will be assessed.

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

BP and PR measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 PR and 1 BP measurements. If the BP reading is abnormal then this should be repeated after 1 minute. Vital signs will be collected in the eCRF.

### 8.2.4. 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. 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 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.

### 8.2.5. 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 second negative pregnancy test result will be required at the baseline visit prior to 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.

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/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.

Contraception check is applicable to both WOCBP and sexually active male participants.

### 8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Not Applicable.

## 8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc.).

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).

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading 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 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 a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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.

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

If the participant 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 permanently 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 information on 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 3. 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.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

### 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 or 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 toward 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. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study 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 EDP:

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

The investigator must report EDB 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 EDB 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 EDB 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 EDB.

### 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 any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be 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 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?

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 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

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

### 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 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. Pharmacokinetics

Trough blood samples of approximately 2 mL, to provide a minimum of serum volume 1 mL, 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. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing.

Samples will be used to evaluate the population PK of recifercept. Each serum sample will be divided into 2 aliquots (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, CCI [redacted]

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.

CCI

CCI

[redacted]

CCI [redacted]

### 8.7. 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.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, CCI [redacted] These data will be used for internal exploratory purposes.

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.

CCI [redacted]

## 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. Statistical Hypotheses

### 9.1.1. Estimands

Not applicable.

## 9.2. Analysis Sets

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

| Participant Analysis Set | Description |
|---|---|
| FAS/Safety | All participants receiving at least 1 dose of recifercept. Participants will be analyzed according to the dose they actually received. |
| PPAS | All participants receiving at least 1 dose of recifercept and have complete data at baseline through month 24 and without protocol deviations that were thought to impact the efficacy evaluation during the treatment period.<br><br>Participants will be analyzed according to their randomized dose. |
| PK Concentration set | All participants who received at least 1 dose of recifercept and have at least 1 evaluable concentration result. |

## 9.3. Statistical Analyses

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

### 9.3.1. 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.

### 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

*Efficacy*

The primary efficacy endpoint of change from baseline of height at 24 months will be analyzed using an 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. The population for the primary analysis will be based on the FAS.

*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.

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 24 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 24.

### 9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

The secondary efficacy endpoint of change from baseline of the difference of arm span to height difference at 24 months will be analyzed using an 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.

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

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### 9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

### 9.3.6. 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.

### 9.3.7. 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.

## 9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

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# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

### 10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 the ICH GCP guidelines 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 and his/her parent(s)/legal guardian and answer all questions regarding the study. The participant and his/her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own assent, the source documents must record why the participant did not provide assent (for example, minor child), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority during the study, as recognized under local law, they must be reconsented as adults to remain in the study. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, they must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. Participant's parent(s)/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's parent(s)/legal guardian and the study participant as applicable 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's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian is fully informed about his or her right to access and correct his or her child's personal data and to withdraw consent for the processing of his or her child's personal data keeping in mind the privacy rights that may restrict access of older adolescents medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

### 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 ID. 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. Committees Structure

#### 10.1.5.1. Data Monitoring Committee

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

The IRC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, investigators, as appropriate.

### 10.1.6. 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 data from these trials available 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.

### 10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

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, including definition of study critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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 retain 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.

### 10.1.8. 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 and its origin can be found in the clinical monitoring plan which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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 guidelines, and all applicable regulatory requirements.

### 10.1.9. 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 enrollment into the 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 the ICH 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.

### 10.1.10. 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.

### 10.1.11. 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 for study-related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, 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 1. Protocol-Required Safety Laboratory Assessments**

| Hematology | Chemistry | Other |
|---|---|---|
| Hemoglobin<br>Hematocrit<br>RBC count<br>MCV<br>MCH<br>MCHC<br>Platelet count<br>WBC count<br>Total neutrophils (Abs)<br>Eosinophils (Abs)<br>Monocytes (Abs)<br>Basophils (Abs)<br>Lymphocytes (Abs) | BUN and creatinine<br>Calcium<br>Sodium<br>Potassium<br>Chloride<br>Total $CO_2$ (bicarbonate)<br>AST, ALT<br>Total bilirubin<br>Alkaline phosphatase<br>Uric acid<br>Albumin<br>Total protein<br>Phosphate (non-fasted) | At times listed in SOA:<br>• 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.

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.

## 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.<br><br>• 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:<br><br>  • Is associated with accompanying symptoms.<br><br>  • Requires additional diagnostic testing or medical/surgical intervention.<br><br>  • 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.<br><br>• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.<br><br>• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.<br><br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br><br>• 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 or 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 that 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 an SAE

**An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:**

**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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Is a 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 participant 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.

**g. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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.

### 10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious 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, | All AEs or SAEs associated with exposure during pregnancy or breastfeeding<br><br>**Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF. | All instances of EDP are reported (whether or not there is an associated SAE)*<br><br>All instances of EDB are reported (whether or not there is an associated SAE). ** |
| Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB). | None. Exposure to a study non-participant is not collected on the CRF. | The exposure (whether or not there is an associated AE or SAE) must be reported.*** |

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 or 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: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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.<br><br>• 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.<br><br>• New or updated information will be recorded in the originally submitted documents.<br><br>• 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 CT SAE Report Form** |
|---|
| • Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.<br><br>• 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.<br><br>• 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 and Barrier 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 111 days after the last dose of study intervention, which corresponds to the 21 days 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 enrollment 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 28 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 <u>not</u> 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 “adaptors” 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 Hy's law cases, 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, or 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, 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: Country-Specific Requirements

### 10.6.1. Italy

#### 10.6.1.1. Exclusion Criteria

In addition to the discontinuation criteria in Section 7.1.1.1 & Section 7.1.1.2 the following additional exclusion criteria will apply to participants enrolled in Italy.

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).

#### 10.6.1.2. Discontinuation Criteria

In addition to the other discontinuation criteria in Section 7, Participants who completed Tanner stage V should be considered to have completed puberty and be discontinued from the study.

#### 10.6.1.3. Data Monitoring Committee

This study will use an eDMC. The eDMC is independent of the study team and includes internal Pfizer members. The eDMC charter describes the role of the eDMC in more detail. The eDMC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the eDMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, investigators, as appropriate.

#### 10.6.1.4. Contraception Methods

Due to the age of the participants, length of the study, and in accordance with the Clinical Trials Facilitation and Coordination Group (CTFG) - Recommendations related to contraception and pregnancy testing in clinical trials Version 1.1.[31] The following revisions have been made to the contraceptive requirements.

The addition of alternatives to sexual abstinence including highly effective hormonal contraceptives and barrier methods are to be used depending on participant preference and local guidelines as appropriate. The requirements of one highly effective method and duration of contraceptive use remain unchanged**.**

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral + barrier*;
    - Intravaginal + barrier*;

- Transdermal + barrier*.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral + barrier*;
   - Injectable + barrier*.

*Acceptable barrier methods to be used concomitantly with options above for the study include any of the following:

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

### 10.6.2. Denmark

The following requirements apply for Denmark, in accordance with local regulation; Section 11 The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products Version 2.0, September 2021.[32]

#### 10.6.2.1. Preparation & Dispensing

Recifercept may be shipped by an appropriate third-party courier or study investigator to study participants if permitted by local regulations and in accordance with storage and transportation requirements for recifercept. The overall responsibility for IMP activities remains with the study investigator as per ICH GCP Section 4.0.

#### 10.6.2.2. Participant Compliance and Home Administration

A home health care service may be utilized to facilitate certain activities per the SoA, in the event of a public emergency, such as COVID-19 or when additional caregivers are trained, see Appendix 10.7.5 Home Health Visits.

All home health care nurses and their responsibilities are recorded on the delegation of authority log. However, the study investigator maintains overall responsibility for all trial activities as per ICH GCP Section 4.0.

In the event that any visits are conducted in the home, a report is provided to the site detailing the assessments conducted, including any completed source documents that were collected to be included in the eCRF and participants medical file.

Any requests for home health support should be submitted to the sponsor for approval.

CCI [redacted]

[redacted]

## 10.7. Appendix 7: 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).

### 10.7.1. 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 SoA 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 10.4.4 of this appendix regarding pregnancy tests.

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

### 10.7.2. Alternative Facilities for Safety Assessments

### 10.7.3. 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 mIU/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.

### 10.7.4. 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.

### 10.7.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the SoA. 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;
- Administer PROs.

### 10.7.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or serious 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.

### 10.7.7. 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.

### 10.7.8. Internal Review Committee

An internal review committee will assess the safety and, where relevant, PK data on a regular basis.

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

## 10.8. Appendix 8: SC Dosing Instructions

**SC DOSING INSTRUCTIONS**

**GENERAL INSTRUCTIONS**

- Allow prepared syringes with the medication to reach ambient 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.

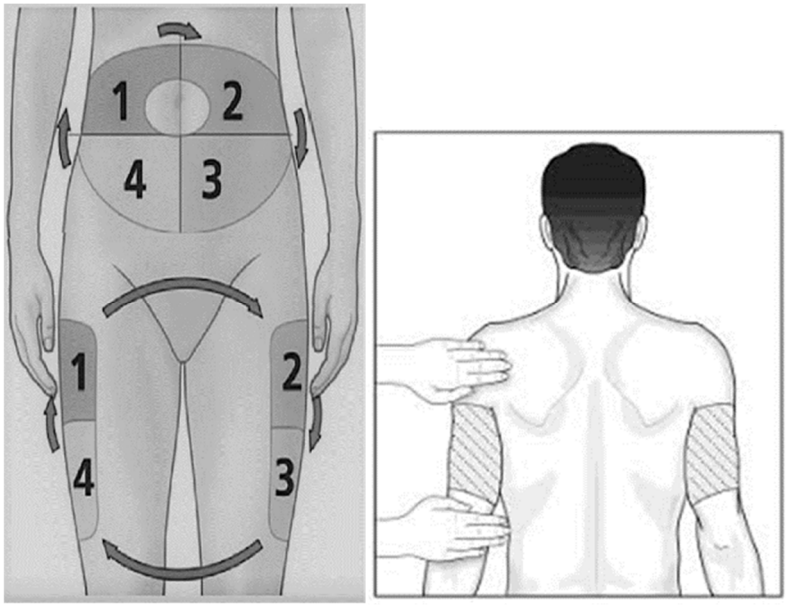
**Choose 1 of the recommended injection sites described below:**

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 1).**

**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 1 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 2 injections are needed for 1 dose), a new injection site must be chosen. Inject at least 2 inches from the previous site.

**Figure 1. Injection Site Rotation**



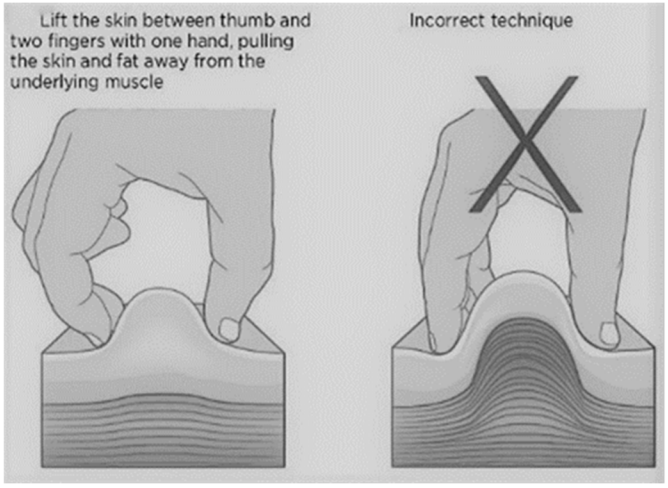

**Preparing the subcutaneous injection site and injecting Recifercept**

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

4. Choose the site from Figure 1 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.

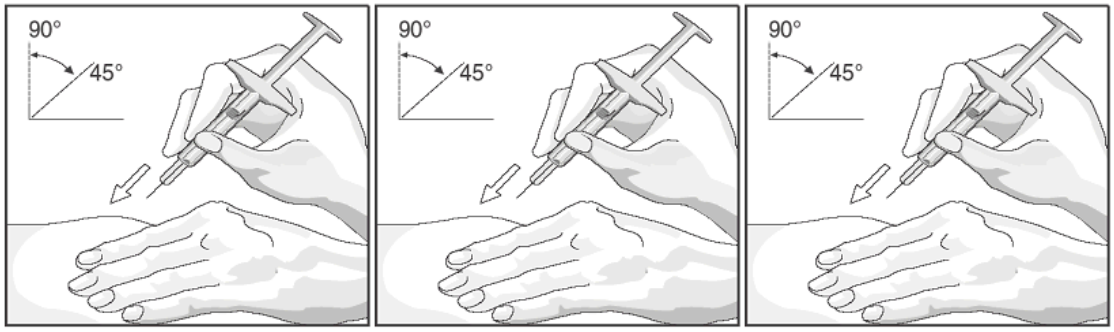
5. Using the thumb and forefinger, lift up a fold of skin with one hand (Figure 2).

**Figure 2. Technique for Holding Skin Prior to Injection**



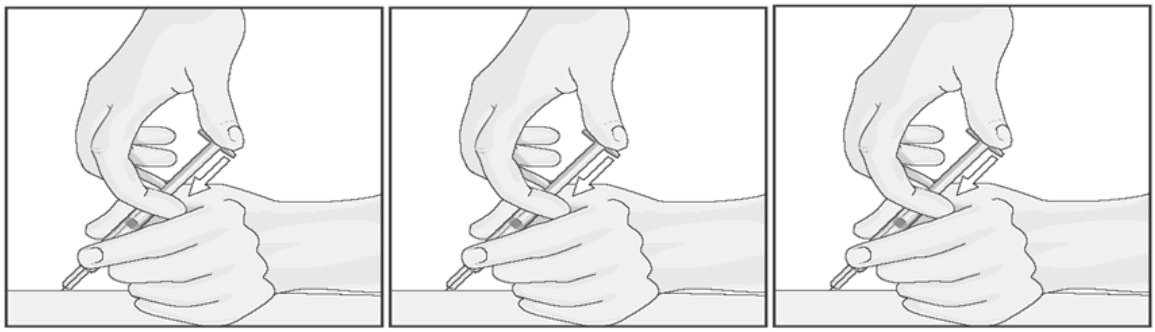
6. With the other hand, hold the syringe like a pencil with the bevel up. With a quick, short motion, push the needle into the skin at an angle of 45° (Figure 3).

**Figure 3. Injection Angle**




7. 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 4).

**Figure 4. Technique for Injecting Study Intervention**



8. 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.

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

10. 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.

## 10.9. Appendix 9: Abbreviations

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

| Abbreviation | Term |
|---|---|
| Abs | absolute |
| ADA | antidrug antibodies |
| ADA - | antidrug antibody negative |
| ADA + | antidrug antibody positive |
| ADL | activities of daily living |
| AE | adverse event |
| AIFA | Agenzia Italiana del Farmaco |
| AESI | adverse events of special interest |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| β-hCG | beta-human chorionic gonadotropin |
| BIW | Twice-weekly |
| BMI | Body mass index |
| BUN | blood urea nitrogen |
| CFR | Code of Federal Regulations |
| CCI | [redacted] |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CL/F | clearance |
| CCI | [redacted] |
| COA | clinical outcome assessment |
| $CO_2$ | carbon dioxide (bicarbonate) |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CrCL | creatinine clearance |
| CRO | contract research organization |
| Cr | creatinine |
| CSF | cerebrospinal fluid |
| CSR | Clinical Study Report |
| CT | clinical trial |
| CTFG | Clinical Trials Facilitation Group |
| CCI [redacted] | [redacted] |
| DILI | drug-induced liver injury |
| DKMA | Danish Medicine Agency |
| eDMC | External Data Monitoring Committee |
| EC | ethics committee |

| Abbreviation | Term |
|---|---|
| ECC | emergency contact card |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| EDP | exposure during pregnancy |
| eGFR | epidermal growth factor receptor |
| EMA | European Medicines Agency |
| ENT | ear, nose & throat |
| EQ-5D | EuroQol-5 Dimensions |
| EQ-5D-Y | EuroQol-5 Dimensions-Youth |
| EQ-VAS | EuroQol – Visual Analog Scale |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| FAS | full analysis set |
| FGFR3 | fibroblast growth factor receptor 3 |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| HIPAA | Health Insurance Portability and Accountability Act |
| HRQoL | 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 |
| IDS iSYS | multi-discipline automated system |
| IGF-1 | insulin-like growth factor 1 |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| IP | investigational product |
| IP manual | investigational product manual |
| IPAL | Investigational Product Accountability Log |
| IRB | Institutional Review Board |
| IRC | internal review committee |
| IRT | interactive response technology |
| ISR | injection site reaction |
| LFT | liver function test |
| MAD | multiple ascending dose |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MRI | Magnetic resonance imaging |

| Abbreviation | Term |
|---|---|
| N/A | not applicable |
| NAb | neutralizing antibodies |
| NC1 | noncollagenous 1 |
| NIMP | noninvestigational medicinal product |
| CCI | [redacted] |
| ObsRO | observer reported outcome |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PopPK | population pharmacokinetics |
| PPAS | per protocol analysis set |
| PRO | patient reported outcome |
| PSG | Polysomnography |
| PT | prothrombin time |
| CCI | [redacted] |
| QD | once daily |
| CCI | [redacted] |
| QTL | quality tolerance limit |
| QW | once weekly |
| Rac | geometric mean accumulation ratio |
| RBC | red blood cell |
| RNA | ribonucleic acid |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SaO2 | oxygen saturation |
| SAP | Statistical Analysis Plan |
| SC | subcutaneous(ly) |
| SoA | schedule of activities |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TA-46 | Recifercept alias |
| TBili | total bilirubin |
| TMax | time of maximum concentration |
| TEAE | treatment-emergent adverse event |
| T 1/2 | terminal half-life |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell |
| WOCBP | woman of childbearing potential |

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