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

Summary

EudraCT number	2020-001189-13
Trial protocol	PT DK BE IT
Global end of trial date	27 March 2023

Results information

Result version number	v1 (current)
This version publication date	07 October 2023
First version publication date	07 October 2023

Trial information

Trial identification

Sponsor protocol code	C4181005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04638153
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objectives: 1) to evaluate the safety and tolerability of recifercept doses and dosing regimes in subjects aged ≥2 to <11 years with achondroplasia; 2) to assess efficacy of recifercept to increase height growth in children with achondroplasia.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	57
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	3
Children (2-11 years)	54
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 63 subjects were screened with 58 subjects assigned to treatment. Of the 58 subjects assigned to treatment, 57 (98.3%) subjects were treated. One subject was assigned to treatment but not treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Recifercept 1 mg/kg QW

Arm description:

Children subjects were enrolled and randomised to receive recifercept 1 mg/kg once weekly (QW) for 12 months.

Arm type	Experimental
Investigational medicinal product name	Recifercept
Investigational medicinal product code	
Other name	PF-07256472
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Recifercept 1 mg/kg was administered once weekly.

Arm title	Recifercept 2 mg/kg BIW

Arm description:

Children subjects were enrolled and randomised to receive recifercept 2 mg/kg twice weekly (BIW) for 12 months.

Arm type	Experimental
Investigational medicinal product name	Recifercept
Investigational medicinal product code	
Other name	PF-07256472
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Recifercept 2 mg/kg was administered twice weekly.

Arm title	Recifercept 1.5 mg/kg QD

Arm description:

Children subjects were enrolled and randomised to receive recifercept 1.5 mg/kg once daily (QD) for 12 months.

Arm type	Experimental

Investigational medicinal product name	Recifercept
Investigational medicinal product code	
Other name	PF-07256472
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Recifercept 1.5 mg/kg was administered once daily.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was a partially blinded study with open-label supplies. In order to minimize bias in measurement of the primary efficacy endpoint (height), the anthropometrist was blinded to dose assignment. There was no additional blinding.

Number of subjects in period 1	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD
Started	20	19	18
Completed	16	17	3
Not completed	4	2	15
Study terminated by sponsor	4	2	14
Withdrawal by parent/guardian	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Recifercept 1 mg/kg QW
Reporting group description:	
Children subjects were enrolled and randomised to receive recifercept 1 mg/kg once weekly (QW) for 12 months.	
Reporting group title	Recifercept 2 mg/kg BIW
Reporting group description:	
Children subjects were enrolled and randomised to receive recifercept 2 mg/kg twice weekly (BIW) for 12 months.	
Reporting group title	Recifercept 1.5 mg/kg QD
Reporting group description:	
Children subjects were enrolled and randomised to receive recifercept 1.5 mg/kg once daily (QD) for 12 months.	

Reporting group values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD
Number of subjects	20	19	18
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	2	1	0
Children (2-11 years)	18	18	18
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	5.75	5.16	5.83
standard deviation	± 2.84	± 2.59	± 2.31
Gender Categorical Units: Subjects			
Female	9	9	6
Male	11	10	12
Race Categorical Units: Subjects			
White	15	19	14
Asian	3	0	2
Multiracial	1	0	1
Not Reported	1	0	1
Ethnicity Categorical Units: Subjects			
Hispanic or Latino	3	0	2
Not Hispanic or Latino	16	19	15
Not Reported	1	0	1

Reporting group values	Total		
Number of subjects	57		
Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	3		
Children (2-11 years)	54		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	24		
Male	33		
Race Categorical Units: Subjects			
White	48		
Asian	5		
Multiracial	2		
Not Reported	2		
Ethnicity Categorical Units: Subjects			
Hispanic or Latino	5		
Not Hispanic or Latino	50		
Not Reported	2		

End points

End points reporting groups

Reporting group title	Recifercept 1 mg/kg QW
Reporting group description:	
Children subjects were enrolled and randomised to receive recifercept 1 mg/kg once weekly (QW) for 12 months.	
Reporting group title	Recifercept 2 mg/kg BIW
Reporting group description:	
Children subjects were enrolled and randomised to receive recifercept 2 mg/kg twice weekly (BIW) for 12 months.	
Reporting group title	Recifercept 1.5 mg/kg QD
Reporting group description:	
Children subjects were enrolled and randomised to receive recifercept 1.5 mg/kg once daily (QD) for 12 months.	

Primary: Number of Subjects With Treatment Emergent Treatment-Related Adverse Events (AEs)

End point title	Number of Subjects With Treatment Emergent Treatment-Related Adverse Events (AEs)[1]
End point description:	
Treatment-related AE was any untoward medical occurrence attributed to study intervention in a subject who received study intervention. Serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study intervention and up to 365 days after last dose that were absent before treatment or that worsened relative to pretreatment state. Relatedness to Recifercept was assessed by the investigator (Yes/No). Subjects with multiple occurrences of an AE within a category were counted once within the category. Analysis population included all subjects who received at least one dose of recifercept.	
End point type	Primary
End point timeframe:	
The first dose up to 28 to 35 days after the last dose of study intervention (27 months).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis was planned only for the end point specified.

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Subjects				
Treatment-related AE	7	15	14	
Treatment-related SAE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Increase in Height Growth Above Expected in Reference Population

End point title	Increase in Height Growth Above Expected in Reference Population

End point description:

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. Analysis population included all subjects (aged 2-10 years) who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Primary

End point timeframe:

Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	18	18	
Units: Ratio				
arithmetic mean (standard deviation)				
Month 3 (n=15,17,17)	1.1 (± 0.49)	71.4 (± 290.85)	130.0 (± 533.42)	
Month 6 (n=16,16,15)	0.9 (± 0.42)	1.1 (± 0.44)	1.0 (± 0.45)	
Month 9 (n=16,16,11)	1.0 (± 0.36)	1.0 (± 0.24)	1.0 (± 0.28)	
Month 12 (n=7,9,2)	0.9 (± 0.30)	1.1 (± 0.22)	0.8 (± 0.04)	

Statistical analyses

Statistical analysis title	Least-Square (LS) Mean Difference at Month 3

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.

Comparison groups	Recifercept 1 mg/kg QW v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.6

Statistical analysis title	LS Mean Difference at Month 3

Statistical analysis description:

The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 2 mg/kg BIW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.1

Statistical analysis title	LS Mean Difference at Month 6

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.

Comparison groups	Recifercept 1 mg/kg QW v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

Statistical analysis title	LS Mean Difference at Month 6

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 1 mg/kg QW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.2

Statistical analysis title	LS Mean Difference at Month 3
Statistical analysis description:	
The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.	
Comparison groups	Recifercept 1 mg/kg QW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.9

Statistical analysis title	LS Mean Difference at Month 6
Statistical analysis description:	
The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.	
Comparison groups	Recifercept 2 mg/kg BIW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.2

Statistical analysis title	LS Mean Difference at Month 9
Statistical analysis description:	
The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.	
Comparison groups	Recifercept 1.5 mg/kg QD v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Statistical analysis title	LS Mean Difference at Month 9
Statistical analysis description: The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.	
Comparison groups	Recifercept 1 mg/kg QW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Statistical analysis title	LS Mean Difference at Month 9
Statistical analysis description: The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.	
Comparison groups	Recifercept 2 mg/kg BIW v Recifercept 1 mg/kg QW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Statistical analysis title	LS Mean Difference at Month 12
Statistical analysis description: The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.	
Comparison groups	Recifercept 1 mg/kg QW v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Statistical analysis title	LS Mean Difference at Month 12

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 1.5 mg/kg QD v Recifercept 1 mg/kg QW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.3

Statistical analysis title	LS Mean Difference at Month 12

Statistical analysis description:

The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 1.5 mg/kg QD v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

Secondary: Change From Baseline in Pulse Rate at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Pulse Rate at Month 3, Month 6, Month 9, and Month 12

End point description:

Pulse rate measurements were preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones) where possible (with consideration of the age of the

child). Pulse rate was summarized by treatment in accordance with the sponsor reporting standards. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: beats per minute (BPM)				
arithmetic mean (standard deviation)				
Baseline (n=20,19,18)	96.40 (± 16.583)	97.58 (± 21.823)	94.50 (± 15.497)	
Change at Month 3 (n=17,19,17)	-1.47 (± 13.639)	-6.05 (± 20.871)	-2.94 (± 16.913)	
Change at Month 6 (n=17,18,15)	-2.65 (± 8.760)	-1.44 (± 15.659)	-2.20 (± 15.880)	
Change at Month 9 (n=17,17,10)	-4.35 (± 16.035)	-2.18 (± 17.746)	-15.20 (± 14.853)	
Change at Month 12 (n=6,8,2)	1.17 (± 15.484)	-0.75 (± 34.012)	-11.50 (± 37.477)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Respiratory Rate at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Respiratory Rate at Month 3, Month 6, Month 9, and Month 12

End point description:

Respiratory rate was obtained with subject in the seated position, after having sat calmly for at least 5 minutes. Respiratory rate was summarized by treatment in accordance with the sponsor reporting standards. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: breaths/min				
arithmetic mean (standard deviation)				

Baseline (n=20,19,18)	23.15 (± 4.603)	24.37 (± 3.905)	23.39 (± 5.863)	
Change at Month 3 (n=17,19,17)	0.47 (± 5.691)	-1.00 (± 2.809)	-1.53 (± 4.939)	
Change at Month 6 (n=17,18,15)	-1.12 (± 3.516)	-0.94 (± 4.221)	0.53 (± 4.502)	
Change at Month 9 (n=17,17,10)	-1.06 (± 3.473)	-0.94 (± 4.507)	-1.30 (± 6.945)	
Change at Month 12 (n=7,8,2)	2.00 (± 5.132)	-3.75 (± 4.979)	2.00 (± 15.556)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Blood Pressure at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Blood Pressure at Month 3, Month 6, Month 9, and Month 12

End point description:

Blood pressure measurements were preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones) where possible (with consideration of the age of the child). Supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) were summarized by treatment in accordance with the sponsor reporting standards. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (Supine DBP) (n=20,19,18)	66.55 (± 9.870)	67.05 (± 9.897)	62.11 (± 13.244)	
Change at Month 3 (Supine DBP) (n=17,19,17)	-0.76 (± 12.179)	-4.47 (± 8.618)	-0.29 (± 12.849)	
Change at Month 6 (Supine DBP) (n=17,18,15)	-3.65 (± 14.845)	-0.83 (± 10.837)	5.27 (± 12.920)	
Change at Month 9 (Supine DBP) (n=17,16,9)	-3.41 (± 12.846)	-2.50 (± 11.408)	-2.44 (± 13.492)	
Change at Month 12 (Supine DBP) (n=7,8,2)	-3.14 (± 16.385)	-1.13 (± 13.953)	-4.50 (± 21.920)	
Baseline (Supine SBP) (n=20,19,18)	105.70 (± 10.732)	118.37 (± 22.056)	106.28 (± 14.199)	
Change at Month 3 (Supine SBP) (n=17,19,17)	10.47 (± 14.261)	-5.68 (± 21.445)	4.82 (± 15.134)	
Change at Month 6 (Supine SBP) (n=17,18,15)	1.88 (± 21.863)	3.94 (± 17.424)	5.73 (± 14.587)	

Change at Month 9 (Supine SBP) (n=17,16,9)	2.59 (± 15.732)	-2.94 (± 16.364)	2.33 (± 19.371)	
Change at Month 12 (Supine SBP) (n=7,8,2)	3.57 (± 27.700)	-11.75 (± 31.865)	-6.50 (± 4.950)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Temperature at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Temperature at Month 3, Month 6, Month 9, and Month 12

End point description:

Temperature was obtained with subject in the seated position, after having sat calmly for at least 5 minutes. Temperature measurements were summarized by treatment in accordance with the sponsor reporting standards. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Degree Celsius (°C)				
arithmetic mean (standard deviation)				
Baseline (n=20,19,18)	36.57 (± 0.441)	36.43 (± 0.519)	36.58 (± 0.466)	
Change at Month 3 (n=17,19,17)	-0.06 (± 0.362)	-0.04 (± 0.297)	0.11 (± 0.493)	
Change at Month 6 (n=17,18,15)	-0.08 (± 0.493)	-0.02 (± 0.298)	-0.03 (± 0.417)	
Change at Month 9 (n=17,17,10)	-0.16 (± 0.614)	-0.12 (± 0.437)	-0.20 (± 0.503)	
Change at Month 12 (n=7,8,2)	-0.21 (± 0.313)	-0.14 (± 0.316)	0.30 (± 0.141)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Physical Examination Findings at Month 3, Month 6, Month 9, and Month 12

End point title	Number of Subjects With Abnormal Physical Examination Findings at Month 3, Month 6, Month 9, and Month 12

End point description:

A physical examination included, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal systems and skin. Physical examination assessments were summarized by treatment in accordance with the sponsor reporting standards. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Subjects				
Abnormal Cardiovascular at Month 3 (n=17,19,17)	0	0	0	
Abnormal Cardiovascular at Month 6 (n=17,19,15)	0	0	0	
Abnormal Cardiovascular at Month 9 (n=16,17,9)	0	0	0	
Abnormal Cardiovascular at Month 12 (n=16,16,3)	0	0	0	
Abnormal Gastrointestinal at Month 3 (n=17,19,17)	0	0	0	
Abnormal Gastrointestinal at Month 6 (n=17,19,15)	0	1	0	
Abnormal Gastrointestinal at Month 9 (n=16,17,9)	0	2	0	
Abnormal Gastrointestinal at Month 12 (n=16,16,3)	0	0	0	
Abnormal Lungs at Month 3 (n=17,19,17)	0	0	0	
Abnormal Lungs at Month 6 (n=17,19,15)	0	2	0	
Abnormal Lungs at Month 9 (n=16,17,9)	0	0	0	
Abnormal Lungs at Month 12 (n=16,16,3)	1	0	0	
Abnormal Skin at Month 3 (n=17,19,17)	2	3	1	
Abnormal Skin at Month 6 (n=17,19,15)	1	4	2	
Abnormal Skin at Month 9 (n=16,17,9)	3	3	2	
Abnormal Skin at Month 12 (n=16,16,3)	2	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities (Without Regard to Baseline Abnormality)

End point title	Number of Subjects With Laboratory Abnormalities (Without Regard to Baseline Abnormality)

End point description:

Laboratory parameters included: hematology (corpuscular volume, corpuscular hemoglobin, corpuscular

hemoglobin concentration, platelet, leukocytes, lymphocytes, neutrophils, eosinophils, and monocytes), and chemistry (bilirubin, alkaline phosphatase, albumin, urea nitrogen, urate, potassium, phosphate, bicarbonate). Clinical significance of laboratory parameters was determined at the investigator's discretion. Analysis population included all subjects who received at least one dose of recifercept.

End point type	Secondary

End point timeframe:

Baseline to Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Subjects				
Mean Corpuscular Volume<0.9xLLN	0	1	2	
Mean Corpuscular Volume>1.1xULN	1	0	0	
Mean Corpuscular Hemoglobin <0.9xLLN	0	1	2	
Mean Corpuscular Hemoglobin Concentration<0.9xLLN	0	1	1	
Platelets>1.75xULN	0	0	1	
Leukocytes<0.6xLLN	1	0	0	
Lymphocytes<0.8xLLN	5	9	4	
Neutrophils<0.8xLLN	1	0	0	
Neutrophils>1.2xULN	1	0	1	
Eosinophils>1.2xULN	1	4	3	
Monocytes >1.2xULN	4	1	1	
Bilirubin>1.5xULN	0	1	0	
Alkaline Phosphatase>3.0xULN	1	0	0	
Albumin >1.2xULN	2	3	1	
Urea Nitrogen>1.3xULN	2	5	0	
Urate >1.2xULN	2	1	0	
Potassium>1.1x ULN	2	4	4	
Phosphate<0.8x LLN	0	0	1	
Bicarbonate<0.9x LLN	2	2	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-Dose Serum Concentration (Ctrough) of Recifercept

End point title	Pre-Dose Serum Concentration (Ctrough) of Recifercept

End point description:

Ctrough was defined as pre-dose serum concentration during dosing and observed directly from data. Analysis population included all subjects who received at least one dose of recifercept and had at least one evaluable concentration. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Pre-dose on Day(s) 4, 8, 15, 29, 61, 91, 183, 273, 365

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Day 4 (n=18,19,16)	215.8 (± 63.28)	517.3 (± 174.18)	1785.2 (± 651.92)	
Day 8 (n=19,19,18)	95.3 (± 23.35)	614.6 (± 228.35)	2682.6 (± 912.79)	
Day 15 (n=18,19,17)	137.1 (± 39.26)	868.1 (± 341.98)	3199.4 (± 1311.65)	
Day 29 (n=17,19,16)	154.3 (± 46.91)	940.8 (± 415.45)	3804.4 (± 1573.91)	
Day 61 (n=17,19,17)	183.8 (± 75.76)	974.8 (± 604.47)	3431.4 (± 1477.48)	
Day 91 (n=17,19,15)	225.5 (± 90.91)	944.8 (± 466.38)	3702.3 (± 2074.64)	
Day 183 (n=17,19,15)	370.9 (± 424.80)	1078.9 (± 563.83)	5185.5 (± 3190.30)	
Day 273 (n=15,16,9)	278.2 (± 140.41)	1340.8 (± 695.10)	3879.6 (± 3027.59)	
Day 365 (n=15,16,3)	249.5 (± 174.54)	1320.4 (± 662.18)	6766.7 (± 3145.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Anti-Drug Antibodies (ADA) and Neutralizing Antibody (NAb) of Recifercept

End point title	Number of Subjects With Positive Anti-Drug Antibodies (ADA) and Neutralizing Antibody (NAb) of Recifercept

End point description:

The immunogenicity was measured by presence of ADA and NAb in subjects treated with recifercept and summarized by dose regimen. Analysis population included all subjects who received at least one dose of recifercept.

End point type	Secondary

End point timeframe:

The first dose up to 28 to 35 days after the last dose of study intervention (27 months).

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Subjects				
Overall incidence of positive ADA	16	18	17	
Overall incidence of positive NAb	13	16	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sitting/Standing Height Ratio at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Sitting/Standing Height Ratio at Month 3, Month 6, Month 9, and Month 12

End point description:

Sitting/standing height ratio was the ratio of sitting height to standing height. Analysis population included all subjects (aged 2-10 years) who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	18	18	
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline (n=18,17,18)	0.7 (± 0.02)	0.7 (± 0.02)	0.7 (± 0.02)	
Change at Month 3 (n=15,17,17)	0.0 (± 0.01)	-0.0 (± 0.01)	0.0 (± 0.01)	
Change at Month 6 (n=16,16,15)	0.0 (± 0.01)	-0.0 (± 0.01)	-0.0 (± 0.01)	
Change at Month 9 (n=16,15,11)	-0.0 (± 0.01)	-0.0 (± 0.01)	-0.0 (± 0.01)	
Change at Month 12 (n=7,9,2)	-0.0 (± 0.01)	-0.0 (± 0.01)	0.0 (± 0.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Arm Span to Standing Height/Length Difference at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Arm Span to Standing Height/Length Difference at Month 3, Month 6, Month 9, and Month 12

End point description:

Arm span to standing height/length difference was the difference between arm span and standing height

(for participants ≥2 years of age). Analysis population included all subjects (aged 2-10 years) who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	18	18	
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=18,17,18)	9.5 (± 3.93)	8.2 (± 3.24)	9.1 (± 3.27)	
Change at Month 3 (n=15,17,17)	0.5 (± 0.96)	0.0 (± 0.88)	-0.5 (± 1.62)	
Change at Month 6 (n=16,16,15)	0.2 (± 1.86)	0.7 (± 1.03)	-0.5 (± 1.93)	
Change at Month 9 (n=16,16,11)	0.6 (± 0.89)	0.7 (± 1.39)	0.1 (± 0.78)	
Change at Month 12 (n=7,9,2)	0.5 (± 1.22)	1.1 (± 1.75)	0.2 (± 0.71)	

Statistical analyses

Statistical analysis title	LS Mean Difference at Month 3

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.

Comparison groups	Recifercept 1 mg/kg QW v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.2

Statistical analysis title	LS Mean Difference at Month 3

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 1 mg/kg QW v Recifercept 1.5 mg/kg QD

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.8

Statistical analysis title	LS Mean Difference at Month 3

Statistical analysis description:

The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 2 mg/kg BIW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.1

Statistical analysis title	LS Mean Difference at Month 6

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.

Comparison groups	Recifercept 1 mg/kg QW v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.6

Statistical analysis title	LS Mean Difference at Month 6

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 1 mg/kg QW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.9

Statistical analysis title	LS Mean Difference at Month 6

Statistical analysis description:

The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 2 mg/kg BIW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.1

Statistical analysis title	LS Mean Difference at Month 9

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.

Comparison groups	Recifercept 2 mg/kg BIW v Recifercept 1 mg/kg QW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.7

Statistical analysis title	LS Mean Difference at Month 9
Statistical analysis description:	
The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.	
Comparison groups	Recifercept 1 mg/kg QW v Recifercept 1.5 mg/kg QD
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.5

Statistical analysis title	LS Mean Difference at Month 9
Statistical analysis description:	
The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.	
Comparison groups	Recifercept 1.5 mg/kg QD v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.2

Statistical analysis title	LS Mean Difference at Month 12
Statistical analysis description:	
The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 2 mg/kg BIW treatment groups.	
Comparison groups	Recifercept 1 mg/kg QW v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.5

Statistical analysis title	LS Mean Difference at Month 12

Statistical analysis description:

The LS mean difference between Recifercept 1 mg/kg QW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 1.5 mg/kg QD v Recifercept 1 mg/kg QW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	2.8

Statistical analysis title	LS Mean Difference at Month 12

Statistical analysis description:

The LS mean difference between Recifercept 2 mg/kg BIW and Recifercept 1.5 mg/kg QD treatment groups.

Comparison groups	Recifercept 1.5 mg/kg QD v Recifercept 2 mg/kg BIW
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	1.4

Secondary: Change From Baseline in Knee Height : Lower Segment Ratio at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Knee Height : Lower Segment Ratio at Month 3, Month 6, Month 9, and Month 12

End point description:

Knee height : lower segment ratio was the ratio of knee to heel length to the difference between standing height and sitting height. Analysis population included all subjects who received at least one

dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline (n=18,16,18)	0.81 (± 0.052)	0.84 (± 0.058)	0.80 (± 0.035)	
Change at Month 3 (n=15,16,17)	-0.00 (± 0.020)	-0.01 (± 0.052)	0.02 (± 0.035)	
Change at Month 6 (n=16,15,14)	-0.00 (± 0.028)	-0.02 (± 0.062)	0.00 (± 0.026)	
Change at Month 9 (n=16,14,11)	-0.00 (± 0.027)	-0.02 (± 0.065)	0.01 (± 0.026)	
Change at Month 12 (n=7,8,2)	0.00 (± 0.028)	-0.02 (± 0.081)	0.02 (± 0.023)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Occipito-Frontal Circumference at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Occipito-Frontal Circumference at Month 3, Month 6, Month 9, and Month 12

End point description:

Occipito-frontal circumference data were summarized for each treatment arm. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=20,18,16)	54.56 (± 2.877)	55.00 (± 2.179)	56.13 (± 1.949)	
Change at Month 3 (n=16,18,15)	0.19 (± 0.345)	0.19 (± 0.382)	0.30 (± 0.515)	
Change at Month 6 (n=17,17,15)	0.33 (± 0.396)	0.35 (± 0.506)	0.30 (± 0.437)	

Change at Month 9 (n=17,17,11)	0.46 (± 0.619)	0.35 (± 0.597)	0.54 (± 0.588)	
Change at Month 12 (n=7,9,2)	0.87 (± 1.106)	0.53 (± 0.557)	0.00 (± 0.424)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Occipito-Frontal to Occipito-Mid-Face Ratio at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Occipito-Frontal to Occipito-Mid-Face Ratio at Month 3, Month 6, Month 9, and Month 12

End point description:

Occipito-Frontal to Occipito-Mid-Face Ratio were summarized for each treatment arm. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline (n=20,18,18)	1.00 (± 0.053)	1.00 (± 0.055)	1.00 (± 0.058)	
Change at Month 3 (n=16,18,17)	0.01 (± 0.024)	0.00 (± 0.039)	-0.01 (± 0.034)	
Change at Month 6 (n=17,17,15)	-0.01 (± 0.056)	-0.00 (± 0.027)	-0.02 (± 0.039)	
Change at Month 9 (n=17,17,11)	-0.01 (± 0.042)	-0.01 (± 0.034)	-0.02 (± 0.031)	
Change at Month 12 (n=7,9,2)	-0.04 (± 0.034)	-0.01 (± 0.028)	0.00 (± 0.018)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height Standard Deviation Score (Z-Score) at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Height Standard Deviation Score (Z-Score) at Month 3, Month 6, Month 9, and Month 12

End point description:

Height Standard Deviation Score (SDS) (z-score) was calculated as the difference between mean observed standing height at each visit and mean value of reference population divided by standard deviation of reference population. Analysis population included all subjects (aged 2-10 years) who

received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	18	18	
Units: Units on scale				
arithmetic mean (standard deviation)				
Baseline (n=18,17,18)	-0.2 (± 0.91)	0.1 (± 0.91)	0.2 (± 1.26)	
Change at Month 3 (n=15,17,17)	0.0 (± 0.13)	-0.0 (± 0.17)	-0.0 (± 0.26)	
Change at Month 6 (n=16,16,15)	-0.0 (± 0.21)	0.0 (± 0.21)	-0.0 (± 0.24)	
Change at Month 9 (n=16,16,11)	0.0 (± 0.26)	-0.0 (± 0.21)	0.0 (± 0.20)	
Change at Month 12 (n=7,9,2)	-0.0 (± 0.33)	0.1 (± 0.26)	-0.2 (± 0.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fixed Flexion Angles at Elbow at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Fixed Flexion Angles at Elbow at Month 3, Month 6, Month 9, and Month 12

End point description:

Fixed flexion angles at elbow data were presented for each treatment arm. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: degrees (°)				
arithmetic mean (standard deviation)				
Baseline (n=20,18,16)	-11.33 (± 20.002)	-18.31 (± 12.707)	-6.45 (± 17.628)	
Change at Month 3 (n=16,18,14)	2.23 (± 8.976)	4.29 (± 10.519)	1.09 (± 5.285)	
Change at Month 6 (n=16,17,14)	-0.02 (± 16.407)	2.80 (± 6.842)	0.83 (± 5.742)	

Change at Month 9 (n=17,17,11)	-0.03 (± 16.659)	4.83 (± 7.658)	0.77 (± 10.621)	
Change at Month 12 (n=7,9,2)	2.78 (± 34.075)	1.00 (± 7.016)	-0.08 (± 0.825)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Polysomnography Index Parameters at Month 12

End point title	Change From Baseline in Polysomnography Index Parameters at Month 12

End point description:

Polysomnography refers to a systematic process used to collect physiologic parameters during sleep. Polysomnography index parameters included apnea-hypopnea index (AHI) (obstructive and total), desaturation index (ie, number of desaturations per hour >3% from baseline). Analysis population included all subjects who received at least one dose of recifercept and with a documented current diagnosis of sleep disordered breathing at enrollment. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	4	8	
Units: Unitis on a scale				
arithmetic mean (standard deviation)				
Baseline (AHI, obstructive) (n=7,4,8)	3.79 (± 4.720)	1.20 (± 1.080)	6.23 (± 6.881)	
Change at Month 12 (AHI, obstructive) (n=3,1,0)	0.31 (± 9.902)	-1.90 (± 999999)	999999 (± 999999)	
Baseline (AHI, total) (n=7,4,8)	6.34 (± 5.837)	2.25 (± 2.872)	16.07 (± 26.299)	
Change at Month 12 (AHI, total) (n=3,1,0)	-1.03 (± 8.671)	-2.90 (± 999999)	999999 (± 999999)	
Baseline (Desaturation Index) (n=7,4,8)	4.90 (± 8.601)	2.18 (± 2.502)	13.53 (± 21.364)	
Change at Month 12 (Desaturation Index) (n=3,1,0)	-4.61 (± 14.598)	0.20 (± 999999)	999999 (± 999999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Polysomnography Other Parameters at Month 12

End point title	Change From Baseline in Polysomnography Other Parameters

	at Month 12

End point description:

Polysomnography refers to a systematic process used to collect physiologic parameters during sleep. Polysomnography other parameters included percentage time spent <90% oxygen saturation (SaO2), percentage time spent with end-tidal (ET) carbon dioxide (CO2) >50 mm Hg, and SaO2 nadir. Analysis population included all subjects who received at least one dose of recifercept and with a documented diagnosis of sleep-disordered breathing at enrollment. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	4	8	
Units: percentage (%)				
arithmetic mean (standard deviation)				
Baseline of <90% SaO2 (n=6,4,8)	16.43 (± 40.155)	24.79 (± 49.472)	0.72 (± 0.758)	
Change at Month 12 of <90% SaO2 (n=2,1,0)	-48.95 (± 69.933)	-99.00 (± 999999)	999999 (± 999999)	
Baseline of ET CO2>50 mm Hg (n=4,4,8)	7.02 (± 14.030)	9.50 (± 19.000)	7.37 (± 17.355)	
Change at Month 12 of ET CO2>50 mm Hg (n=2,1,0)	-14.03 (± 19.841)	-38.00 (± 999999)	999999 (± 999999)	
Baseline of SaO2 nadir (n=7,4,8)	92.29 (± 3.147)	94.25 (± 6.397)	91.06 (± 5.882)	
Change at Month 12 of SaO2 nadir (n=3,1,0)	-2.67 (± 7.095)	1.00 (± 999999)	999999 (± 999999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI) at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Body Mass Index (BMI) at Month 3, Month 6, Month 9, and Month 12

End point description:

Body Mass Index (BMI) = Weight (kg)/[(Standing Height (m))^2]. Standing height and weight were averaged over a visit before BMI was computed. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: kg/m^2				
arithmetic mean (standard deviation)				
Baseline (n=17,17,18)	19.83 (± 1.022)	20.18 (± 1.318)	21.57 (± 2.566)	
Change at Month 3 (n=15,17,17)	0.10 (± 0.376)	-0.13 (± 0.400)	-0.01 (± 0.635)	
Change at Month 6 (n=15,16,14)	0.25 (± 0.547)	0.04 (± 0.500)	-0.21 (± 0.843)	
Change at Month 9 (n=15,15,11)	0.36 (± 0.565)	0.06 (± 0.593)	0.02 (± 0.996)	
Change at Month 12 (n=6,9,2)	0.12 (± 0.671)	-0.28 (± 0.569)	-0.50 (± 0.735)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Waist : Chest Circumference Ratio at Month 9 and Month 12

End point title	Change From Baseline in Waist : Chest Circumference Ratio at Month 9 and Month 12

End point description:

Waist : Chest Ratio = Waist Circumference / Chest Circumference. Waist and chest circumference were averaged over a visit before waist : chest circumference ratio was computed. Analysis population included all subjects who received at least one dose of recifercept. Here, "n" signifies subjects evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	18	
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline (n=19,17,16)	0.93 (± 0.048)	0.94 (± 0.051)	0.97 (± 0.052)	
Change at Month 9 (n=1,1,1)	0.07 (± 999999)	0.00 (± 999999)	-0.01 (± 999999)	
Change at Month 12 (n=6,9,2)	0.05 (± 0.074)	0.00 (± 0.063)	-0.01 (± 0.007)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life in Short Stature Youth (QoLISSY) Brief Total Score at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Quality of Life in Short Stature Youth (QoLISSY) Brief Total Score at Month 3, Month 6, Month 9, and Month 12

End point description:

QoLISSY Brief measures health-related quality of life (HRQoL) in children 4-18 years old from the subject and parent perspectives. The 9 items on the QoLISSY Brief were selected from the full QoLISSY physical, social and emotional HRQoL dimensions. The QoLISSY Brief questions ask the subject or caregiver about their status currently. Intended for children or caregivers of children, the instrument uses a 5-point Likert Scale ranging from 'not at all/never' to 'extremely/always'. The QoLISSY Brief total score is the 0-100 transformed sum of the 9 item scores, with higher scores representing better quality of life. Analysis population included all subjects who received at least one dose of recifercept.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Units on scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[2] - The results were not summarized due to the study early termination.

[3] - The results were not summarized due to the study early termination.

[4] - The results were not summarized due to the study early termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Childhood Health Assessment Questionnaire (CHAQ) Component and Index Scores at Month 3, Month 6, Month 9, and Month 12

End point title	Change From Baseline in Childhood Health Assessment Questionnaire (CHAQ) Component and Index Scores at Month 3, Month 6, Month 9, and Month 12

End point description:

CHAQ (adapted for achondroplasia) is a 36-item measure of health status and physical function, which includes 8 components and 2 scale (pain and well being). Both a disability and discomfort index can be calculated. The CHAQ (adapted for achondroplasia) has a recall period of “over the past week”. A 5 point Likert Scale was utilized ranging from “without any difficulty” to “unable to do” and a “not applicable” option. Lower component and index scores indicate better health status/functioning. Analysis population included all subjects who received at least one dose of recifercept.

End point type	Secondary

End point timeframe:

Baseline, Month 3, Month 6, Month 9, and Month 12

End point values	Recifercept 1 mg/kg QW	Recifercept 2 mg/kg BIW	Recifercept 1.5 mg/kg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: Units on scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[5] - The results were not summarized due to the study early termination.

[6] - The results were not summarized due to the study early termination.

[7] - The results were not summarized due to the study early termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: The first dose up to 28 to 35 days after the last dose of study intervention (27 months).	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0
Reporting groups	
Reporting group title	Recifercept 1 mg/kg QW
Reporting group description: -	
Reporting group title	Recifercept 1.5 mg/kg QD
Reporting group description: -	
Reporting group title	Recifercept 2 mg/kg BIW
Reporting group description: -	

Serious adverse events	Recifercept 1 mg/kg QW	Recifercept 1.5 mg/kg QD	Recifercept 2 mg/kg BIW
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 19 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Recifercept 1 mg/kg QW	Recifercept 1.5 mg/kg QD	Recifercept 2 mg/kg BIW
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	16 / 18 (88.89%)	19 / 19 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Melanocytic naevus			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	3 / 19 (15.79%)
occurrences (all)	1	0	3
Hyperaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	5	0
Haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Injection site oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Injection site mass			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	3
Injection site induration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	0	2	5
Injection site hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injection site haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	2 / 19 (10.53%)
occurrences (all)	0	2	4
Injection site haematoma			

subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			
subjects affected / exposed	4 / 20 (20.00%)	4 / 18 (22.22%)	5 / 19 (26.32%)
occurrences (all)	30	11	17
Injection site bruising			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	0 / 19 (0.00%)
occurrences (all)	5	3	0
Chest pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Injection site pruritus			
subjects affected / exposed	3 / 20 (15.00%)	2 / 18 (11.11%)	3 / 19 (15.79%)
occurrences (all)	3	9	8
Injection site swelling			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	1 / 19 (5.26%)
occurrences (all)	1	4	1
Injection site reaction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	3 / 19 (15.79%)
occurrences (all)	0	3	5
Injection site rash			
subjects affected / exposed	4 / 20 (20.00%)	2 / 18 (11.11%)	4 / 19 (21.05%)
occurrences (all)	7	5	12
Injection site urticaria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Injection site warmth			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	4 / 18 (22.22%)	3 / 19 (15.79%)
occurrences (all)	4	5	5
Respiratory, thoracic and mediastinal disorders			
Tonsillar inflammation			

subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	0	1	2
Obstructive sleep apnoea syndrome			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Cough			
subjects affected / exposed	2 / 20 (10.00%)	1 / 18 (5.56%)	2 / 19 (10.53%)
occurrences (all)	2	4	2
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Antisocial behaviour			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Product issues			
Device malfunction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
SARS-CoV-2 test positive			

subjects affected / exposed	3 / 20 (15.00%)	4 / 18 (22.22%)	7 / 19 (36.84%)
occurrences (all)	3	4	7
Lymphocyte count decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haemoglobin increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haematocrit increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Blood urea increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood phosphorus increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	3 / 19 (15.79%)
occurrences (all)	0	1	3
Blood creatinine decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Blood calcium increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Blood bicarbonate increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blood albumin increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood potassium increased			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	2 / 19 (10.53%)
occurrences (all)	0	2	2

Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Bite			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Burns second degree			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Hand fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Post procedural discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nervous system disorders			

Tension headache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Psychomotor hyperactivity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 20 (10.00%)	2 / 18 (11.11%)	2 / 19 (10.53%)
occurrences (all)	5	8	3
Dyskinesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Thrombocytosis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	2 / 19 (10.53%)
occurrences (all)	0	3	3
Monocytosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Otorrhoea			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Ear pain			
subjects affected / exposed	1 / 20 (5.00%)	3 / 18 (16.67%)	2 / 19 (10.53%)
occurrences (all)	2	3	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Anal pruritus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Dental caries			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Intra-abdominal haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	2 / 19 (10.53%)
occurrences (all)	4	1	2

Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Drug eruption			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dermatitis atopic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cafe au lait spots			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Acanthosis nigricans			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin swelling			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Skin reaction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Rash papular			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Neurodermatitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Erythema			

subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
Eczema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Ecchymosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	2 / 19 (10.53%)
occurrences (all)	1	1	4
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	4	1	2
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	3 / 19 (15.79%)
occurrences (all)	3	2	5
Neck pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Herpes virus infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Herpangina			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Gastrointestinal infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)	2 / 18 (11.11%)	2 / 19 (10.53%)
occurrences (all)	2	2	2
Ear infection			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	2 / 19 (10.53%)
occurrences (all)	4	1	3
COVID-19			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
Suspected COVID-19			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	3 / 19 (15.79%)
occurrences (all)	3	2	5
Varicella			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin candida			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinitis			

subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	0	1	2
Otitis media bacterial			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	1 / 19 (5.26%)
occurrences (all)	3	1	1
Oral herpes			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
Nasopharyngitis			
subjects affected / exposed	5 / 20 (25.00%)	2 / 18 (11.11%)	5 / 19 (26.32%)
occurrences (all)	6	2	7
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	3
Viral rash			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2020	The following changes were made due to regulatory requests from different countries which the sponsor classified as substantial. Section 1.3: Additional ECG at close to Cmax (Day 4) and additional pharmacokinetic & immunogenicity sample at Month 9 were added. Clarify that monitoring after first 5 doses be done by appropriately trained individuals with access to facilities necessary to manage hypersensitivity MRI at baseline was added and only applicable for those without scan in last 12 months. Section 4.1: Clarify age range to align with inclusion criteria. Section 4.2: Clarify language around baseline MRI. Section 5.1: Provide clear demarcation between main and exploratory cohorts. Section 5.2: Exclude those with evidence of significant renal or hepatic impairment, or with history of hypersensitivity to study intervention or excipients. Section 6.1.1: To clarify that only parent/caregiver/ healthcare professional should administer the study medication. Section 6.6: Clarify age of those in block A. Section 6.6.1: There will be a planned eDMC review after block A prior to progressing to block B. Change SUSAR to SAR. Clarify that the primary efficacy analysis will be done on treatment naïve subjects enrolled to each cohort. Section 7.1: To clarify the role of the investigator in stopping study intervention as a result of adverse events or need for prohibited treatments. Section 8.2.4: Add D4 ECG. Section 8.3.1: Confirm that investigator should enquire about both AEs and SAEs at follow-up visit. Section 9.4.2: Clarify the analysis to be performed as ANOVA not ANCOVA. Sections 9.4.2 & 9.4.3: Clarify the analysis to be performed (removal of stratification). Section 9.6: Describe control of familywise error rate. Section 10.4.2: Confirm that WOCBP cannot enroll in the study since subjects must be Tanner stage 1 at enrolment. Section 10.5: Clarify that LFTs are measured in routine safety assessments.
14 April 2021	The changes in this amendment were made due to eDMC recommendations and additional regulatory requests from different countries. Section 1.2: Block B enrollment of high dose subjects was reduced from n=8 to n=3 and enrollment using a sentinel approach. In addition, Block B 2-6yrs old at low & medium doses was expanded from n=3 to n=8 per dose with enrollment also using a sentinel approach. Sections 4.1 & 6.6: Block B to Block C progression rules were revised in line with the sentinel approach from n=3 per dose to n=2 per dose. The number of high dose children included in the safety review will stay the same (n=3). Appendix 2: Addition of Phosphate to chemistry panel and collection of time since last food intake. Section 1.3: Addition of Hematology & Chemistry Labs at Month 9. Section 2.2.1: Final data from study C4181002 added. Summary safety & PK data from Block A added. Section 5.2: Criterion No. 6 CrCL GFR formula 'bedside' Schwartz was added. Section 6.2.1: Clarification of what should be considered adequate training for caregivers for home drug administration was added. Section 6.4.1: Clarified instructions for caregivers regarding injection site reactions during home dosing is documented in the caregiver dosing diary. Sections 8.6, 8.7.2, and 8.7.7: Confirmation this section is not applicable in Denmark.

23 March 2022	The changes in this amendment were made due to eDMC recommendations, regulatory requests from different countries and addition of a PK cohort. Section 1.2: Update to expand recruitment of those aged 2-<6y in block C at the high dose (1.5 mg/kg daily) from a total of n=3 to n=8 (ie, move all 5 subjects from block D). Section 6.6.1: Update to a sentinel dosing approach for recruiting those aged 2-<6 years in block C such that n=2 at high dose will be dosed followed by a 2-week delay before further dosing occurs in that age group. Section 1.3: Added footnote for blood chemistry that subjects are required to fast for >4 hours prior to blood sampling. Section 8.2.5 & Appendix 2: Subjects are required to fast for >4 hours prior to blood sampling. Section 2.2.1: Updated clinical safety as of September 2021, to include number of subjects per Block and AEs. Section 4.1: Updated to include a PK cohort that will include 12 subjects who will randomly receive 1 dose of Phase 2 (process 1c) followed by 1 dose of proposed Phase 3 (process 2) recifercept formulation or vice versa in a cross-over study, at select sites only. PK analysis following each dose will be conducted to evaluate the two formulations. Single dose of 3 mg/kg will be used for the PK study cohort. Dose of the cohort could be changed due to emerging safety and efficacy data in the study. Section 4.3: Updated to include a PK cohort of 12 subjects. The tentative dose for the PK study cohort is 3 mg/kg. The dose selected for the PK cohort could be changed after evaluating the entirety of the safety, PK and efficacy data collected in the program before initiating the cohort. The dose selected will not exceed the highest dose found to be safe and tolerated. Section 8.0: Updated to include the PK cohort, as the total blood volume collected for individual subjects is approximately 67 mL in this cohort. Sections 1.2, 1.3, 8.5, 9.2, 9.3, and 9.4: Updated to include PK cohort.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 November 2022	Following the results of an interim analysis in this study (C4181005) and the temporary halt decision of 20 October 2022, 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.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The additional PK cohort for 2 formulations was not completed as the study was early terminated prior to enrolling any subjects in the PK cohort. No data was collected for additional PK cohort.

Notes: