Clinical trial results:
An open label exploratory study to evaluate the safety, pharmacokinetics and efficacy of CRN00808 in patients with acromegaly treated with somatostatin analogue based treatment regimens (ACROBAT EDGE)

Summary

EudraCT number	2018-002230-20
Trial protocol	HU SK DE GR PL GB IT RO
Global end of trial date	31 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	CRN00808-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03789656
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, Inc., , Crinetics Pharmaceuticals, clinicaltrials@crinetics.com
Scientific contact	Crinetics Clinical Trials, Crinetics Pharmaceuticals, Inc., , 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	01 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 August 2020
Global end of trial reached?	Yes
Global end of trial date	31 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1.To evaluate the efficacy of paltusotine (CRN00808) in acromegaly subjects treated with somatostatin receptor ligand (SRL) based treatment regimens;
2.To evaluate the safety and tolerability of paltusotine (CRN00808)in acromegaly subjects;
3.To evaluate the pharmacokinetics (PK) of paltusotine (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: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2019
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	Poland: 2
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Brazil: 13
Worldwide total number of subjects	47
EEA total number of subjects	19

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)	39
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 45 subjects were planned to be enrolled in the study. 47 subjects participated in the study.

Pre-assignment

Screening details:

A total of 88 subjects were screened for eligibility, of which 41 were screen failures, and 47 subjects were enrolled in the study. Of the 47 subjects who received paltusotine (CRN00808), 42 subjects completed the trial, 4 subjects withdrew from the treatment period, and 1 subject withdrew during follow-up.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study, the study drug was not blinded. However, after the initial dose, further dose increases/decreases were blinded to the Investigator and subject.

Arms

Arm title	Treatment

Arm description:

This was a Phase 2, open-label, dose blinded, exploratory study designed to evaluate the efficacy, safety, and PK of paltusotine in subjects with acromegaly treated with SRL based treatment regimens. All patients enrolled in the study were treated with paltusotine. The first dose was 10mg for all subjects and uptitrated in a blinded manner from week 4 onwards.

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 first dose was 10 mg for all subjects at V3, which occurred 4 weeks after V1b, when the last dose of standard acromegaly treatment was administered. Subjects self administered the study drug (4 capsules daily).

During the V6/W4 and V9/W7, the dose was titrated up in a blinded fashion, if the preceding IGF-1 values collected in V4/W2, and in V7/W5, respectively, were >0.9× ULN and if the subject tolerated the current dose. At V12/W10, the dose was titrated up in a blinded fashion, if the preceding IGF-1 value collected in V10/W8 was >ULN and if the subject tolerated the current dose.

Dose increases in 10 mg increments were allowed only at the V6/W4 (from 10 mg to 20 mg), V9/W7 (from 10 mg to 20 mg, or from 20 mg to 30 mg), and V12/W10 (from 10 mg to 20 mg, from 20 mg to 30 mg, or from 30 mg to 40 mg). No further up-titration was allowed. The daily dose did not exceed 40 mg.

No further treatment with the study drug was allowed after completion of V14/W13.

Number of subjects in period 1	Treatment
Started	47
Completed	42
Not completed	5
Consent withdrawn by subject	1
Unable to travel	1
COVID-19	1
Prohibited Medication	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

All subjects who received at least 1 dose of study drug. Of the 47 subjects who received CRN00808-03, 42 subjects completed the trial, 4 subjects withdrew from treatment period, and 1 subject withdrew consent during follow up. No subjects withdrew due to adverse events.

Reporting group values	Overall Trial	Total	
Number of subjects	47	47	
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)	39	39	
From 65-84 years	8	8	
85 years and over	0	0	
Age continuous			
The median age of all subjects participating in the study			
Units: years			
median	51.0		
inter-quartile range (Q1-Q3)	43.0 to 61.0	-	
Gender categorical Units: Subjects			
Male	20	20	
Female	27	27	
Ethnicity Units: Subjects			
Hispanic or Latino	13	13	
Not Hispanic or Latino	34	34	
Race Units: Subjects			
White	42	42	
Asian	1	1	
Black or African American	2	2	
Other	2	2	
Geographic Region Units: Subjects			
North America	8	8	
Europe	24	24	
Rest of World	15	15	

Height			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: centimetre			
median	170.25		
inter-quartile range (Q1-Q3)	165.00 to 176.10	-	
Weight			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s)			
median	87.15		
inter-quartile range (Q1-Q3)	75.10 to 104.20	-	
BMI			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s)/square metre			
median	29.95		
inter-quartile range (Q1-Q3)	26.50 to 34.80	-	
Ring Size			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: millimetre(s)			
median	12.0		
inter-quartile range (Q1-Q3)	9.0 to 13.0	-	
IGF-1 (x ULN) at Baseline			
Units: x ULN			
median	1.214		
inter-quartile range (Q1-Q3)	0.965 to 1.466	-	
Serum Growth Hormone Levels			
Units: nanogram(s)/millilitre			
median	0.8733		
inter-quartile range (Q1-Q3)	0.4688 to 1.6127	-	
Acromegaly Symptom Diary (ASD) Score			
For overall trial, based on n=20 For group 1, based on n=13 For group 2, based on n=4 For group 3, based on n=2			
Units: ASD Score			
median	12.00		
inter-quartile range (Q1-Q3)	4.21 to 23.93	-	
IGFBP-3			
Units: x ULN			
median	0.786		
inter-quartile range (Q1-Q3)	0.687 to 0.882	-	

Subject analysis sets

Subject analysis set title	Group 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Efficacy Analysis Set - Primary Analysis Population for all efficacy analyses. Only includes subjects from Group 1.

Eligibility to enter this group was specified as: Partial responders on a stable treatment of octreotide

long-acting release (LAR) or lanreotide depot (at least 1 Screening IGF-1 value was greater than upper limit of normal (ULN), and the V2 value was ≤2.5× ULN)

Subject analysis set title	Group 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Partial responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (at least 1 Screening IGF-1 value was >ULN, and the V2 value was ≤2.5 × ULN)

Subject analysis set title	Group 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values were ≤ULN)

Subject analysis set title	Group 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Complete responders on a stable dose of pasireotide LAR (mean of Screening IGF-1 values were ≤ULN)

Subject analysis set title	Group 5
Subject analysis set type	Safety analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values were ≤ULN).

Subject analysis set title	Group 1 - Octreotide LAR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects in Group 1 previously treated with Octreotide LAR

Subject analysis set title	Group 1 - Lanreotide depot
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects in Group 1 previously treated with Lanreotide depot

Subject analysis set title	Group 3, 4, and 5
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter group 3 was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values were ≤ULN)
Eligibility to enter group 4 was specified as: Complete responders on a stable dose of pasireotide LAR(mean of Screening IGF-1 values were ≤ULN)
Eligibility to enter group 5 was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values were ≤ULN).

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	25	10	5
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

Adults (18-64 years)	22	8	4
From 65-84 years	3	2	1
85 years and over	0	0	0
Age continuous			
The median age of all subjects participating in the study			
Units: years			
median	52	52.5	51.0
inter-quartile range (Q1-Q3)	46.0 to 59.0	39.0 to 61.0	49.0 to 54.0
Gender categorical			
Units: Subjects			
Male	14	3	2
Female	11	7	3
Ethnicity			
Units: Subjects			
Hispanic or Latino	4	6	2
Not Hispanic or Latino	21	4	3
Race			
Units: Subjects			
White	25	5	5
Asian	0	1	0
Black or African American	0	2	0
Other	0	2	0
Geographic Region			
Units: Subjects			
North America	3	1	0
Europe	18	2	1
Rest of World	4	7	4
Height			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: centimetre			
median	173.95	167.75	173.00
inter-quartile range (Q1-Q3)	166.50 to 178.50	160.00 to 173.00	164.00 to 176.00
Weight			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s)			
median	90.95	84.95	87.30
inter-quartile range (Q1-Q3)	76.05 to 103.60	75.00 to 117.00	79.70 to 88.20
BMI			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s)/square metre			
median	29.25	30.30	28.50
inter-quartile range (Q1-Q3)	26.30 to 34.15	27.90 to 38.10	28.20 to 30.40
Ring Size			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: millimetre(s)			
median	12.5	12.0	11.0
inter-quartile range (Q1-Q3)	9.5 to 14.5	9.0 to 12.0	10.0 to 12.0
IGF-1 (x ULN) at Baseline			
Units: x ULN			

median	1.335	1.400	0.922
inter-quartile range (Q1-Q3)	1.078 to 1.471	1.214 to 1.650	0.864 to 0.928
Serum Growth Hormone Levels			
Units: nanogram(s)/millilitre			
median	0.6907	1.0490	0.8733
inter-quartile range (Q1-Q3)	0.4910 to 1.5545	0.5118 to 1.6127	0.7088 to 1.5585
Acromegaly Symptom Diary (ASD) Score			
For overall trial, based on n=20 For group 1, based on n=13 For group 2, based on n=4 For group 3, based on n=2			
Units: ASD Score			
median	13.50	8.79	2.21
inter-quartile range (Q1-Q3)	5.29 to 24.00	3.29 to 17.71	1.00 to 3.43
IGFBP-3			
Units: x ULN			
median	0.789	0.803	0.684
inter-quartile range (Q1-Q3)	0.736 to 0.899	0.725 to 0.886	0.668 to 0.693

Reporting group values	Group 4	Group 5	Group 1 - Octreotide LAR
Number of subjects	4	3	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)	3	2	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
The median age of all subjects participating in the study			
Units: years			
median	56.0	38.0	
inter-quartile range (Q1-Q3)	48.0 to 64.5	35.0 to 66.0	
Gender categorical			
Units: Subjects			
Male	1	0	
Female	3	3	
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	4	2	
Race			
Units: Subjects			
White	4	3	
Asian	0	0	
Black or African American	0	0	

Other	0	0	
Geographic Region Units: Subjects			
North America	2	2	
Europe	2	1	
Rest of World	0	0	
Height			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: centimetre			
median	169.45	157.50	
inter-quartile range (Q1-Q3)	168.45 to 179.65	155.50 to 169.00	
Weight			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s)			
median	107.00	77.50	
inter-quartile range (Q1-Q3)	88.75 to 114.35	59.00 to 82.40	
BMI			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s)/square metre			
median	34.85	31.20	
inter-quartile range (Q1-Q3)	29.55 to 37.25	20.70 to 34.10	
Ring Size			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: millimetre(s)			
median	12.5	8.0	
inter-quartile range (Q1-Q3)	9.5 to 19.0	8.0 to 9.0	
IGF-1 (x ULN) at Baseline Units: x ULN			
median	0.659	0.909	
inter-quartile range (Q1-Q3)	0.600 to 0.842	0.806 to 0.964	
Serum Growth Hormone Levels Units: nanogram(s)/millilitre			
median	0.1976	2.8763	
inter-quartile range (Q1-Q3)	0.1518 to 0.6460	0.1403 to 10.2843	
Acromegaly Symptom Diary (ASD) Score			
For overall trial, based on n=20 For group 1, based on n=13 For group 2, based on n=4 For group 3, based on n=2			
Units: ASD Score			
median	43.14	-	
inter-quartile range (Q1-Q3)	43.14 to 43.14	- to -	
IGFBP-3 Units: x ULN			
median	0.585	0.716	
inter-quartile range (Q1-Q3)	0.540 to 0.788	0.662 to 0.754	

Reporting group values	Group 1 - Lanreotide depot	Group 3, 4, and 5	
Number of subjects	12	7	

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
The median age of all subjects participating in the study			
Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Male Female			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino			
Race Units: Subjects			
White Asian Black or African American Other			
Geographic Region Units: Subjects			
North America Europe Rest of World			
Height			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: centimetre median inter-quartile range (Q1-Q3)			
Weight			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s) median inter-quartile range (Q1-Q3)			
BMI			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: kilogram(s)/square metre			

median inter-quartile range (Q1-Q3)			
Ring Size			
For overall trial, based on n=46, one participant did not report. For group 1, based on n=24.			
Units: millimetre(s) median inter-quartile range (Q1-Q3)			
IGF-1 (x ULN) at Baseline Units: x ULN median inter-quartile range (Q1-Q3)			
Serum Growth Hormone Levels Units: nanogram(s)/millilitre median inter-quartile range (Q1-Q3)			
Acromegaly Symptom Diary (ASD) Score			
For overall trial, based on n=20 For group 1, based on n=13 For group 2, based on n=4 For group 3, based on n=2			
Units: ASD Score median inter-quartile range (Q1-Q3)			
IGFBP-3 Units: x ULN median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

This was a Phase 2, open-label, dose blinded, exploratory study designed to evaluate the efficacy, safety, and PK of paltusotine in subjects with acromegaly treated with SRL based treatment regimens. All patients enrolled in the study were treated with paltusotine. The first dose was 10mg for all subjects and uptitrated in a blinded manner from week 4 onwards.

Subject analysis set title	Group 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Efficacy Analysis Set - Primary Analysis Population for all efficacy analyses. Only includes subjects from Group 1.

Eligibility to enter this group was specified as: Partial responders on a stable treatment of octreotide long-acting release (LAR) or lanreotide depot (at least 1 Screening IGF-1 value was greater than upper limit of normal (ULN), and the V2 value was ≤2.5× ULN)

Subject analysis set title	Group 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Partial responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (at least 1 Screening IGF-1 value was >ULN, and the V2 value was ≤2.5 × ULN)

Subject analysis set title	Group 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values were ≤ULN)

Subject analysis set title	Group 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Complete responders on a stable dose of pasireotide LAR (mean of Screening IGF-1 values were ≤ULN)

Subject analysis set title	Group 5
Subject analysis set type	Safety analysis

Subject analysis set description:

Eligibility to enter this group was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values were ≤ULN).

Subject analysis set title	Group 1 - Octreotide LAR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects in Group 1 previously treated with Octreotide LAR

Subject analysis set title	Group 1 - Lanreotide depot
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects in Group 1 previously treated with Lanreotide depot

Subject analysis set title	Group 3, 4, and 5
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Eligibility to enter group 3 was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values were ≤ULN)
Eligibility to enter group 4 was specified as: Complete responders on a stable dose of pasireotide LAR

(mean of Screening IGF-1 values were ≤ULN)
Eligibility to enter group 5 was specified as: Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values were ≤ULN).

Primary: Efficacy Analysis Set (EAS)

End point title	Efficacy Analysis Set (EAS)[1]

End point description:

Change from baseline in IGF-1 level at Week 13/End of Treatment (W13/EoT) in Group 1 subjects Efficacy Analysis Set (EAS).
The primary efficacy analyses, using the EAS, evaluated change from Baseline to W13, at an alpha level of 0.05, using the Wilcoxon Signed-Rank test. Descriptive statistics of values and change from Baseline by group and total were presented including the arithmetic and geometric means with associated 95% CIs. Baseline value was defined as mean of IGF-1 prior to first dose. Last on treatment assessment was used for W13/EoT if subject discontinued before W13. p = 0.6285

End point type	Primary

End point timeframe:

Change from baseline in IGF-1 level at W13/EoT in Group 1 subjects Efficacy Analysis Set (EAS).

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 review endpoint description for details of statistical analyses performed

End point values	Group 1			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: × ULN				
median (inter-quartile range (Q1-Q3))				
Change from Baseline	-0.034 (-0.107 to 0.107)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with IGF-1 ≤ULN in Groups 3, 4 and 5 subjects only at W13/EoT

End point title	Proportion of subjects with IGF-1 ≤ULN in Groups 3, 4 and 5 subjects only at W13/EoT

End point description:

The secondary endpoint was the proportion of subjects who maintained IGF-1 response, defined as the last assessment before the EoT with IGF-1 ≤1.0× ULN meet responder criteria, in Group 3, 4, and 5 subjects only at W13/EoT.
Data were analysed using Clopper-Pearson method. The number/percentage, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category (response/non-response) were presented by group and total for the full analysis set (FAS), limited to Groups 3, 4, and 5, including a nominal p-value from an exact binomial test. p value =0.3877 for groups 3, 4, and 5.

End point type	Secondary

End point timeframe:

Proportion of subjects with IGF-1 ≤ULN in Groups 3, 4, and 5 subjects at W13/EoT.

End point values	Group 3, 4, and 5			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Subjects				
W13/EoT (Response)	4			
W13/EoT (No Response)	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with IGF-1 ≤1.5× ULN at W13/EoT

End point title	Proportion of subjects with IGF-1 ≤1.5× ULN at W13/EoT

End point description:

Proportion of subjects who maintained ICG-1 response, defined as last assessment before EoT with IGF-1 ≤1.5× ULN. Values, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category (number and percentage) were presented by group and total for FAS, including a nominal p-value from an exact binomial test. Endpoint was analyzed for lanreotide vs octreotide subgroup using EAS.
p value = 0.0041

End point type	Secondary

End point timeframe:

Proportion of subjects with IGF-1 ≤1.5× ULN at W13/EoT.

End point values	Group 1			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: Subjects				
W13/EoT (Response)	20			
W13/EoT (No Response)	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Subjects were monitored until the end of the 4-week follow-up period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Partial responders on a stable treatment of octreotide long-acting release (LAR) or lanreotide depot (at least 1 Screening IGF-1 value was greater than upper limit of normal (ULN), and the V2 value was ≤2.5× ULN)	
Reporting group title	Group 2
Reporting group description:	
Partial responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (at least 1 Screening IGF1 value was >ULN, and the V2 value was ≤2.5 × ULN)	
Reporting group title	Group 3
Reporting group description:	
Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values were ≤ULN)	
Reporting group title	Group 4
Reporting group description:	
Complete responders on a stable dose of pasireotide LAR (mean of Screening IGF1 values were ≤ULN)	
Reporting group title	Group 5
Reporting group description:	
Complete responders on a stable combination treatment of SRL (ie, octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values were ≤ULN).	

Serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 4	Group 5	
Total subjects affected by serious adverse events			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 25 (80.00%)	8 / 10 (80.00%)	3 / 5 (60.00%)
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 25 (32.00%)	4 / 10 (40.00%)	1 / 5 (20.00%)
occurrences (all)	15	13	2
Paresthesia			
subjects affected / exposed	4 / 25 (16.00%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	10	6	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 25 (20.00%)	5 / 10 (50.00%)	0 / 5 (0.00%)
occurrences (all)	9	12	0
Peripheral swelling			
subjects affected / exposed	3 / 25 (12.00%)	3 / 10 (30.00%)	0 / 5 (0.00%)
occurrences (all)	4	6	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Abdominal discomfort			

subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Abdominal distension			
subjects affected / exposed	3 / 25 (12.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Dyspepsia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Abdominal pain upper			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	5	0	0
Flatulence			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Sleep apnea syndrome			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	4 / 25 (16.00%)	4 / 10 (40.00%)	1 / 5 (20.00%)
occurrences (all)	5	6	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 25 (20.00%)	4 / 10 (40.00%)	0 / 5 (0.00%)
occurrences (all)	9	5	0
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Group 4	Group 5	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 3 (100.00%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 4 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	4	2	
Paresthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Abdominal discomfort			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Abdominal pain			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Flatulence			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Sleep apnea syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	
occurrences (all)	5	2	
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Sinusitis			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

Metabolism and nutrition disorders Hyperglycemia subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0	 1 / 3 (33.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2019	• Added patient-facing QoL 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 additional stopping criteria for cardiac, liver, and other clinical conditions. • Changed to the pre-dose collection of IGF-1 samples for endpoint-related visits. • Modification of certain inclusion/exclusion criteria and additional administrative updates.
07 June 2019	• 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 PI and subject. These home health assessments were performed by qualified and trained staff and under the supervision of each site PI, with activities specifically delegated by the PI. • 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 enroll in the study if there was recent documented evidence of elevated IGF-1 values, which indicated that the radiation therapy was not contributing to efficacy at baseline.
24 March 2020	COVID-19 Emergency Amendment - Changes to Study visit schedule and assessments - Changes to Subject Withdrawal Criteria - Changes to Provision of Study Drug and Study Supplies - Changes to IGF-1 Measurements and Titration For Titration Visits, if prior IGF-1 data are not available at the time of potential dose up-titration visits, and tolerability has been evaluated by the Investigator and considered acceptable, the study drug dose will be up-titrated in 10 mg increments as per current protocol titration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported