Clinical trial results:
A double-blind, placebo-controlled, randomized withdrawal study to evaluate the safety, pharmacokinetics and efficacy of CRN00808 in patients with acromegaly that are responders to octreotide LAR or lanreotide depot (ACROBAT EVOLVE)

Summary

EudraCT number	2018-001833-42
Trial protocol	HU SK GR PL GB IT RO
Global end of trial date	12 August 2020

Results information

Result version number	v1 (current)
This version publication date	27 September 2024
First version publication date	27 September 2024

Trial information

Trial identification

Sponsor protocol code	CRN00808-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03729555
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Crinetics Pharmaceuticals, Inc.
Sponsor organisation address	6055 Lusk Blvd, San Diego, United States, CA 92121
Public contact	Crinetics Clinical Trials, Crinetics Pharmaceuticals, clinicaltrials@crinetics.com
Scientific contact	Crinetics Clinical Trials, Crinetics Pharmaceuticals, clinicaltrials@crinetics.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	13 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2020
Global end of trial reached?	Yes
Global end of trial date	12 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1.To determine the efficacy of CRN00808 in acromegaly subjects that are complete responders to parenteral octreotide LAR or lanreotide depot monotherapy;
2.To evaluate the safety and tolerability of CRN00808 in acromegaly subjects;
3.To evaluate the pharmacokinetics (PK) of CRN00808 in acromegaly subjects.

Protection of trial subjects:

This study was conducted in accordance with the protocol and the Declaration of Helsinki, as well as current ICH GCP guidelines and applicable regulatory requirements

Background therapy:

Inclusion criteria states diagnosis of acromegaly must be controlled on a stable approved dose of octreotide LAR or lanreotide depot

Evidence for comparator: -

Actual start date of recruitment	10 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Hungary: 3
Worldwide total number of subjects	13
EEA total number of subjects	6

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Medically stable adult subjects 18 to 75 years of age, inclusive, with a confirmed acromegaly diagnosis that was controlled on a stable approved dose of octreotide LAR or lanreotide depot. At a minimum, there had to be documentation available of a pituitary tumor and elevated IGF-1 in the past.

Pre-assignment

Screening details:

Medically stable adult subjects 18 to 75 years of age, with a confirmed acromegaly diagnosis that was controlled on a stable approved dose of octreotide LAR or lanreotide depot. There had to be documentation available of a pituitary tumour and elevated IGF-1 in the past.

Period 1

Period 1 title	Titration
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Arm title	Treatment

Arm description:

During the titration period, the study drug dose was titrated up in a blinded fashion, provided that the current dose was tolerated by the subject and the IGF-1 value at V4/W2 was >0.9×ULN.

Arm type	Experimental
Investigational medicinal product name	paltusotine
Investigational medicinal product code	CRN00808
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The Treatment Period started with the first dose of study drug (10 mg for all subjects). Paltusotine (10 mg oral capsule) was administered once daily after an overnight fast of at least 6 hours. At V6/W4, the study drug dose was titrated up in a blinded fashion, provided that the current dose was tolerated by the subject and the IGF-1 value at V4/W2 was >0.9×ULN. Dose increases in 10 mg increments were allowed only at the V6/W4 (from 10 mg to 20 mg) and V9/W7 (from 10 mg to 20 mg, or from 20 mg to 30 mg) visits. No further up-titration was allowed. The daily dose did not exceed 30 mg.

Number of subjects in period 1	Treatment
Started	13
Completed	11
Not completed	2
Consent withdrawn by subject	1
Unable to attend visits due to pandemic	1

Period 2

Period 2 title	Randomised Withdrawal
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomised Withdrawal -Treatment with Paltusotine

Arm description:

Eligibility for randomization into the RWP was made based on information at the V10/W8 and V11/W10. To be eligible for randomization, the subject had to have IGF-1 value ≤ULN at V10/W8 and an Investigator determination at V11/W10 that the subject tolerated the study drug.

Arm type	Experimental
Investigational medicinal product name	paltusotine
Investigational medicinal product code	CRN00808
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The subject administered paltusotine (oral capsule) once daily at the dose level tolerated at the end of the treatment period (10 mg, 20 mg or 30 mg). The daily dose did not exceed 30 mg.

Arm title	Randomised Withdrawal - Placebo

Arm description:

Eligibility for randomization into the RWP was made based on information at the V10/W8 and V11/W10. To be eligible for randomization, the subject had to have IGF-1 value ≤ULN at V10/W8 and an Investigator determination at V11/W10 that the subject tolerated the study drug. The subjects were randomized at V11/W10 in a blinded manner to be switched to a placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo to match paltusotine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match paltusotine was administered once daily for the duration of the randomised withdrawal period

Number of subjects in period 2[1]	Randomised Withdrawal - Treatment with Paltusotine	Randomised Withdrawal - Placebo
Started	3	4
Completed	3	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 7 subjects were enrolled in RWP, 6 were not, due to IGF-1 (n=4), discontinuation (n=1), and other (n=1). No subjects discontinued due to tolerability.

Period 3

Period 3 title	Not Randomised in Withdrawal Study
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Arm title	Treatment (not randomised)

Arm description:

Subjects not eligible for randomisation into the RWP were allowed to stay in the study and continue a study drug dose that was tolerated until the subject completed all study visits or until criteria to resume standard acromegaly therapy and discontinuation from the study were met.

Arm type	Experimental
Investigational medicinal product name	paltusotine
Investigational medicinal product code	CRN00808
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered paltusotine (oral capsule) once daily at the dose tolerated at the end of the titration/treatment period (10 mg, 20 mg or 30 mg). The daily dose did not exceed 30 mg.

Number of subjects in period 3[2]	Treatment (not randomised)
Started	6
Completed	6

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 7 subjects were enrolled in RWP, 6 were not, due to IGF-1 (n=4), discontinuation (n=1), and other (n=1). No subjects discontinued due to tolerability.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
During the titration period, the study drug dose was titrated up in a blinded fashion, provided that the current dose was tolerated by the subject and the IGF-1 value at V4/W2 was >0.9×ULN.	

Reporting group values	Treatment	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	53.5		
standard deviation	± 13.76	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	7	7	
Ethnicity Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	10	10	
Unknown	0	0	
Race Units: Subjects			
White	12	12	
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other	1	1	
UGT1A1 Genotype Units: Subjects			
*1/*1	5	5	
*1/*80	5	5	
*80/*80	2	2	

Not reported	1	1	
UGT1A1 Phenotype Units: Subjects			
Normal Metabolizer	5	5	
Intermediate Metabolizer	5	5	
Poor Metabolizer	2	2	
Not reported	1	1	
Height Units: cm			
arithmetic mean	171.02		
standard deviation	± 13.748	-	
Weight Units: kg			
arithmetic mean	80.97		
standard deviation	± 18.088	-	
BMI Units: kg/m2			
arithmetic mean	27.52		
standard deviation	± 4.903	-	
Ring Size Units: mm			
arithmetic mean	12.8		
standard deviation	± 3.63	-	

Subject analysis sets	
Subject analysis set title	ITT Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who received at least one dose of the study drug	
Subject analysis set title	mITT Analysis Set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All subjects from the ITT analysis set who were randomised into the RWP	

Reporting group values	ITT Analysis Set	mITT Analysis Set	
Number of subjects	13	7	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	5	
From 65-84 years	4	2	
85 years and over	0	0	

Age continuous Units: years			
arithmetic mean	53.5	50	
standard deviation	± 13.76	± 15.41	
Gender categorical Units: Subjects			
Female	6	4	
Male	7	3	
Ethnicity Units: Subjects			
Hispanic or Latino	3	1	
Not Hispanic or Latino	10	6	
Unknown	0	0	
Race Units: Subjects			
White	12	7	
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific	0	0	
Islander	0	0	
Other	1	0	
UGT1A1 Genotype Units: Subjects			
*1/*1	5	3	
*1/*80	5	3	
*80/*80	2	1	
Not reported	1		
UGT1A1 Phenotype Units: Subjects			
Normal Metabolizer	5	3	
Intermediate Metabolizer	5	3	
Poor Metabolizer	2	1	
Not reported	1		
Height Units: cm			
arithmetic mean	171.02	173.83	
standard deviation	± 13.748	± 15.092	
Weight Units: kg			
arithmetic mean	80.97	82.63	
standard deviation	± 18.088	± 16.230	
BMI Units: kg/m2			
arithmetic mean	27.52	26.52	
standard deviation	± 4.903	± 2.236	
Ring Size Units: mm			
arithmetic mean	12.8	14.7	
standard deviation	± 3.63	± 3.88	

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

During the titration period, the study drug dose was titrated up in a blinded fashion, provided that the current dose was tolerated by the subject and the IGF-1 value at V4/W2 was >0.9×ULN.

Reporting group title	Randomised Withdrawal -Treatment with Paltusotine

Reporting group description:

Eligibility for randomization into the RWP was made based on information at the V10/W8 and V11/W10. To be eligible for randomization, the subject had to have IGF-1 value ≤ULN at V10/W8 and an Investigator determination at V11/W10 that the subject tolerated the study drug.

Reporting group title	Randomised Withdrawal - Placebo

Reporting group description:

Eligibility for randomization into the RWP was made based on information at the V10/W8 and V11/W10. To be eligible for randomization, the subject had to have IGF-1 value ≤ULN at V10/W8 and an Investigator determination at V11/W10 that the subject tolerated the study drug. The subjects were randomized at V11/W10 in a blinded manner to be switched to a placebo.

Reporting group title	Treatment (not randomised)

Reporting group description:

Subjects not eligible for randomisation into the RWP were allowed to stay in the study and continue a study drug dose that was tolerated until the subject completed all study visits or until criteria to resume standard acromegaly therapy and discontinuation from the study were met.

Subject analysis set title	ITT Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received at least one dose of the study drug

Subject analysis set title	mITT Analysis Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects from the ITT analysis set who were randomised into the RWP

Primary: The proportion of randomized subjects who met responder criteria at week 13

End point title	The proportion of randomized subjects who met responder criteria at week 13[1]

End point description:

Responder criteria was based on the mean of two consecutive IGF-1 measurements ≤ULN at Week 13 (visit 13 and visit 14).
CRN00808 and placebo was compared for the mITT Analysis Set on change from RWP Baseline/Week 10 to Week 13 using a rank ANCOVA model including fixed effects for randomization strata and treatment, and with the ranked RWP Baseline/Week 10 value includedas a covariate. The Hodges-Lehman estimate of the median treatment difference with associated 95% CI was calculated. p value = 0.6203

End point type	Primary

End point timeframe:

Week 13

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: Please refer to the endpoint description for details of statistical analyses

End point values	Randomised Withdrawal - Treatment with Paltusotine	Randomised Withdrawal - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Percentage of responders				
number (confidence interval 95%)	66.7 (9.4 to 99.2)	25.0 (0.6 to 80.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGF-1 between Week 10 and Week 13

End point title	Change in IGF-1 between Week 10 and Week 13

End point description:

End point type	Secondary

End point timeframe:

Between RWP week 10 and RWP week 13

End point values	Randomised Withdrawal - Treatment with Paltusotine	Randomised Withdrawal - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Percent change in IGF1 x ULN				
arithmetic mean (standard deviation)	4.04 (± 5.064)	48.17 (± 41.408)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in growth hormone (GH) levels between Week 8 and Week 13

End point title	Change in growth hormone (GH) levels between Week 8 and Week 13

End point description:

End point type	Secondary

End point timeframe:

From RWP baseline (week 8) to RWP week 13

End point values	mITT Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: precent change in GH				
number (confidence interval 95%)	40.6 (-361.6 to 106.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in symptoms of acromegaly as measured by total Acromegaly symptom diary (ASD) score between Week 10 and Week 13

End point title	Change in symptoms of acromegaly as measured by total Acromegaly symptom diary (ASD) score between Week 10 and Week 13

End point description:

End point type	Secondary

End point timeframe:

From RWP week 10 to RWP week 13

End point values	mITT Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Difference in total ASD score change				
median (confidence interval 95%)	-1.1 (-4.3 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of participation for each subject after obtaining a signed informed consent was up to 23 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Safety analysis set/titration period

Reporting group description:

All participants who received a dose of Paltusotine during the titration period

Reporting group title	Randomised withdrawal period- Paltusotine

Reporting group description:

Adverse events reported during the randomised withdrawal period by those receiving Paltusotine treatment during the randomised withdrawal stage

Reporting group title	Randomised withdrawal period- Placebo

Reporting group description:

Adverse events reported during the randomised withdrawal period by those receiving Paltusotine treatment

Reporting group title	Total Paltusotine

Reporting group description:

Includes those not eligible for the trial randomised withdrawal period were allowed to stay in the study and continue a study drug dose that was tolerated until the subject completed all study visits

Serious adverse events	Safety analysis set/titration period	Randomised withdrawal period- Paltusotine	Randomised withdrawal period- Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Total Paltusotine		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety analysis set/titration period	Randomised withdrawal period-Paltusotine	Randomised withdrawal period-Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 13 (61.54%)	3 / 3 (100.00%)	4 / 4 (100.00%)
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 13 (23.08%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Paraesthesia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 13 (15.38%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Peripheral swelling			
subjects affected / exposed	2 / 13 (15.38%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	2
Back pain			

subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
COVID-19			
subjects affected / exposed	1 / 13 (7.69%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Total Paltusotine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 13 (76.92%)		
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood triglycerides increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			

Headache			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	3		
Peripheral swelling			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sleep apnoea syndrome			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Skin exfoliation subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1		

Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2019	Summary of changes made in amendment 1: - Added patient-facing quality of life and acromegaly symptom scales with corresponding adjustments to the study secondary/exploratory endpoints. The purpose of these scales was to collect patient-reported data to further the development of a scale to assess the symptom burden of acromegaly. - Added stopping criteria for cardiac, liver, and other clinical conditions. - Changed to pre-dose collection of IGF-1 samples for endpoint-related visits. - Modification of certain inclusion/exclusion criteria and additional administrative updates.
06 June 2019	Summary of changes made in amendment 2: - The demotion of a Secondary Endpoint to an Exploratory Endpoint (Proportion of subjects who achieved serum GH <5.0 ng/mL at W13). - Certain visits where minimal study procedures were performed were changed to Phone Call visits instead of site visits to reduce visit burden on subjects. - Changes to IGF-1 sample collection and titration criteria were made due to the change in visit structure of certain visits from site to Phone Visits. - Included the option to allow for certain visits to be conducted by mobile home health professionals at the option of the principal investigator and subject. These home health assessments were performed by qualified and trained staff and under the supervision of each site principal investigator, with activities specifically delegated by the principal investigator. - Reduction in collection time points of the ASD. - Changes to ASD scale question, wording, and scoring of the total ASD. - Subjects with prior radiation therapy in some circumstances were allowed to enrol in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 March 2020	The Sponsor halted enrollment in the study early due to business reasons; subjects already enrolled in this study at the time of enrollment cessation continued until study completion.	-

Notes:

Limitations and caveats

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

Due to small sample size, a number of endpoints were listed but not summarised.

Notes: