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SYNOPSIS

Study Title: A Phase 2 Multiple Dose, Randomized Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Recifercept in Children With Achondroplasia

Study Number: C4181005

Regulatory Agency or Public Disclosure Identifier Number: ClinicalTrials.gov ID: NCT04638153; EudraCT Number: 2020-001189-13; US IND Number: 136773

Study Phase: 2b

Name of Study Intervention: Recifercept (PF-07256472)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR (Last Participant Last Visit date [LPLV]) Version 1.0, 14 September 2023

Number of Study Center(s) and Investigator(s): A total of 58 participants were randomized at 11 centers in 8 countries (Australia, Belgium, Denmark, Italy, Japan, Portugal, Spain, and United States). A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None.

Study Period:

Study Initiation Date (First Participant First Visit): 02 December 2020.

Study Completion Date (Last Participant Last Visit): 27 March 2023.

Following the results of an interim analysis in this study (C4181005), a temporary halt was implemented on 20 October 2022 and Pfizer Inc. made the decision to terminate this study as of 18 November 2022 (date of decision of the global study termination by the sponsor). The decision to terminate this study was due to not meeting the pre-specified 6-month efficacy criteria at the tested doses and not due to any safety concerns.

Rationale:

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.

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

Multiple changes had been made in the manufacturing process of the drug product (process 2) which was to be used in Phase 3. Therefore, an additional PK cohort (at selected sites only) was planned to evaluate the PK of single subcutaneous doses of 2 recifercept formulations, Phase 2 formulation (process 1c) and Phase 3 formulation (process 2). The additional PK cohort for 2 formulations was not completed as the study was terminated early prior to enrolling any participants in the PK cohort.

Objectives, Endpoints, and Statistical Methods:

The study objectives and endpoints are presented in Table S1 (main study cohort) and in Table S2 (PK study cohort only).

A primary efficacy estimand was used for the primary efficacy endpoint, and was intended to provide a population level estimate of the effect of recifercept on a continuous endpoint. Population-level summary: ratio between participants in the trial and a reference population[1] in growth of height at 12-month; ratio between treated and reference population was observed change-from-baseline of treated participants standardized by reference participant given age and gender. A secondary estimand was the population treatment effect of the mean change from baseline of a continuous response, defined as the decline in the difference of arm span to standing height.

The Full Analysis Set (FAS) and safety analysis set were defined as all participants receiving at least 1 dose of recifercept. Participants were analyzed according to the dose they actually received. The Per-Protocol Analysis Set (PPAS) was defined as all participants receiving at least 1 dose of recifercept and had complete data at baseline through Month 12 and without protocol deviations that were thought to impact the efficacy evaluation during the treatment period. Participants were analyzed according to the randomized intervention. The PK concentration set was defined as all participants who received at least 1 dose of recifercept and had at least 1 evaluable concentration.

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Table S1. Study Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Safety	Evaluate the safety and tolerability of recifercept doses and dosing regimes in participants aged ≥2 to <11 years with achondroplasia	• Safety and tolerability of recifercept as assessed through frequency and severity of AEs/SAEs
Efficacy	To assess efficacy of recifercept to increase height growth in children with achondroplasia	• Increase in height growth above expected in reference population[1]
Secondary		
PK	To evaluate the PK of recifercept in children aged ≥2 to <11 years old with achondroplasia	• Population PK characterization in children aged ≥2 to <11 years old with achondroplasia. CL/F and other PK parameters of recifercept to assess exposures in different age group
Efficacy	To assess efficacy of recifercept to improve achondroplasia-related complications	• Sitting height/standing height ratio. • Arm span to height/length difference. • Knee height:lower segment ratio. • Occipito-frontal circumference. • Ratio of occipito-frontal distance to occipito-mid-face measurements. • z-score of the above proportionality and skull morphology where achondroplasia reference datasets existed (occipito-frontal circumference, arm span, sitting height). • Fixed flexion angles at elbow. • Polysomnography parameters in those with pre-existing sleep-disordered breathing at the time of enrollment. • BMI. • Waist:chest circumference ratio. • Change from baseline in CHAQ (adapted for achondroplasia) component and index scores, QoLISSY Brief total score.
Safety; Immunogenicity	Assess change in individual safety parameters	• Change from baseline in safety labs, vital signs, physical examination. • Rate of ADAs

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMI = body mass index; CHAQ = Childhood Health Assessment Questionnaire; CL/F = clearance; CSR = clinical study report; PK = pharmacokinetic(s); QoLISSY = Quality of Life in Short Stature Youth; SAE = serious adverse event.

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Table S2. Study Objectives and Endpoints for PK Study Cohort Only

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

Abbreviations: AE = adverse event; AUC_{168} = area under the serum concentration-time profile from time 0 to 168 hours, AUC_{360} = area under the serum concentration-time profile from 0 to 360 hours; AUC_{inf} = area under the serum concentration-time profile from time 0 extrapolated to infinite time; C_{max} = maximum serum concentration; PK = pharmacokinetic(s); SC = subcutaneous; $t_{½}$ = terminal elimination half-life; T_{max} = time for Cmax.
The PK study cohort was not enrolled due to early study termination, therefore, the endpoints for the PK cohort were not analyzed.

Methodology:

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

The main cohort: The study was planned to enroll approximately 54 children with achondroplasia aged 2-10 years (inclusive) who were enrolled and randomized to receive one of 3 doses of recifercept (1 mg/kg once weekly [QW], 2 mg/kg twice weekly [BIW] or 1.5 mg/kg once daily [QD], n=18 per dose) such that approximately 45 participants were evaluable (up to 15 participants per dose). Additionally, an exploratory cohort of approximately 9 children with achondroplasia, aged 3 months to 2 years, was planned to be enrolled later in the study (n=3 per dose). All these 63 participants in this part of the study were planned to receive recifercept for 12 months.

Enrollment followed an age and dose-staggered approach (descending age and ascending dose) with review of safety and PK data by the study team before progression to the next enrollment block (Figure S1).

An interim analysis was performed when approximately 45 participants (up to 15 participants per dose) aged ≥2 to <11 years had received 6 months of treatment with recifercept. The external data monitoring committee (eDMC) reviewed safety, PK and efficacy data to confirm ongoing positive benefit:risk in participants. The decision of terminating this study was made by the sponsor based on the interim analysis results that the pre-specified 6-month

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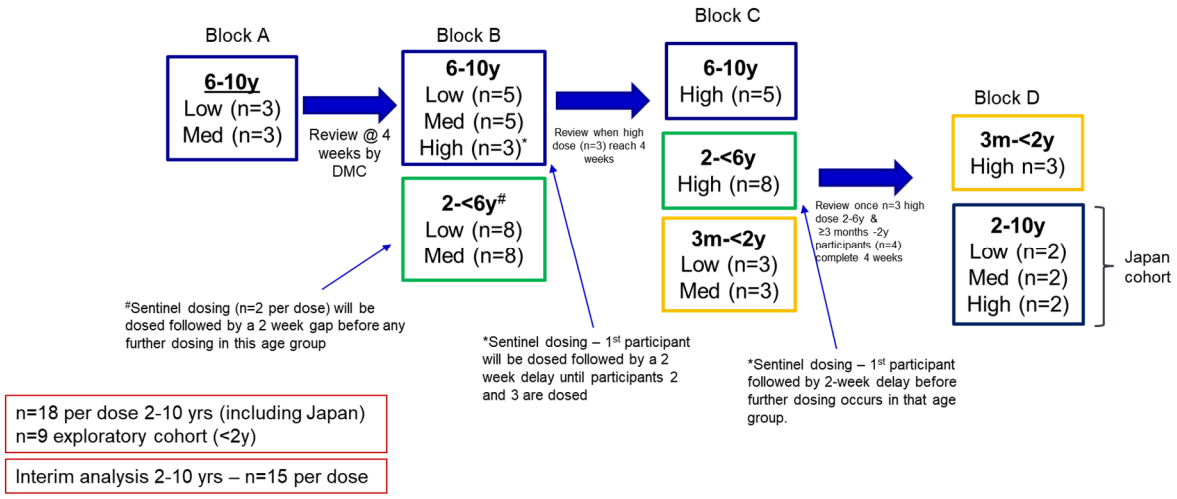
efficacy criteria were not met. All participants who completed the study prior to the early termination and in the opinion of the investigator, continued to have a positive risk:benefit profile, were offered to enroll into an open-label extension (OLE) study.

Figure S1. Study Schema for Blocks A-D



This clinical study report (CSR) presents the final analyses results for all endpoints as of LPLV.

Number of Participants (planned and analyzed):

Approximately 63 participants were planned to be randomized to one of 3 doses (1 mg/kg QW, 2 mg/kg BIW, 1.5 mg/kg QD) for 12 months.

A total of 63 participants were screened with 58 participants assigned to treatment and 57 participants treated. All 57 treated participants were included in the FAS and safety analysis set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants with achondroplasia, aged ≥2 years to <11 years (up to the day before the eleventh birthday inclusive) for main cohort who were able to stand independently for height measurements, and aged ≥3 months to <2 years (up to the day before the second birthday inclusive) for exploratory cohort who had a documented historical Magnetic Resonance Imaging (MRI) brain/cervical spine within the previous 12 months. Participants were Tanner stage 1 and completed the C4181001 natural history study with ≥2 valid height/length measurements (at least 3 months apart and one measurement within 3 months prior to enrollment).

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Study intervention in the study was recifercept (PF-07256472) provided as lyophilized powder for solution for injection, 50 mg/vial. All doses were given by subcutaneous

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injection. The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table S3.

Table S3. Study Interventions Administered

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
PF-07256472 Powder for Solution for Injection, 50 mg/vial	20-003970	20-DP-00277	50 mg	LYOPHILE
PF-07256472 Powder for Solution for Injection, 50 mg/vial	N/A	21-DP-00649	50 mg	LYOPHILE
PF-07256472 Powder for Solution for Injection, 50 mg/vial	N/A	22-DP-00925	50 mg	LYOPHILE
PF-07256472 Powder for Solution for Injection, 50 mg/vial	N/A	22-DP-01008	50 mg	LYOPHILE
PF-07256472 Powder for Solution for Injection, 50 mg/vial	N/A	22-DP-01105	50 mg	LYOPHILE
PF-07256472 Powder for Solution for Injection, 50 mg/vial	20-DP-00146	20-001010	50 mg	LYOPHILE
PF-07256472 Powder for Solution for Injection, 50 mg/vial	N/A	22-DP-00992	50 mg	LYOPHILE
PF-07256472 Powder for Solution for Injection, 50 mg/vial	FY6201	22-DP-01143	50 mg	LYOPHILE

Abbreviation: N/A = not applicable.

Duration of Study Intervention:

The planned duration of study intervention in main study cohort was 12 months.

Summary of Results:

Demographic and Other Baseline Characteristics:

Of the 57 participants in FAS, 33 (57.9%) were male participants and 24 (42.1%) were female participants. The study populations were generally comparable across the 3 dose groups with respect to age, race and ethnicity.

- The median (range) of age was 5.0 (1-10) years. Of the 57 participants in FAS, 3 participants were 1 year, 27 participants were 2-5 years, and 27 participants were 6-10 years of age. The number of participants of 2-10 years of age was 18 in each of the 3 dose groups.

- Most of the participants were White (84.2%) and not Hispanic or Latino (87.7%).

In recifercept 1 mg/kg QW group, recifercept 2 mg/kg BIW group and recifercept 1.5 mg/kg QD group, the mean standing height was 92.53 cm, 89.23 cm and 93.24 cm, respectively. The mean weight was 16.33 kg, 16.01 kg and 19.23 kg, respectively. The mean body mass index (BMI) was 19.83 kg/m^2, 20.18 kg/m^2 and 21.57 kg/m^2, respectively.

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Exposure:

The mean (standard deviation [SD]) duration of treatment (ie, duration from first dose to and including the last dose) was 307.5 (125.27) days in recifercept 1 mg/kg QW group, 355.2 (37.48) days in recifercept 2 mg/kg BIW group, and 255.9 (10.82) days in recifercept 1.5 mg/kg QD group. The mean (SD) duration of treatment (ie, actual dosing days) was 44.6 (18.02) days in recifercept 1 mg/kg QW group, 102.1 (10.62) days in recifercept 2 mg/kg BIW group, and 251.7 (99.38) days in recifercept 1.5 mg/kg QD group.

Efficacy Results:

Primary Efficacy Endpoint

Increase in Height Growth Above Expected in Reference Population: Height growth was defined as the ratio of observed change from baseline in standing height to the expected change from baseline in the reference population. An Mixed-Effect Repeated Measures (MMRM) method was used to analyze height growth at Months 3, 6, 9 and 12 relative to the reference population in the FAS. The least-square (LS) mean height growth compared to the reference population as the ratio was 1.1 in recifercept 1 mg/kg QW group, 0.9 in recifercept 2 mg/kg BIW group, and 0.6 in recifercept 1.5 mg/kg QD group at Month 3. At Month 12, the LS mean height growth compared to the reference population as the ratio was 1.0 in recifercept 1 mg/kg QW group, 1.0 in recifercept 2 mg/kg BIW group, and 0.9 in recifercept 1.5 mg/kg QD group. The LS mean height growth was comparable across the 3 dose groups at Months 6, 9 and 12, with the greatest LS mean difference of 0.1 across the dose groups.

Secondary Efficacy Endpoint

Arm Span to Standing Height/Length Difference: An MMRM method was used to analyze arm span to standing height/length difference at Months 3, 6, 9 and 12 in the FAS. The LS mean of change from baseline in arm span to standing height/length difference was 1.0 cm in recifercept 1 mg/kg QW group, 0.9 cm in recifercept 2 mg/kg BIW group, and 0.3 cm in recifercept 1.5 mg/kg QD group at Month 12. The LS mean change from baseline in arm span to standing height/length difference was numerically greater in recifercept 1 mg/kg QW group and recifercept 2 mg/kg BIW group compared with recifercept 1.5 mg/kg QD group at Months 9 and 12.

Sitting/Standing Height Ratio: For the participants of 2-10 years of age with observed values, the mean change from baseline in sitting/standing height ratio was 0.0 for each dose group at each visit (Months 3, 6, 9 and 12).

Knee Height : Lower Segment Ratio: The mean change from baseline in knee height : lower segment ratio was comparable across the 3 dose groups at Months 3, 6, 9 and 12, with the greatest mean change from baseline of 0.02 or -0.02.

Occipito-Frontal Circumference: For each dose group, the mean change from baseline in occipito-frontal circumference generally increased from Months 3 to 9. At Months 12, the

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mean change from baseline was 0.87 cm in recifercept 1 mg/kg QW group, 0.53 cm in recifercept 2 mg/kg BIW group, and 0.00 cm in recifercept 1.5 mg/kg QD group.

Occipito-Frontal to Occipito-Mid-Face Ratio: The mean change from baseline in occipito-frontal to occipito-mid-face ratio was comparable across the 3 dose groups at Months 3, 6, 9 and 12, with the greatest mean change from baseline of -0.04.

Height Standard Deviation Score [SDS] (z-score): For the participants of 2-10 years of age, the mean change from baseline in height SDS (z-score) was 0.0 at each visit in each dose group, except for recifercept 2 mg/kg BIW group at Month 12(mean change from baseline of 0.1) and recifercept 1.5 mg/kg QD group at Month 12 (mean change from baseline of -0.2).

Annualized Height Velocity: For the participants of 2-10 years of age, the mean annualized height velocity was 3.9 cm/year in recifercept 1 mg/kg QW group, 4.3 cm/year in recifercept 2 mg/kg BIW group, and 4.0 cm/year in recifercept 1.5 mg/kg QD group at Month 6. The mean annualized height velocity was 4.0 cm/year in recifercept 1 mg/kg QW group, 4.6 cm/year in recifercept 2 mg/kg BIW group, and 3.4 cm/year in recifercept 1.5 mg/kg QD group at Month 12.

Fixed Flexion Angles at Elbow: The mean baseline fixed flexion angle at elbow was -11.33° in recifercept 1 mg/kg QW group, -18.31° in recifercept 2 mg/kg BIW group, and -6.45° in recifercept 1.5 mg/kg QD group. Mean increase from baseline in fixed flexion angles at elbow was observed at most visits, with the greatest mean increase of 4.83° in recifercept 2 mg/kg BIW group at Month 9.

BMI: Mean increase and decrease from baseline in BMI were observed at visits of the 3 dose groups. The greatest mean increase from baseline in BMI was 0.36 kg/m^2 in recifercept 1 mg/kg QW group at Month 9, and the greatest mean decrease from baseline in BMI was -0.50 kg/m^2 in recifercept 1.5 mg/kg QD group at Month 12.

Waist : Chest Circumference Ratio: The mean waist : chest circumference ratio at baseline was 0.93 in recifercept 1 mg/kg QW group, 0.94 in recifercept 2 mg/kg BIW group, and 0.97 in recifercept 1.5 mg/kg QD group. At Month 12, the mean change from baseline in waist : chest circumference ratio was 0.05 in recifercept 1 mg/kg QW group, 0.00 in recifercept 2 mg/kg BIW group, and -0.01 in recifercept 1.5 mg/kg QD group.

Polysomnography: At Month 12,

- For apnea-hypopnea index (obstructive) and apnea-hypopnea index (total), mean decrease from baseline or minimal mean increase from baseline was observed in recifercept 1 mg/kg QW group (0.31 and -1.03, respectively) and recifercept 2 mg/kg BIW group (-1.90 and -2.90, respectively).

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- For desaturation index (ie, number of desaturations per hour >3% from baseline), mean change from baseline was -4.61 in recifercept 1 mg/kg QW group and 0.20 in recifercept 2 mg/kg BIW group.

- For percentage time spent <90% oxygen saturation (SaO2), mean change from baseline was -48.95% in recifercept 1 mg/kg QW group and -99.00% in recifercept 2 mg/kg BIW group.

- For percentage time spent with end-tidal carbon dioxide >50 mmHg, mean change from baseline was -14.03% in recifercept 1 mg/kg QW group and -38.00% in recifercept 2 mg/kg BIW group.

- For SaO2 nadir, mean change from baseline was -2.67% in recifercept 1 mg/kg QW group and 1.00% in recifercept 2 mg/kg BIW group.

- No value was observed for participants in recifercept 1.5 mg/kg QD group for the above parameters.

Childhood Health Assessment Questionnaire (CHAQ, Adapted for Achondroplasia): No consistent trend over the treatment period was observed for the CHAQ components in any of the dose groups.

Quality of Life in Short Stature Youth (QoLISSY) Brief: No significant improvement over the treatment period was observed for the 9 items in any of the dose groups.

Acceptability and Tolerability Questionnaire – Achondroplasia: Throughout the visits, the general results showed good acceptability and tolerability of the injection, including pain/stinging/bruising/bleeding/swelling ratings, satisfaction with the overall experience and willingness to continue injection, etc. No significant changes over the treatment period were observed for the 10 items in any of the dose groups.

Euro-Qol 5 Dimensions - Youth (EQ-5D-Y) and Youth Proxy (EQ-5D-Y Proxy): In each dose group, the majority of participants with reported responses indicated “no problems” or “some problems” for each dimension at most visits. The mean rating score of health was ≥80.0 at each visit in each dose group.

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC): In each dose group, the majority of participants with reported responses indicated the impact of achondroplasia on the ability to do physical activities or overall emotional and social well-being over the past 7 days was “none” or “mild” at most visits. In each dose group, the majority of participants with reported responses indicated no change in the ability to do physical activities or overall emotional and social well-being since they started taking the treatment at most visits. More participants indicated improvement in the ability to do physical activities or overall emotional and social well-being compared with those indicating worsening at each visit.

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Tanner Staging: Tanner stage of development at screening were Stage I for all evaluated male and female participants (100%). At each visit after screening, most participants (≥80.0% for male and ≥94.4% for female) with reported results were Tanner stage I.

Safety Results:

Most participants experienced at least 1 treatment-emergent adverse event (TEAE) (85.0% in recifercept 1 mg/kg QW group, 100% in recifercept 2 mg/kg BIW group, and 88.9% in recifercept 1.5 mg/kg QD group). Treatment-related adverse events (AEs) were reported in 35.0% in recifercept 1 mg/kg QW group, 78.9% in recifercept 2 mg/kg BIW group, and 77.8% in recifercept 1.5 mg/kg QD group.

- The most frequently reported all-causality TEAEs were severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test positive (14 [24.6%] participants), Injection site erythema (13 [22.8%] participants), Nasopharyngitis (12 [21.1%] participants), and Injection site rash (10 [17.5%] participants). The most frequently reported treatment-related TEAEs were Injection site erythema (13 [22.8%] participants), and Injection site rash (10 [17.5%] participants).

Most of the TEAEs were mild in severity. No events of death were reported in the study. One SAE of Sinus bradycardia was reported for 1 (5.0%) participant in recifercept 1 mg/kg QW group, with onset day on Day 50 and resolved on the same day. The event was severe and considered not related to treatment. No participants discontinued from study or study intervention due to AE.

Injection site reactions were considered AE of special interest. Most injection site reactions were mild in severity. The mean time from the most recent dosing to occurrence of injection site reaction was 0.5 day, 0.3 day, and 0.1 day in recifercept 1 mg/kg QW group, recifercept 2 mg/kg BIW group, and recifercept 1.5 mg/kg QD group, respectively. The mean duration for injection site reaction was 2.3 days, 2.8 days, and 6.9 days in recifercept 1 mg/kg QW group, recifercept 2 mg/kg BIW group, and recifercept 1.5 mg/kg QD group, respectively.

No clinically significant trends were noted for laboratory test. No clinically meaningful findings in the vital signs measurements, electrocardiograms (ECGs), physical examination assessments, or other observations related to safety were observed in this study.

Pharmacokinetic Results:

Intact PK of recifercept were assessed as trough serum concentration (pre-dose) at visits of Day 8, Day 15 and Months 1, 2, 3, 6, 9 and 12 in all 3 dose groups. PK samples were also collected 20 hours post-dose at Month 2 and 40 hours post-dose at Month 3 for recifercept 1 mg/kg QW and 2 mg/kg BIW groups. As expected, recifercept concentration increased from 1 mg/kg QW to 1.5 mg/kg QD dose. Looking at the pre-dose (trough) concentration at steady-state (trough serum concentration [C_{trough}]), it appeared that recifercept concentrations were stable over 12 months of dosing. Observed steady-state serum recifercept exposures in achondroplasia participants at dosing regimens of 1 mg/kg QW, 2 mg/kg BIW and 1.5 mg/kg

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QD were consistent with the exposures predicted earlier (at the start of the study) by a Population PK model developed using healthy participants data.

Other Results:

Rate of anti-drug antibody (ADA)/ neutralizing antibody (NAb):

At screening, no participants were ADA positive or NAb positive in recifercept 1 mg/kg QW group and 2 mg/kg BIW group, and 1 (5.6%) participant was ADA and NAb positive in recifercept 1.5 mg/kg QD group. Most participants (80.0% in recifercept 1 mg/kg QW group, 94.7% in recifercept 2 mg/kg BIW group and 94.4% recifercept 1.5 mg/kg QD group) had ADA positive result for at least 1 visit post baseline. The majority of participants (65.0% in recifercept 1 mg/kg QW group, 84.2% in recifercept 2 mg/kg BIW group and 88.9% recifercept 1.5 mg/kg QD group) had NAb positive result for at least 1 visit post baseline.

Intact and Total Recifercept Concentration by ADA/NAb Status:

No apparent relationship between recifercept exposures and ADA status or ADA titers was observed in the study.

Conclusions:

- Recifercept doses at 1 mg/kg QW, 2 mg/kg BIW and 1.5 mg/kg QD were safe and well-tolerated in participants aged ≥3 months to <11 years with achondroplasia.
- The study did not meet the pre-specified 6-month efficacy criteria at the tested doses at interim analysis. Recifercept did not demonstrate meaningful changes in the efficacy endpoints at 12 months.
- Observed steady-state serum recifercept exposures were consistent with the exposures predicted at the start of the study using healthy participants data.
- Majority of the participants in the study had ADA positive (>80%) and NAb positive (>65%) results for at least 1 visit post baseline.

References:

1. Merker A, Neumeyer L, Hertel NT, et al. Growth in achondroplasia: development of height, weight, head circumference, and body mass index in a European cohort. Am J Med Genet A. 2018;176(8):1723–34.