# 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<br>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<br>Units: years | | | |
| arithmetic mean | 53.5 | | |
| standard deviation | ± 13.76 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 6 | |
| Male | 7 | 7 | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 3 | 3 | |
| Not Hispanic or Latino | 10 | 10 | |
| Unknown | 0 | 0 | |
| Race<br>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<br>Units: Subjects | | | |
| *1/*1 | 5 | 5 | |
| *1/*80 | 5 | 5 | |
| *80/*80 | 2 | 2 | |

| | | | |
|---|---|---|---|
| Not reported | 1 | 1 | |
| UGT1A1 Phenotype<br>Units: Subjects | | | |
| Normal Metabolizer | 5 | 5 | |
| Intermediate Metabolizer | 5 | 5 | |
| Poor Metabolizer | 2 | 2 | |
| Not reported | 1 | 1 | |
| Height<br>Units: cm | | | |
| arithmetic mean | 171.02 | | |
| standard deviation | ± 13.748 | - | |
| Weight<br>Units: kg | | | |
| arithmetic mean | 80.97 | | |
| standard deviation | ± 18.088 | - | |
| BMI<br>Units: kg/m2 | | | |
| arithmetic mean | 27.52 | | |
| standard deviation | ± 4.903 | - | |
| Ring Size<br>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:<br>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:<br>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<br>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<br>Units: years | | | |
| arithmetic mean | 53.5 | 50 | |
| standard deviation | ± 13.76 | ± 15.41 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 4 | |
| Male | 7 | 3 | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 3 | 1 | |
| Not Hispanic or Latino | 10 | 6 | |
| Unknown | 0 | 0 | |
| Race<br>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<br>Units: Subjects | | | |
| *1/*1 | 5 | 3 | |
| *1/*80 | 5 | 3 | |
| *80/*80 | 2 | 1 | |
| Not reported | 1 | | |
| UGT1A1 Phenotype<br>Units: Subjects | | | |
| Normal Metabolizer | 5 | 3 | |
| Intermediate Metabolizer | 5 | 3 | |
| Poor Metabolizer | 2 | 1 | |
| Not reported | 1 | | |
| Height<br>Units: cm | | | |
| arithmetic mean | 171.02 | 173.83 | |
| standard deviation | ± 13.748 | ± 15.092 | |
| Weight<br>Units: kg | | | |
| arithmetic mean | 80.97 | 82.63 | |
| standard deviation | ± 18.088 | ± 16.230 | |
| BMI<br>Units: kg/m2 | | | |
| arithmetic mean | 27.52 | 26.52 | |
| standard deviation | ± 4.903 | ± 2.236 | |
| Ring Size<br>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<br>occurrences (all) | 0 / 13 (0.00%)<br>0 | | |
| Skin and subcutaneous tissue disorders<br>Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin exfoliation<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 13 (7.69%)<br>1<br><br><br>1 / 13 (7.69%)<br>1 | | |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Sleep disorder<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 13 (7.69%)<br>1<br><br><br>0 / 13 (0.00%)<br>0 | | |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Joint swelling<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 13 (7.69%)<br>1<br><br><br>1 / 13 (7.69%)<br>1<br><br><br>1 / 13 (7.69%)<br>1<br><br><br>1 / 13 (7.69%)<br>1 | | |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>COVID-19<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 13 (15.38%)<br>2<br><br><br>1 / 13 (7.69%)<br>1 | | |

| | | | |
|---|---|---|---|
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0 | | |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>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:<br>- 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.<br>- Added stopping criteria for cardiac, liver, and other clinical conditions.<br>- Changed to pre-dose collection of IGF-1 samples for endpoint-related visits.<br>- Modification of certain inclusion/exclusion criteria and additional administrative updates. |
| 06 June 2019 | Summary of changes made in amendment 2:<br>- The demotion of a Secondary Endpoint to an Exploratory Endpoint (Proportion of subjects who achieved serum GH <5.0 ng/mL at W13).<br>- Certain visits where minimal study procedures were performed were changed to Phone Call visits instead of site visits to reduce visit burden on subjects.<br>- 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.<br>- 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.<br>- Reduction in collection time points of the ASD.<br>- Changes to ASD scale question, wording, and scoring of the total ASD.<br>- 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: