**Official Title:** A Randomized, Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Acromegaly Treated with Long-acting Somatostatin Receptor Ligands

**NCT Number:** NCT04837040

**Document Date:** Clinical Study Protocol Version 5.0 06 December 2024

# A Randomized, Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects With Acromegaly Treated With Long-Acting Somatostatin Receptor Ligands

**Study Name:** *PATHFNDR-1: **P**altusotine **A**cromegaly **T**herapy **F**eaturing a **N**on-Invasive **D**aily **R**egimen*

**Protocol** Number: CRN00808-09

**Compound:** Paltusotine

**Study Phase:** 3

**Sponsor Name:** Crinetics Pharmaceuticals, Inc.

**Legal Registered Address:** 6055 Lusk Blvd, San Diego, CA 92121

**Regulatory Agency Identifier Number(s):**

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**Version 5.0 - Approval Date: 06 December 2024**

# DOCUMENT HISTORY/PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| **DOCUMENT HISTORY** | |
|---|---|
| **Document** | **Date** |
| Version 5.0 | 06 December 2024 |
| Version 4.0 | 21 November 2023 |
| Version 3.0 | 14 September 2021 |
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| Original Protocol (Version 1.0) | 18 December 2020 |

# SPONSOR SIGNATURE PAGE

**Sponsor's Approval**
The protocol has been approved by Crinetics Pharmaceuticals, Inc. (herein, Crinetics or Sponsor).

**Responsible Medical Officer:**

[redacted]

**Sponsor's Medical Contact:**

| See last page for electronic signature manifestation |
|---|

[redacted]

Date

# INVESTIGATOR'S AGREEMENT

A Randomized, Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Acromegaly Treated with Long-acting Somatostatin Receptor Ligands

Protocol Number: CRN00808-09

Protocol Version: 5.0

Protocol Date: 06 December 2024

I have read and I understand this protocol. I will conduct this protocol as outlined herein and will make all reasonable efforts to complete the study within the designated time.

I agree to conduct this trial in accordance with the Declaration of Helsinki, the International Council for Harmonization (ICH), Guideline for Good Clinical Practice (GCP), applicable local legislation including the EU Clinical Trials Regulation (CTR) (EU No 536/2014) and all applicable regulatory requirements.

I will provide copies of the protocol and access to all information furnished by Crinetics Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss material with them to ensure that they are fully informed about the study.

I understand that the study may be terminated, or enrollment suspended at any time, by Crinetics Pharmaceuticals, Inc., with or without cause, or by me, if it becomes necessary to do so in the best interests of the study subjects.

**Site name:** _____

**Site address:** _____

**Phone number:** _____

**Principal Investigator:**

Name and title (printed): _____

Signature: _____

Date: _____

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Protocol Title:** A Randomized, Controlled, Multi-Center Study, to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Acromegaly Treated with Long-acting Somatostatin Receptor Ligands

**Rationale**

Therapy for acromegaly is targeted at decreasing growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels, ameliorating patients' symptoms and decreasing any local compressive effects of the pituitary adenoma. The therapeutic options for acromegaly include surgery, radiotherapy, and medical therapies, such as somatostatin receptor ligands, dopamine agonists, and the GH receptor antagonist pegvisomant.

When surgery, which is the usual first-line treatment, fails to correct GH/IGF-1 hypersecretion, medical treatment can be used. Somatostatin receptor ligands (SRLs) are, at present, the most widely used drugs to control acromegaly. Octreotide has been approved as an immediate-release injectable solution by the FDA since 1988 and in the United Kingdom since 1989. Octreotide is available under the brand name Sandostatin® by Novartis or as a generic form sold by several different suppliers. Octreotide long-acting formulation is marketed under the brand name Sandostatin LAR® by Novartis. It is administered as monthly deep intragluteal intramuscular injection. Lanreotide long-acting formulation is marketed under the brand name Somatuline® Depot in the United States by Ipsen. It is administered every 4 weeks (or 6 to 8 weeks at the higher dose).

Paltusotine is a nonpeptide orally bioavailable somatostatin receptor 2 (SST2) agonist that is administered once per day. In Phase 2 studies, daily oral administration of paltusotine has been shown to maintain GH and IGF-1 levels in subjects with acromegaly that were previously on octreotide long-acting release (LAR) or lanreotide depot monotherapy. An orally bioavailable somatostatin agonist should reduce acromegaly patient burden by eliminating the pain and complications (e.g., subcutaneous, or intramuscular nodules) of injections and the cost and inconvenience of the health care provider office visits required for those injections. Additionally, it may allow physicians to determine an optimized dosing regimen more quickly compared with existing therapies. To our knowledge, paltusotine is the first nonpeptide oral somatostatin agonist being evaluated for the treatment of acromegaly.

This study is a Phase 3, randomized, placebo-controlled trial. This is a standard design in this disease and, by avoiding potential bias in assessing clinical efficacy and safety, will allow the comparison between paltusotine versus placebo. IGF-1 levels as well as acromegaly-related symptoms will be monitored regularly throughout the study and criteria for rescue therapy have been defined to ensure subject safety.

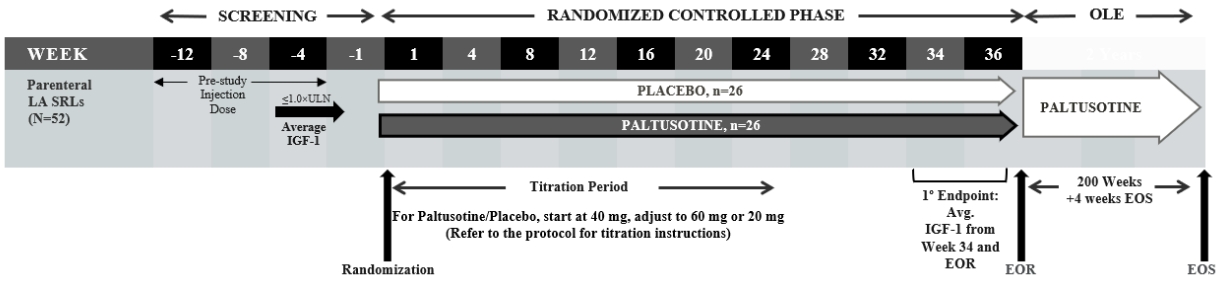
The proposed titration design aims to maintain subjects in their baseline biochemical status and optimize their dose while minimizing the period in which their IGF-1 is above baseline. Subjects will be switched from a stable regimen of octreotide/lanreotide to 40 mg paltusotine and their dose titrated up to 60 mg based on biochemical status and tolerability. Down-titration will be allowed based on tolerability. It is expected that by the end of titration period (Week 24) the concentrations of residual pre-trial octreotide or lanreotide will be too low to contribute to

efficacy. Finally, the dose-titration design reflects how the drug is likely to be used in clinical practice. Rescue criteria are in place to ensure safety for those who require resumption of standard acromegaly treatment, in those randomized to paltusotine or placebo.

## Overall Design

This is a randomized, placebo-controlled, multi-center study. The study includes a Screening Period of up to 12 weeks. After the Screening Period, subjects will be randomly assigned in a 1:1 ratio to receive either paltusotine or placebo. At the end of the Treatment Period, subjects who, in the opinion of the Investigator, may benefit from treatment with paltusotine, may be enrolled in a long-term open-label extension (OLE) for up to 200 weeks. During the OLE, all subjects will receive paltusotine. An End of Study (EOS) Visit will occur approximately 4 weeks after the last dose of study drug.

**Figure 1: Study Schema**




Average IGF-1 = Average of all (up to 3) study assessments taken during Screening.
EOR=End of Treatment (randomized, controlled phase), EOS=End of Study, IGF-1=insulin-like growth factor-1, LA SRL=long-acting somatostatin receptor ligand (octreotide/lanreotide only), OLE=open-label extension, ULN=upper limit of normal

## Screening

The Screening Period consists of 2 to 3 visits over 4 to 12 weeks. Administration of the last pre-randomization long-acting SRL (octreotide/lanreotide) injections should be performed before or during Screening to maintain the dosing interval between octreotide/lanreotide and the first dose of the study drug, i.e., the first dose of study drug will be administered when the next dose of lanreotide/octreotide would have been due.

IGF-1 values must be confirmed by the average of at least 2 central laboratory tests during the Screening Period. If a third IGF-1 measurement is needed per the Investigator, the Medical Monitor should be consulted and the average of the 3 measurements must meet the IGF-1 criteria for eligibility.

The last octreotide or lanreotide injection will be given during the Screening Period.

The octreotide/lanreotide injection can be administered any time during the Screening Period provided **1)** Day 1 aligns with the approximate scheduled date of the subject's next octreotide/lanreotide injection (±3 days), and **2)** the Screening Period does not exceed 12 weeks.

The octreotide/lanreotide injection is the key **temporal event** during Screening. Day 1 (start of treatment) must be 4 weeks (±3 days) or 6 weeks (±3 days) after the last dose of octreotide/lanreotide if a subject is administered his/her octreotide/lanreotide every 4 weeks or

6 weeks, respectively. Additionally, if a subject is administering his/her lanreotide every 8 weeks, Day 1 (start of treatment) must be 8 weeks (±3 days) after the last dose of lanreotide.

**Treatment Period (Randomized, Controlled Phase)**

Once all Screening assessments are completed, the subject's eligibility is verified by the Investigator and confirmed by the Medical Monitor via submission of the Medical Monitor Eligibility Verification Form. Subjects meeting all eligibility criteria and an average Screening IGF-1 ≤1.0×ULN will be randomized (1:1) to either paltusotine (n=26) or placebo (n=26) (Figure 1).

The Treatment Period will be approximately 36 weeks.

Subjects will not be administered octreotide/lanreotide on Day 1. Instead, subjects will receive their first dose of study drug on site (paltusotine or placebo).

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 24, with no dose titrations/adjustments after Week 24. Up-titration after Week 24 should not occur; subjects who require dose up-titration after Week 24 will be considered non-responders. Down-titration will be allowed based on tolerability.

Rescue criteria are in place for those who require standard acromegaly treatment in those randomized to paltusotine or placebo. If rescue therapy is required during the Randomized Controlled (RC) phase, subjects will discontinue paltusotine or placebo, initiate rescue therapy and should continue the visits and surveillance in the study for the remainder of the 36-week RC phase (see Section 6.8.1 for Rescue Criteria). Subjects who discontinue treatment for any reason prior to End of Randomized Control Phase (EOR), including those undergoing rescue procedures, will be considered non-responders. Only rescue therapy with approved SRLs (octreotide LAR or lanreotide depot monotherapy) will be permitted during the study. A Follow-up Visit, approximately 4 weeks after the last dose of study drug, will occur at Week 40 for subjects who do not enter the OLE.

If the subject withdraws consent or, in the opinion of the Investigator, should be permanently discontinued from the study, the Early Termination (ET) Visit should be completed as specified in the Schedules of Activities (SOAs) and the subject should return to standard acromegaly treatment as prescribed by the Investigator.

**Open-label Extension Phase**

Subjects who complete the 36-week RC phase or who meet rescue criteria and complete the 36-week RC phase with rescue medication can continue participation in the OLE phase if the subject is willing to participate and, in the opinion of the Investigator, the subject may benefit from continued participation and treatment with paltusotine. The OLE Treatment Period is 200 weeks. Data from the EOR visit of the RC phase will be used as baseline of the OLE, unless otherwise specified.

**End of Study**

An EOS Visit, approximately 4 weeks after the last dose of study drug, will occur at Week 240 to collect final safety data and other assessments as detailed in the SOAs.

**Table 1: Objectives and Endpoints for the Controlled Part of the Study**

| Objectives | Endpoints |
|---|---|
| ***Primary*** | |
| To evaluate the effect of paltusotine versus placebo on IGF-1 response | Proportion of subjects who maintain biochemical response in IGF-1 (≤1.0×the upper limit of normal [ULN]) at the End of the Randomized Control Phase (EOR) |
| ***Secondary*** | |
| To evaluate the effect of paltusotine versus placebo on IGF-1 level | Change from baseline in IGF-1, in units of ULN, to EOR |
| To evaluate the effect of paltusotine versus placebo on GH response | Proportion of subjects with GH <1.0 ng/mL at Week 34, out of those who had GH <1.0 ng/mL at baseline |
| To evaluate the effect of paltusotine versus placebo on acromegaly symptoms | Change from baseline in Total Acromegaly Symptoms Diary (ASD) score to EOR |
| ***Exploratory*** | |
| To evaluate the effect of paltusotine versus placebo on GH level | Change from baseline to Week 34 in GH |
| To evaluate the effect of paltusotine versus placebo on the need for rescue therapy | Proportion of subjects who receive rescue therapy |
| To evaluate the effect of paltusotine versus placebo on IGF-1 response | Proportion of subjects who achieve IGF-1 <1.3×ULN at EOR |
| To evaluate the effect of paltusotine versus placebo on GH response | Proportion of subjects with GH <2.5 ng/mL at Week 34 |
| To evaluate the effect of paltusotine versus placebo on tumor volume | Change from baseline in residual tumor volume at EOR |
| To evaluate loss of biochemical control | Time from randomization to the first IGF-1 >1.0×ULN for 2 consecutive visits<br>Time from randomization to the first IGF-1 ≥1.3×ULN for 2 consecutive visits |
| ***Safety*** | |
| To evaluate the safety and tolerability of paltusotine versus placebo in subjects with acromegaly | Incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and TEAEs that lead to discontinuation<br>Change in safety parameters: clinical laboratory tests (hematology, serum chemistry, lipid panel, and hormones), vital signs, and 12-lead electrocardiogram (ECG) parameters<br>Incidence of clinically significant changes in abdominal (gallbladder) ultrasound compared with baseline |

**Table 2: Objective and Endpoints for the Open-label Extension**

| Objective | Endpoints |
|---|---|
| To evaluate the long-term safety and efficacy of paltusotine | Safety endpoints:<br>Incidence of TEAEs, including serious adverse events (SAEs) and TEAEs leading to discontinuation of study drug<br>Change in quantitative safety parameters: clinical laboratory tests, lipid panel, hormones, vital signs, and 12-lead ECG parameters<br>Ophthalmic assessments<br>The same efficacy endpoints that are in the main study but at subsequent timepoints with the following additional efficacy endpoint:<br>Proportion of subjects who receive permitted adjunctive standard acromegaly treatment |

### Number of Subjects

The total sample size is 52 subjects (26 in the paltusotine arm, 26 in the placebo arm).

Refer to Section 9.2 for more information about determination of sample size.

### Duration and Intervention Groups

### Total Duration of the Study

The study comprises 2 phases: an RC phase and long-term OLE phase. Subjects who participate in both phases will complete approximately 240 weeks (approximately 4 ½ years) of treatment and observation. The study will consist of:

- Screening Period: Up to 12 weeks; Week -12 through Day -1 (There are 2 to 3 visits during the Screening Period)
- RC phase: 36 weeks
  - Treatment Period: Day 1 through Week 36 with up to 11 planned visits; the end of Week 36 is the last planned visit of the RC phase and is defined as EOR
  - Week 1 through Week 24 will be the dose titration Period
- OLE: 200 weeks
  - 1 visit approximately every 12 weeks
  - Eligible subjects who complete the RC phase may enter the OLE and continue or initiate treatment with paltusotine until end of treatment (EOT); the end of 200 weeks of the OLE phase is the planned EOT
  - EOS: Defined as the day final study data are collected and should occur 4 weeks after the last dose of study drug; the end of the Week 240/EOS is the last planned visit of the study (Follow-up Visit), but EOS could occur at Week 40 for subjects who do not enter the OLE

- Subjects who withdraw consent or are permanently discontinued from the study before Week 240 are to complete an ET Visit, as specified in the SOAs, unless the subject completes the RC phase and concludes study participation at Week 40 in which assessments specified at EOS are to be completed.

**Study Drug**

Paltusotine will be provided as [redacted]tablets. Matching placebo tablets will be identical in appearance to paltusotine and will be administered orally according to the randomization scheme, on an identical schedule to those receiving paltusotine. Paltusotine and matching placebo tablets will each be packed in [redacted] Drug labels will comply with the legal requirements of each country and will be printed in local language.

**Scientific Rationale for Study Design**

A prospective randomized, placebo-controlled trial is the gold standard methodology to define the safety and efficacy profile of an experimental drug. Placebo controlled trials have been successfully conducted and are feasible in rare orphan diseases, including acromegaly. Protocol safeguards are in place to ensure subjects who experience worsening of symptoms associated with rise in IGF-1 receive rescue injections of standard therapy, to ensure that they can safely complete the trial (Section 6.8.1).

**Dose Adjustment During the RC Phase**

The starting daily dose will be 40 mg ([redacted] tablets of active paltusotine or matching placebo) once daily (QD) for oral self-administration. The dose of study drug can be titrated up to 60 mg QD. Dose levels may increase from 40 mg [redacted] tablets) to 60 mg [redacted] tablets) based on IGF-1 response.

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 24, with no dose titrations/adjustments after Week 24. Up-titration after Week 24 should not occur; subjects who require dose up-titration after Week 24 will be considered non-responders. Down-titration will be allowed based on tolerability.

Protocol specified dose adjustments are summarized in Figure 2.

**Figure 2: Dose Titration Options**

| Dose Titration/Adjustment | IGF-1 Criteria | Tolerability Criteria |
|---|---|---|
| 40 mg→60 mg | Subject's most recent IGF-1 results on 40 mg is >0.9×ULN | Increase allowed due to acceptable tolerability on 40 mg |
| 40 mg→20 mg | -- | Dose reduction required due to unacceptable tolerability on 40 mg |
| 20 mg→40 mg | Subject's most recent IGF-1 results on 20 mg is >0.9×ULN | Tolerability is acceptable on 20 mg |
| 60 mg→40 mg | -- | Dose reduction required due to unacceptable tolerability on 60 mg |

If the Investigator determines that a dose titration/adjustment after Week 24 is required, the Investigator should contact the Medical Monitor to ensure that a consistent approach to dose titration/adjustment is applied across the study.
IGF-1=insulin-like growth factor-1; ULN=upper limit of normal

Dose up-titration will be based on 2 criteria:

- Acceptable tolerability at the current dose, as evaluated by the Investigator,

  **AND**

- The subject's most recent IGF-1 result is >0.9×ULN

If needed, an unscheduled dose titration Visit may be performed. The study drug dose may be decreased at any time during the study if study drug toleration is unacceptable in the judgment of the Investigator. A dose reduction based on tolerability may be necessary for subjects who are taking P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) inhibitors (see Section 6.7.1). In general, a TEAE of severe intensity for which there is a reasonable possibility it is caused by (related to) study drug would be expected to result in study drug dose reduction. If tolerance improves following a dose reduction, the Investigator may increase the dose in [redacted] increments, if needed, based on protocol-specified dose titration criteria to a maximum of 60 mg ([redacted] tablets). See Section 10.3.1 for the definition of a TEAE and Section 10.3.3 for definitions of intensity and causality. When, in the Investigator's judgment, the study medication is not tolerated, the study medication may be held for up to a total of 14 days per year, but no more than 7 consecutive days per year during the study, followed by resumption of the study medication at the same or reduced dose as appropriate.

During the RC phase, planned study visits are to occur approximately every 4 weeks; however, unscheduled visits may be required for more frequent monitoring, dose titration, and to assess rescue criteria.

**RC Phase Rescue Medication (Auxiliary Medicinal Products)**

During the RC phase, acromegaly treatments other than study drug are prohibited, unless the subject meets the rescue criteria described as follows:

- Significant worsening of 1 or more acromegaly symptoms or the development of a new acromegaly symptom, at the highest dose (60 mg) for at least 2 weeks, as assessed by the Investigator. Symptoms should be attributed to uncontrolled acromegaly in the opinion of the Investigator and could include, but are not limited to, the following: headache, arthralgia, fatigue, hyperhidrosis, or soft tissue swelling. ("Significant worsening" in the opinion of the Investigator may be defined as

symptoms requiring a substantial increase in level of clinical care [e.g., significant intervention needed to avert hospitalization or clinically notable increase in frequency or intensity of subject contact required] or substantial clinical deterioration [e.g., worsening from a mild to severe AE or the onset of an SAE would meet these criteria]).

**AND**

- IGF-1 value ≥1.3×ULN at the highest dose (60 mg) measured at 2 successive planned visits or at an unscheduled visit if an earlier result is needed (as evaluated by the Investigator).

If rescue therapy is required during the RC phase, subjects will discontinue paltusotine or placebo, initiate rescue therapy, and should continue the visits and surveillance in the study for the remainder of the 36-week RC phase (see Section 6.8.1 for Rescue Criteria). Only rescue therapy with approved SRLs (octreotide LAR or lanreotide depot monotherapy [auxiliary medicinal products (AuxMPs)]) will be permitted during the study. Rescue therapy should be used according to approved marketing authorization or standard clinical practice.

Investigators should contact the Medical Monitor about any subjects who do not meet criteria for rescue, but for whom the Investigator recommends discontinuation of study drug and initiation of standard acromegaly medication, to discuss the possibility of continuation in the RC phase on rescue therapy with approved SRLs and eligibility for OLE on a case-by-case basis.

**Dosage and Dose Adjustment During the Open-label Extension**

The starting daily dose regimen for all subjects who participate in the OLE will be paltusotine 40 mg QD, dispensed in an open-label manner, i.e., subjects will be given bottles of paltusotine containing [redacted] tablets and instructed to take 2 tablets daily until their next visit.

Dose escalation in the OLE may occur once the first IGF-1 result is available. At that time, the Investigator can determine whether the dose can be up-titrated to 60 mg.

**Open-label Extension Adjunctive Treatments (Auxiliary Medicinal Products)**

If there is evidence of paltusotine efficacy and at 6 months, subjects have not reached therapeutic target goals, adjunctive treatment may be initiated if clinically appropriate beginning at Week 60. If these criteria are met, non-SRL acromegaly treatments, such as oral cabergoline or GH receptor antagonist pegvisomant are permitted and may be initiated as an adjunct when a subject has experienced at least 2 consecutive elevated IGF-1 (≥1.3×ULN) measurements at the highest paltusotine dose level (60 mg), or otherwise not at the subject's therapeutic target in the judgement of the Investigator.

- The adjunctive medications cabergoline and pegvisomant are considered AuxMPs. Use of any adjunctive medications should be discussed with the Medical Monitor and should be used according to approved marketing authorization or standard practice. Adjunct medications are not provided by the Sponsor.
- If it is determined that adjunctive medication is required, then use of cabergoline would be the expected first-line adjunct, as clinically appropriate. If after an adequate period of assessment, study medication combined with a cabergoline does not achieve therapeutic targets, then pegvisomant may be added as a second-line adjunct, if

clinically appropriate (Katznelson, 2014). In this situation, the Investigator should assess if there was evidence of an IGF-1 lowering response from the cabergoline. If so, the pegvisomant may be added to the paltusotine + cabergoline drug combination. If there was no evidence of a therapeutic response to combined paltusotine + cabergoline, the cabergoline should be stopped and pegvisomant added to paltusotine therapy.

- Short- and long-acting somatostatin receptor agonists (other than paltusotine) remain prohibited and are not permitted during the study (subjects will be discontinued from the study if these are needed and an ET Visit will be scheduled prior to resuming these treatments).

**Statistical Methods**

The primary endpoint assumes that IGF-1 ≤1×ULN rates for paltusotine versus placebo are 70% and 20%, respectively. Based on a 2-sample Fisher's Exact test at a 2-sided alpha=0.05 level of significance, a total sample size of 52 subjects (26 in the paltusotine arm, 26 in the placebo arm) will provide 93.6% power to achieve superiority of paltusotine over placebo.

The estimates used for the power are based on Phase 2 data with paltusotine as well as the observed placebo response in similarly designed clinical study of oral octreotide (Chiasma Inc.; Optimal Study; EudraCT: 2017-000737-31). In the Phase 2 paltusotine acromegaly studies, the drop-out (discontinuation) rates were approximately 10%. These study discontinuation rates are accounted for in the estimates of overall non-response seen in a in similarly designed clinical study of oral octreotide (Chiasma Inc.; Optimal Study; EudraCT: 2017-000737-31) where 68% of the placebo group either dropped out or were on rescue medications defining them as a non-responder.

**Data Monitoring Committee**

An unblinded Data Monitoring Committee (DMC), comprising independent subject matter experts, will be established to assess the risk versus benefit of the interventions during the trial. The DMC will meet at intervals as specified in the DMC charter and may convene for ad hoc meetings if there are immediate safety concerns identified during the study. In the event an interim futility analysis is undertaken when 50% of subjects have completed the Treatment Period of the RC phase, the DMC will be responsible for evaluating those data.

## 1.2. Schedule of Activities: Randomized, Controlled Phase

| STUDY PROCEDURES | SCREENING PERIOD | | | TREATMENT PERIOD (36 Weeks) | | | | | | | | | | | | F/U | REFs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | TITRATION PERIOD | | | | | STABLE DOSE | | | | | | | |
| DAY/WEEK | W -12 to D -1 S1, S2, or S3 (as needed) | | | D1 | W4 | W8 | W12 | W16 | W20 | W24 | W28 | W32 | W34 | W36 EOR | ET | DT* | W40 | |
| **WINDOW (DAYS)** | - | | | - | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±3 | - | - | ±3 | - |
| **Visit to be in-clinic** | X | - | - | X | - | - | X | - | - | X | - | - | - | X | X | X | X | - |
| **Visit to be in-clinic or subject's home/suitable alternate location** | | X | X | - | X | X | - | X | X | - | X | X | X | - | - | - | - | - |
| Obtain informed consent | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 10.1.3 |
| Register subject in IWRS | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 6.3 |
| Verify eligibility | X | X | X | X | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 5.1<br>Section 5.2 |
| Randomization | - | - | - | X | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 6.3 |
| *Demographics and Baseline Characteristics* | | | | | | | | | | | | | | | | | | |
| Health history, demographics, baseline characteristics | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.1 |
| Pre-trial acromegaly symptoms | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.1 |
| *Safety Assessments* | | | | | | | | | | | | | | | | | | |
| Full physical exam, weight, ring size (height at screening only) | X | | | X | | | X | | | X | | | | X | X | | | Section 8.3.1 |
| Symptom-directed physical exam | - | - | - | - | X | X | - | X | X | - | X | X | X | - | - | | X | Section 8.3.1 |
| Vital signs | X | - | - | X | X | X | X | X | X | X | X | X | X | X | X | | X | Section 8.3.2 |
| 12-lead ECG (triplicate) | X | - | - | X | X | - | X | - | X | - | X | - | - | X | X | - | X | Section 8.3.3 |

| STUDY PROCEDURES | SCREENING PERIOD | | | TREATMENT PERIOD (36 Weeks) | | | | | | | | | | | | F/U | REFs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | W -12 to D -1 S1, S2, or S3 (as needed) | | | D1 | TITRATION PERIOD | | | | | STABLE DOSE | | | | | ET | DT* | | |
| DAY/WEEK | | | | | W4 | W8 | W12 | W16 | W20 | W24 | W28 | W32 | W34 | W36 EOR | | | W40 | |
| **WINDOW (DAYS)** | - | | | - | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±3 | - | - | ±3 | - |
| **Visit to be in-clinic** | X | - | - | X | - | - | X | - | - | X | - | - | - | X | X | X | X | - |
| **Visit to be in-clinic or subject's home/suitable alternate location** | | X | X | - | X | X | - | X | X | - | X | X | X | - | - | - | - | - |
| Biliary/gallbladder ultrasound<br>Ultrasound may be done at any Screening visit, but results MUST be available to determine eligibility | X | - | - | - | - | - | - | - | - | - | - | - | - | X | X | - | - | Section 8.3.5 |
| Pituitary MRI<br>MRI may be done at any Screening visit, but results MUST be available to determine eligibility | X | - | - | - | - | - | - | - | - | - | - | - | - | X | X | - | - | Section 8.3.6 |
| AE monitoring | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X* | X | Section 8.4<br>Appendix 3 |
| Prior & concomitant therapies | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X* | X | Section 6.7 |
| *Laboratory Tests* | | | | | | | | | | | | | | | | | | |
| Monthly pregnancy test | X | - | - | X | X | X | X | X | X | X | X | X | - | X | X | - | X | Section 8.4.5<br>Appendix 2 |
| Clinical laboratory tests (hematology, chemistry, urinalysis) | X | - | - | X | X | X | - | X | - | X | - | X | - | X | X | - | X | Section 8.3.4<br>Appendix 2 |
| HbA1c | X | - | - | X | - | X | - | - | - | X | - | - | - | X | X | - | - | Section 8.3.4 |
| Lipid panel (fasting) | - | - | - | X | - | - | - | - | - | - | - | - | - | X | X | - | - | Section 8.3.4<br>Appendix 2 |

| STUDY PROCEDURES | SCREENING PERIOD | | | TREATMENT PERIOD (36 Weeks) | | | | | | | | | | | ET | DT* | F/U | REFs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | W -12 to D -1 S1, S2, or S3 (as needed) | | | D1 | TITRATION PERIOD | | | | | STABLE DOSE | | | | | | | | |
| DAY/WEEK | | | | | W4 | W8 | W12 | W16 | W20 | W24 | W28 | W32 | W34 | W36 EOR | | | W40 | |
| **WINDOW (DAYS)** | - | | | - | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±3 | - | - | ±3 | - |
| **Visit to be in-clinic** | X | - | - | X | - | - | X | - | - | X | - | - | - | X | X | X | X | - |
| **Visit to be in-clinic or subject's home/suitable alternate location** | | X | X | - | X | X | - | X | X | - | X | X | X | - | - | - | - | - |
| Serology (HIV, Hepatitis B and Hepatitis C) | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.3.4 Appendix 2 |
| TSH and Free T4 | X | - | - | X | - | - | - | - | - | - | - | - | - | X | X | - | - | Section 8.3.4 Appendix 2 |
| Screening fasting Integrated GH 5 samples collected at least 30 minutes apart drawn within a 3-hour period | - | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.3.4 Appendix 2 |
| Screening IGF-1 | X | X | X** | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.3.4 Appendix 2 |
| Genotype blood sample (optional) | | | | X | | | | | | | | | | | | | | Section 8.6 |
| Pre-dose fasting PK | | | | | | X | | X | | X | | X | X | | X | | | Section 8.5 |
| PK (any time) | | | | | | | | | | | | | | X | | | | Section 8.5 |
| Pre-dose fasting IGF-1 (W40 can be done any time) | - | - | - | X | - | X | - | X | - | X | - | X | X | X | X | - | X | Section 8.3.4 Appendix 2 |

| STUDY PROCEDURES | SCREENING PERIOD | | | TREATMENT PERIOD (36 Weeks) | | | | | | | | | | | | F/U | REFs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | W -12 to D -1 S1, S2, or S3 (as needed) | | | D1 | TITRATION PERIOD | | | | | STABLE DOSE | | | | | ET | DT* | | |
| DAY/WEEK | | | | | W4 | W8 | W12 | W16 | W20 | W24 | W28 | W32 | W34 | W36 EOR | | | W40 | |
| **WINDOW (DAYS)** | - | | | - | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±3 | - | - | ±3 | - |
| **Visit to be in-clinic** | X | - | - | X | - | - | X | - | - | X | - | - | - | X | X | X | X | - |
| **Visit to be in-clinic or subject's home/suitable alternate location** | | X | X | - | X | X | - | X | X | - | X | X | X | - | - | - | - | - |
| Fasting Integrated GH 5 samples collected at least 30 minutes apart within a 3-hour period. At W34, collection should be started approximately 1-2 hours after study drug dose | - | - | - | - | - | - | - | - | - | - | - | - | X (Post-dose) | - | X | - | - | Section 8.3.4 Appendix 2 |
| Post dose PK, GH, and IGF-1 One sample between 1 and 8 hours post-dose | - | - | - | - | X | - | X | - | X | - | X | - | - | - | - | - | - | Section 8.3.4 Appendix 2 |
| *Drug Administration* | | | | | | | | | | | | | | | | | | |
| Screening octreotide/ lanreotide injection | - | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 6 |
| Study drug administration during visit (W36 study drug administration (paltusotine 40 mg) for subjects continuing into the OLE only) | - | - | - | X | - | X | - | X | - | X | - | X | X | X | - | - | - | Section 6.1 |
| Dispense study drug (via IWRS) (W36 dispensation for subjects continuing into OLE only) | - | - | - | X | X | X | X | X | X | X | X | X | - | X | - | X* | - | Section 6.1 |
| Study drug compliance | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X* | - | Section 6.4 |

| STUDY PROCEDURES | SCREENING PERIOD | | | TREATMENT PERIOD (36 Weeks) | | | | | | | | | | | | F/U | REFs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | TITRATION PERIOD | | | | | STABLE DOSE | | | | | | | |
| DAY/WEEK | W -12 to D -1 S1, S2, or S3 (as needed) | | | D1 | W4 | W8 | W12 | W16 | W20 | W24 | W28 | W32 | W34 | W36 EOR | ET | DT* | W40 | |
| **WINDOW (DAYS)** | - | | | - | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±4 | ±3 | - | - | ±3 | - |
| **Visit to be in-clinic** | X | - | - | X | - | - | X | - | - | X | - | - | - | X | X | X | X | - |
| **Visit to be in-clinic or subject's home/suitable alternate location** | | X | X | - | X | X | - | X | X | - | X | X | X | - | - | - | - | - |
| Study drug accountability | - | - | - | - | X | X | X | X | X | X | X | X | - | X | X | X* | - | Section 6.4 |
| *Subject-reported Assessments* | | | | | | | | | | | | | | | | | | |
| ASD<br>ASD should be completed by the subject daily at home beginning at least approximately 2 weeks prior to study drug dosing for the duration of the RC | - | X | X | X | X | X | X | X | X | X | X | X | X | X | X | - | - | Section 8.2.1 |
| [redacted] | - | - | - | X | - | - | - | - | - | X | - | - | - | X | X | - | - | Section 8.2.2<br>Section 8.2.3 |
| [redacted] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | - | - | Section 8.2.4 |
| [redacted] | - | - | - | - | - | - | - | - | - | - | - | - | - | X | X | - | - | Section 8.2.4 |
| [redacted] | - | - | - | - | - | - | - | - | - | - | - | - | - | X | - | - | - | Section 8.2.5 |

Notes:
To the extent practical, conduct all study assessments at the same time of day, unless otherwise specified. The screening MRI and/or ultrasound do not need to be performed on the same day as the screening study visit (SV1) but must be performed within the screening window. The pituitary MRI and biliary/gallbladder ultrasound may be performed within ± 2 weeks of the Week 36/EOR visit.
The Screening Period consists of 2 to 3 visits over 4 to 12 weeks. Subjects administer their pre-trial octreotide (every 4 weeks)/lanreotide (every 4, 6, or 8 weeks) according to their pre-trial routine dosing interval. The date and dose level of the most recent octreotide/lanreotide prior to consent will be recorded as prior medication, to the extent reasonable.
*A DT Visit may occur as an unscheduled visit when an in-person dose adjustment visit is necessary. In cases of poor tolerability, the Investigator may reduce dose based on his/her assessment during a telemedicine (phone, video) evaluation.
**IGF 1 values must be confirmed by the average of at least 2 central laboratory tests during the Screening Period. If a third IGF 1 measurement is needed per the Investigator, the Medical Monitor should be consulted and the average of the 3 measurements must meet the criteria for eligibility. A third screening visit should be completed only if a third IGF-1 sample is needed.

Fasting integrated GH will be collected during screening, Week 34, and ET only. Integrated GH consists of 5 samples collected at least 30 minutes apart within a 3-hour period. Integrated GH should be measured after at least a 4 hour fast and the subjects should remain fasting during the 3 hours of GH sampling. The integrated GH sampling at Week 34 should be started approximately 1-2 hours after last study drug dose.
At other visits (W4, W12, W20, W28), single samples for GH will be collected.
Female subjects of childbearing potential must have a negative serum pregnancy test at Screening. All other pregnancy tests will be urine tests. Pregnancy tests may be obtained at any time during the study as an unscheduled test if clinically appropriate.
Fasting blood samples (unless otherwise indicated) should be collected after an overnight fast of at least 6 hours.
The last dose of study drug for the RC phase will be self-administered the day prior to the W36/EOR visit. The first dose of the OLE phase will be administered during the W36/EOR visit for subjects continuing into the OLE.
Follow-up Visit is to occur approximately 4 weeks after the last dose of study drug for subjects who do not enter the OLE (Week 40).
The last octreotide/lanreotide injection during Screening does not need to occur on the same day as the other S2 assessments. The date of Day 1 should align within ±3 days of the routine dosing interval following the last octreotide/lanreotide injection.
Unscheduled visits for octreotide/lanreotide injections may be necessary for subjects who meet criteria for rescue therapy.
[redacted] AE=adverse event, ASD=Acromegaly Symptoms Diary, D=day, DT=dose titration, ECG=electrocardiogram, [redacted] EOR=End of Treatment (randomized, controlled phase), ET=Early Termination Visit, F/U=follow-up, GH=growth hormone, HbA1c=hemoglobin A1c, HIV=human immunodeficiency virus, IGF-1=insulin-like growth factor-1, IWRS=interactive web response system, MRI=magnetic resonance imaging, OLE=open-label extension, [redacted] PK=pharmacokinetic, REFs=references, S=Screening, TSH=thyroid-stimulating hormone, W=Week

## 1.3. Schedule of Activities: Open-label Extension Phase

| STUDY PROCEDURES | INITIAL OLE PERIOD | | | | | | | | | 2-YEAR EXTENSION | | | | EOS | Refs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEK | EOR W36 | W39 | W48 | W60 | W72 | W84 | W96 | W108 | W120 | W132/ W156/ W180/ W204/ W228/ | W144/ W168 W192/ W216/ | -W236 EOT/ ET | DT[a] | W240 | |
| WINDOW (DAYS) | ±3 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±3 | - | ±7 | |
| **Visit to be in-clinic** | X | | X | | X | | X | | X | | X | X | X | X | |
| **Visit to be in-clinic or subject's home/suitable alternate location** | - | X | - | X | - | X | - | X | - | X | - | - | - | - | |
| Verify eligibility | X | | | | | | | | | | | | | | Section 5.1 Section 5.2 |
| Safety Assessments | | | | | | | | | | | | | | | |
| Full physical exam, weight, ring size | X | | X | | X | | X | | X | | X | X | | | Section 8.3.1 |
| Symptom directed physical exam | - | - | - | X | - | X | - | X | - | X | - | - | - | X | Section 8.3.1 |
| Vital signs | X | - | X | X | X | X | X | X | X | X | X | X | - | X | Section 8.3.2 |
| 12-lead ECG (triplicate) | X | X | X | X | X | X | X | X | X | X | X | X | - | X | Section 8.3.3 |
| Biliary/gallbladder ultrasound | X | | X[b] | X[b] | X[b] | X[b] | X[b] | X[b] | X[b] | X[b] | X[b] | X[b] | | | Section 8.3.5 |
| Pituitary MRI | X | - | - | - | - | X | - | - | - | X[c] | - | X | - | - | Section 8.3.6 |
| Ophthalmic Assessments | | | | | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] | | | Section 8.3.7 |
| AE monitoring | X | X | X | X | X | X | X | X | X | X | X | X | X* | X | Section 8.4 Appendix 3 |
| Concomitant therapies | X | X | X | X | X | X | X | X | X | X | X | X | X* | X | Section 6.7 |
| Laboratory Tests | | | | | | | | | | | | | | | |
| Monthly pregnancy test[e] | X | X | X | X | X | X | X | X | X | X | X | X | - | X | Section 8.3.4 Appendix 2 |

| STUDY PROCEDURES | INITIAL OLE PERIOD | | | | | | | | | 2-YEAR EXTENSION | | | | EOS | Refs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEK | EOR W36 | W39 | W48 | W60 | W72 | W84 | W96 | W108 | W120 | W132/ W156/ W180/ W204/ W228/ | W144/ W168 W192/ W216/ | -W236 EOT/ ET | DT[a] | W240 | |
| **WINDOW (DAYS)** | **±3** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **±3** | **-** | **±7** | |
| **Visit to be in-clinic** | **X** | - | **X** | - | **X** | - | **X** | - | **X** | - | **X** | **X** | **X** | **X** | |
| **Visit to be in-clinic or subject's home/suitable alternate location** | - | **X** | - | **X** | - | **X** | - | **X** | - | **X** | - | - | - | - | |
| Clinical laboratory tests (hematology, chemistry, urinalysis) and HbA1c | X | X | X | X | X | X | X | X | X | X | X | X | - | X | Section 8.3.4 Appendix 2 |
| Fasting lipid panel | X | - | - | - | - | X | - | - | - | X | - | X | - | - | Section 8.3.4 Appendix 2 |
| TSH and Free T4 | X | - | - | - | - | X | - | - | - | X | - | X | - | - | Section 8.3.4 Appendix 2 |
| PK (any time) | X | - | - | X | - | - | - | - | - | X[f] | - | X | - | - | Section 8.5 |
| Pre-dose fasting IGF-1 | X | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.3.4 Appendix 2 |
| GH and IGF-1 (any time) | - | X | X | X | X | X | X | X | X | X | X | X | - | - | Section 8.3.4 Appendix 2 |
| Drug Administration | | | | | | | | | | | | | | | |
| Dispense study drug (via IWRS) | X | X | X | X | X | X | X | X | X | X | X | - | X* | - | Section 6.1 |
| Study drug administration during visit | X | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 6.1 |
| Study drug compliance | X | X | X | X | X | X | X | X | X | X | X | - | X* | - | Section 6.4 |
| Study drug accountability | X | X | X | X | X | X | X | X | X | X | X | X | X* | - | Section 6.4 |

| STUDY PROCEDURES | INITIAL OLE PERIOD | | | | | | | | | 2-YEAR EXTENSION | | | | EOS | Refs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEK | EOR W36 | W39 | W48 | W60 | W72 | W84 | W96 | W108 | W120 | W132/ W156/ W180/ W204/ W228/ | W144/ W168 W192/ W216/ | -W236 EOT/ ET | DT[a] | W240 | |
| **WINDOW (DAYS)** | ±3 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±3 | - | ±7 | |
| **Visit to be in-clinic** | X | - | X | - | X | - | X | - | X | - | X | X | X | X | |
| **Visit to be in-clinic or subject's home/suitable alternate location** | - | X | - | X | - | X | - | X | - | X | - | - | - | - | |
| Subject-reported Assessments | | | | | | | | | | | | | | | |
| ASD and [redacted] Sparse periodic administrations at home or at study visits | X | X | X | X | X | X | X | X | X | X | X | X | - | - | Section 8.2.1 Section 8.2.4 |
| [redacted] | X | | | | | X | | | | X[g] | | X | | | Section 8.2.2 Section 8.2.3 |
| [redacted] | X | - | - | - | - | - | - | - | - | X[g] | - | X | - | - | Section 8.2.4 |
| [redacted] | X | - | - | - | - | - | - | - | - | X[g] | - | - | - | - | Section 8.2.5 |

Notes:
To the extent practical, conduct all study assessments at the same time of day, unless otherwise specified.
The pituitary MRIs and biliary/gallbladder ultrasounds do not need to be performed on the same day as the study visit. They may be performed within ± 2 weeks of the study visit.
EOS/Follow-up Visit is to occur approximately 4 weeks after the last dose of study drug for subjects (Week 240).
Data from the EOR Visit in the RC Phase will be used as baseline (D1) data in the OLE.
Fasting blood samples (unless otherwise indicated) should be collected after an overnight fast of at least 6 hours.
The first dose of the OLE phase will be administered during the W36/EOR visit.
[a] A DT Visit may occur as an unscheduled visit when an in-person dose adjustment visit is necessary. In cases of poor tolerability, the Investigator may reduce dose based on his/her assessment during a telemedicine (phone, video) evaluation.
[b] Biliary/gallbladder ultrasounds are required at Week 132 and Week 236/ET visits but may be performed at any time if clinically indicated in the opinion of the Investigator.
[c] Pituitary MRI performed at Week 132 and Week 180 only.
[d] Visual Acuity, Fundus Photography, Optical Coherence Tomography, Visual Fields. Initial ophthalmic testing should be performed as soon as practical and then at approximately 6- month intervals, preferably associated with scheduled visits whenever possible, through study completion. If the most recent ophthalmic assessment is performed within 3 months of ET, there is no need to repeat at ET.
[e] Urinary pregnancy tests will be performed monthly for women of childbearing potential, and may be obtained at any time during the study as an unscheduled test if clinically appropriate.
[f] PK sample collections at Week 132, Week 180 and Week 228 only.
[g] [redacted], and [redacted] at Week 132, Week 156, Week 180. and Week 204 only. [redacted] at Week 132 only.

[redacted] AE=adverse event, ASD=Acromegaly Symptoms Diary, D=Day, DT=Dose Titration, [redacted] EOR=End of Treatment (RC phase), EOS=End of Study, EOT=End of Treatment, ET=Early Termination Visit, GH=growth hormone, HbA1c=hemoglobin A1c, IGF-1=insulin-like growth factor-1, IWRS=interactive web response system, MRI=magnetic resonance imaging, OLE=open-label extension, [redacted], PK=pharmacokinetic, RC=randomized, controlled phase, REFs=references, TSH=thyroid-stimulating hormone; W=week

# 2. INTRODUCTION

## 2.1. Study Rationale

Therapy for acromegaly is targeted at decreasing growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels, ameliorating patients' symptoms and decreasing any local compressive effects of the pituitary adenoma. The therapeutic options for acromegaly include surgery, radiotherapy, and medical therapies such as somatostatin receptor ligands, dopamine agonists, and the GH receptor antagonist pegvisomant.

When surgery, which is the usual first-line treatment, fails to correct GH/IGF-1 hypersecretion, medical treatment can be used. Somatostatin receptor ligands (SRL) are, at present, the most widely used drugs to control acromegaly. Octreotide has been approved as an immediate-release injectable solution by the Food and Drug Administration since 1988 and in United Kingdom in 1989. Octreotide is available under the brand name Sandostatin® by Novartis or as a generic form sold by several different suppliers. Octreotide long-acting formulation is marketed under the brand name Sandostatin LAR® by Novartis. It is administered as monthly deep intragluteal intramuscular injection. Lanreotide long-acting formulation is marketed under the brand name Somatuline® Depot in the United States by Ipsen. It is administered every 4 weeks (or 6 to 8 weeks at the higher dose).

Paltusotine is a nonpeptide orally bioavailable somatostatin receptor 2 (SST2) agonist that is administered once per day. In Phase 2 studies, daily oral administration of paltusotine has been shown to maintain GH and IGF-1 levels in subjects with acromegaly that were previously on octreotide LAR or lanreotide depot monotherapy. An orally bioavailable somatostatin agonist should reduce acromegaly patient burden by eliminating the pain and complications (e.g., subcutaneous, or intramuscular nodules) of injections and the cost and inconvenience of the health care provider office visits required for those injections. Additionally, it may allow physicians to determine an optimized dosing regimen more quickly compared with existing therapies. To our knowledge, paltusotine is the first nonpeptide oral somatostatin agonist being evaluated for the treatment of acromegaly.

This study is a Phase 3 randomized, placebo-controlled trial. This is a standard design in this disease and, by avoiding potential bias in assessing clinical efficacy and safety, will allow the comparison between paltusotine versus placebo. IGF-1 levels as well as acromegaly-related symptoms will be monitored regularly throughout the study and criteria for rescue therapy have been defined to ensure subject safety.

The proposed titration design aims to maintain subjects in their baseline biochemical status and optimize their dose while minimizing the period in which their IGF-1 is above baseline. Subjects will be switched from a stable regimen of octreotide/lanreotide to 40 mg paltusotine and their dose titrated up to 60 mg based on biochemical status and tolerability. Down-titration will be allowed based on tolerability. It is expected that by the end of titration period (Week 24) the concentrations of residual pre-trial octreotide or lanreotide will be too low to contribute to efficacy. Finally, the dose-titration design reflects how the drug is likely to be used in clinical practice.

## 2.2. Background

Acromegaly is typically caused by a GH secreting tumor (adenoma) in the pituitary. Excess GH secretion results in excess secretion of IGF-1 from the liver, which causes bone overgrowth, organ enlargement, and changes in glucose and lipid metabolism. The symptoms of acromegaly include abnormal growth of hands and feet and changes in shape of the bones that result in alteration of facial features. Overgrowth of bone and cartilage and thickening of tissue leads to arthritis, carpal tunnel syndrome, joint aches, enlargement of lips, nose, and tongue, deepening of voice due to enlarged vocal cords, sleep apnea due to obstruction of airways, and enlargement of heart, liver, and other organs. Additional symptoms include thick, coarse, oily skin, skin tags, excessive sweating and skin odor, fatigue and weakness, headaches, impaired vision, goiter, decreased libido, menstrual abnormalities in women, and erectile dysfunction in men (Melmed and Kleinberg, 2016; Carroll and Jenkins, 2016; NIDDK diseases online health information).

The major goals of treatment are to normalize serum GH and IGF-1, relieve pressure of the growing tumors, treat hormonal deficiencies, and normalize pituitary function. Surgical removal of pituitary adenoma, if possible, is the first option and often results in rapid symptom improvement. Parenterally administered SRLs are the most commonly employed primary pharmacological treatment options for patients that are not candidates for surgical removal of the tumor or when surgery is only partially successful or unsuccessful in achieving treatment goals (Melmed and Kleinberg, 2016; Carroll and Jenkins, 2016; NIDDK diseases online health information). Parenteral SRLs require large bore needles for monthly injections which often need to be administered by health care providers. Additionally, because these injections are depot preparations, dose optimization is prolonged, leading to delays in biochemical and symptomatic control of the disease. These agents, when used as monotherapy, achieve IGF-1 normalization in approximately 20 to 40% of patients.

Paltusotine is a nonpeptide orally bioavailable SST2 agonist that is administered once daily (QD) under development for the treatment of acromegaly. Phase 1 clinical data suggest that QD paltusotine administration for up to 10 days can result in IGF-1 lowering in healthy volunteers. Phase 2 studies in subjects with acromegaly have shown subjects can successfully switch from long-acting octreotide or lanreotide therapy to QD oral paltusotine for a 13-week treatment period while maintaining IGF-1 levels, and that paltusotine appears to be well tolerated.

The purpose of this current study is to evaluate the safety and efficacy of paltusotine in acromegaly subjects who are currently treated with either long-acting octreotide or lanreotide monotherapy.

Additional details on the background of acromegaly, treatment options, and nonclinical and clinical data on paltusotine can be found in the current Investigator's Brochure (IB).

This study will be conducted in compliance with the protocol, the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with applicable local legislation including the Clinical Trial Regulation (CTR) EU No 536/2014.

## 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of paltusotine may be found in the current version of the IB.

### 2.3.1. Risk Assessment

**Table 3: Risk Assessment Table**

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Drug - Paltusotine** | | |
| Side effects | Diarrhea, abdominal pain, nausea, abdominal discomfort, bradycardia (including sinus bradycardia and bradycardia), and cholelithiasis have been identified as ADRs associated with paltusotine.<br>Rationale: these AEs are generally mild or moderate and did not lead to discontinuations. | Clinical monitoring, symptomatic measures, study drug interruption if necessary. Regular safety surveillance, including laboratory testing, physical examinations, AE monitoring, ECG monitoring, and gall bladder monitoring, and evaluations for protocol specified study drug stopping rules per protocol. |
| **Study Procedures** | | |
| Participation in a placebo-controlled trial evaluating an experimental agent | Rise in GH/IGF-1 and worsening in acromegaly symptoms | Clinical monitoring including frequent assessment of symptoms, AEs, safety laboratories, GH/IGF-1 monitoring, and protocol defined rescue criteria |
| Blood draws | Pain, bleeding infection possible.<br>Rationale: Needed for safety evaluation of study drug | Symptomatic measures |
| Pituitary magnetic resonance imaging scans (MRI) | Claustrophobia, dizziness, mild nausea, numbness, tingling, muscle twitches, tiny flashing lights in field of vision, or momentary imbalance after leaving the magnet.<br>Possible use of intravenous contrast with associated risk of renal injury (in people with severe kidney disease) or hypersensitivity reaction<br>Rationale: Needed for monitoring of residual pituitary tumor volume | Standard of care symptomatic and preventative management measures |
| Biliary/gallbladder ultrasound | Ultrasound waves may heat the tissues slightly and, in some cases, it can also produce small pockets of gas in body fluids or tissues.<br>Rationale: Needed for monitoring gallbladder and biliary ducts | Symptomatic measures |
| Distance-corrected visual acuity testing<br>Visual field testing | There are no known risks or complications associated with these tests | None needed |
| Fundus photography<br>Optical coherence tomography of the macula | Some participants may experience some eye dryness or fatigue | Symptomatic measures |

AE=adverse event; ADR=adverse drug reaction; ECG=electrocardiogram; GH/IGF-1=growth hormone/insulin-like growth factor 1

### 2.3.2. Benefit Assessment

On the basis of nonclinical data, paltusotine is expected to have benefit in the treatment of acromegaly.

Completed Phase 2 studies CRN00808-02 and CRN00808-03 showed evidence for IGF-1 maintenance in acromegaly subjects previously treated with long-acting injected octreotide or lanreotide who were switched to paltusotine oral monotherapy for a period of 13 weeks. Overall, IGF-1 levels after the switch to paltusotine were similar to those at baseline during treatment with long-acting injections.

The overall safety profile of paltusotine appears to be consistent with those reported for other SRLs and common AEs observed with paltusotine are likely related to this mechanism of action. In addition to protocol specified safety surveillance, Investigators in clinical trials for paltusotine are advised to monitor subjects based on the known side effect profile of SRLs and manage as clinically appropriate.

The ongoing COVID-19 pandemic has not presented a substantial new risk to the acromegaly subjects participating in the Phase 2 trials evaluating the safety and efficacy of paltusotine (CRN00808-02, CRN00808-03, and CRN00808-05). This protocol (Section 10.1.8) has incorporated flexibility in the need for in-person visits at study sites while safeguarding the health and well-being of trial participants and minimizing risk to trial and study data integrity.

### 2.3.3. Overall Benefit: Risk Conclusion

Based on the available information, the known and potential risks of treatment with paltusotine are considered acceptable in relation to the potential benefits of treatment in subjects with acromegaly.

# 3. OBJECTIVES AND ENDPOINTS

## 3.1. Objectives and Endpoints for the Controlled Part of the Study

| Objectives | Endpoints |
|---|---|
| ***Primary*** | |
| To evaluate the effect of paltusotine versus placebo on IGF-1 response | Proportion of subjects who maintain biochemical response in IGF-1 (≤1.0×the upper limit of normal [ULN]) at the End of the Randomized Control Phase (EOR) |
| ***Secondary*** | |
| To evaluate the effect of paltusotine versus placebo on IGF-1 level | Change from baseline in IGF-1, in units of ULN, to EOR |
| To evaluate the effect of paltusotine versus placebo on GH response | Proportion of subjects with GH <1.0 ng/mL at Week 34, out of those who had GH <1.0 ng/mL at baseline |
| To evaluate the effect of paltusotine versus placebo on acromegaly symptoms | Change from baseline in Total Acromegaly Symptoms Diary (ASD) score to EOR |
| ***Exploratory*** | |
| To evaluate the effect of paltusotine versus placebo on GH level | Change from baseline to Week 34 in GH |
| To evaluate the effect of paltusotine versus placebo on the need for rescue therapy | Proportion of subjects who receive rescue therapy |
| To evaluate the effect of paltusotine versus placebo on IGF-1 response | Proportion of subjects who achieve IGF-1 <1.3×ULN at EOR |
| To evaluate the effect of paltusotine versus placebo on GH response | Proportion of subjects with GH <2.5 ng/mL at Week 34 |
| To evaluate the effect of paltusotine versus placebo on tumor volume | Change from baseline in residual tumor volume at EOR |
| To evaluate loss of biochemical control | Time from randomization to the first IGF-1 >1.0×ULN for 2 consecutive visits<br>Time from randomization to the first IGF-1 ≥1.3×ULN for 2 consecutive visits |

| Objectives | Endpoints |
|---|---|
| ***Safety*** | |
| To evaluate the safety and tolerability of paltusotine versus placebo in subjects with acromegaly | Incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and TEAEs that lead to discontinuation<br>Change in safety parameters: clinical laboratory tests (hematology, serum chemistry, lipid panel, and hormones), vital signs, and 12-lead electrocardiogram (ECG) parameters<br>Incidence of clinically significant changes in abdominal (gallbladder) ultrasound compared with baseline |

## 3.2. Objective and Endpoints for the Open-label Extension

| Objective | Endpoints |
|---|---|
| To evaluate the long-term safety and efficacy of paltusotine | Safety endpoints:<br>• Incidence of TEAEs, including serious adverse events (SAEs) and TEAEs leading to discontinuation of study drug<br>• Change in quantitative safety parameters: clinical laboratory tests, lipid panel, hormones, vital signs, and 12-lead ECG parameters<br>• Ophthalmic assessments<br>The same efficacy endpoints that are in the main study but at subsequent timepoints with the following additional efficacy endpoint:<br>Proportion of subjects who receive permitted adjunctive standard acromegaly treatment |

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a randomized, placebo-controlled, multi-center study. The study includes a Screening Period of up to 12 weeks. After the Screening Period, subjects will be enrolled in parallel in a 36-week Treatment Period. Subjects will be randomly assigned in a 1:1 ratio to receive either paltusotine or placebo. At the end of the Treatment Period, subjects, who in the opinion of the Investigator, may benefit from treatment with paltusotine, may be enrolled in a long-term, open-label extension (OLE) for up to 200 weeks. During the OLE, all subjects will receive paltusotine.

Subjects who meet rescue criteria in the RC Phase will have treatment with paltusotine or placebo discontinued and will be considered non-responders, but they should be encouraged to continue in the study on rescue therapy for assessment and observation. These subjects can participate in the OLE phase if they meet all eligibility requirements including willingness to participate, and in the opinion of the Investigator, the subject may benefit from continued participation and treatment with paltusotine. See Figure 1 for the study schema.

### 4.1.1. Screening

The Screening Period consists of 2 to 3 visits over 4 to 12 weeks. Administration of the last pre-randomization long-acting SRL (octreotide/lanreotide) injections should be performed during Screening to maintain the dosing interval between octreotide/lanreotide and the first dose of the study drug, i.e., the first dose of study drug will be administered when the next dose of lanreotide/octreotide would have been due.

The octreotide/lanreotide injection can be administered any time during the Screening Period provided **1)** Day 1 aligns with the approximate scheduled date of the subject's next octreotide/lanreotide injection (±3 days), and **2)** the Screening Period does not exceed 12 weeks.

The octreotide/lanreotide injection is the key **temporal event** during Screening. Day 1 (start of treatment) must be 4 weeks (±3 days) or 6 weeks (±3 days) after the last dose of octreotide/lanreotide if a subject is administered his/her octreotide/lanreotide every 4 weeks or 6 weeks, respectively. Additionally, if a subject is administering his/her lanreotide every 8 weeks, Day 1 (start of treatment) must be 8 weeks (±3 days) after the last dose of lanreotide.

IGF-1 values must be confirmed by the average of at least 2 central laboratory tests during the Screening Period. If a third IGF-1 measurement is needed per the Investigator, the Medical Monitor should be consulted and the average of the 3 measurements must meet the IGF-1 criteria for eligibility.

### 4.1.2. Treatment Period (Randomized, Controlled Phase)

Once all Screening assessments are completed, the subject's eligibility is verified by the Investigator and confirmed by the Medical Monitor via submission of the Medical Monitor Eligibility Verification Form. Subjects meeting all eligibility criteria and an average Screening IGF-1 ≤1.0×ULN will be randomized (1:1) to either paltusotine (n=26) or placebo (n=26) (Figure 1).

The Treatment Period will be approximately 36 weeks.

Subjects will not be administered octreotide/lanreotide on Day 1. Instead, subjects will receive their first dose of study drug on site (paltusotine or placebo).

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 24, with no dose titrations/adjustments after Week 24. Up-titration after Week 24 should not occur; subjects who require dose up-titration after Week 24 will be considered non-responders. Down-titration will be allowed based on tolerability. See Figure 2 for the dose titration schema.

If rescue therapy is required during the RC phase, subjects will discontinue paltusotine or placebo, initiate rescue therapy, and should continue the visits and surveillance in the study for the remainder of the 36-week RC phase (see Section 6.8.1 for Rescue Criteria). Only rescue therapy with approved SRLs (octreotide LAR or lanreotide depot monotherapy) will be permitted during the study. A Follow-up Visit will occur approximately 4 weeks after the last dose of study drug at Week 40, for subjects who do not enter the OLE.

If the subject withdraws consent or, in the opinion of the Investigator, should be permanently discontinued from the study, the Early Termination (ET) Visit should be completed as specified in the Schedules of Activities (SOAs) and the subject should return to standard acromegaly treatment as prescribed by the Investigator.

### 4.1.3. Open-label Extension Phase

Subjects who complete the 36-week RC phase or who meet rescue criteria and complete the 36-week RC phase with rescue medication can continue participation in the OLE phase if the subject is willing to participate and, in the opinion of the Investigator, the subject may benefit from continued participation and treatment with paltusotine. The OLE Treatment Period is 200 weeks. Data from the EOR visit of the RC phase will be used as baseline of the OLE, unless otherwise specified.

### 4.1.4. End of Study

An End of Study (EOS) Visit, approximately 4 weeks after the last dose of study drug, will occur at Week 240 to collect final safety data and other assessments as detailed in the SOAs.

### 4.1.5. Patient Input into Study Design

Patient insight was collected over several meetings (November 2019-August 2020) through a formalized Patient Leadership Council made up of 12 individuals living with acromegaly. These patients had a range of experiences including treating physician, medication treatments, geographic location, and age of diagnosis. In these meetings, the following topics were discussed: treatment naïve and maintenance treatment study protocols, use of placebo, rescue therapy, frequency of visits, daily diary execution, study recruitment tactics, and participants' preferred method of learning about potential studies. Results of these discussions were shared with the internal paltusotine study team and incorporated into study design where possible.

## 4.2. Scientific Rationale for Study Design

A prospective randomized, placebo-controlled trial is the gold standard methodology to define the safety and efficacy profile of an experimental drug. Placebo controlled trials have been

successfully conducted and are feasible in rare orphan diseases, including acromegaly. Protocol safeguards are in place to ensure subjects who experience worsening of symptoms associated with acromegaly receive rescue injections of standard therapy, to ensure that they can safely complete the trial (see Section 6.8.1).

## 4.3. Justification for Dose and Treatment Duration

The dose rationale and the proposed titration is designed to achieve the goal of maintaining subjects in a controlled state and optimizing their dose while minimizing the duration of being biochemically uncontrolled (i.e., elevated IGF-1) and experiencing the return of symptoms. Subjects will be switched from labeled stable regimen of octreotide/lanreotide to 40 mg paltusotine and titrated up to 60 mg based on biochemical control or down to 20 mg if 40 mg is not tolerable. Based on dose and exposure analysis of data from completed studies CRN00808-02 and CRN00808-03, the 40 mg dose is expected to be an effective dose for majority of the subjects. The systemic exposures associated with the lower 20 mg dose are expected to be sub-therapeutic in the majority of the subjects, but this lower dose is available for the few subjects who do not tolerate the 40 mg dose. A higher 60 mg dose is available for those subjects who may not derive a full benefit from the 40 mg dose. The safety of these doses has been evaluated in healthy volunteers and found to be similar to that of lower doses and other somatostatin receptor ligands. The dose-titration design reflects how the drug is likely to be used in clinical practice and provides a simple mechanism to switch subjects from parenteral therapy to oral therapy.

Treatment duration was extended up to 240 weeks (approximately 4 ½ years), to allow participants, who in the opinion of the Investigator, are benefiting from treatment with paltusotine, to continue treatment.

Data from an ongoing Phase 2 OLE clinical study (CRN00808-05) show that paltusotine lowered and maintained IGF-1 and GH at levels comparable to prior injected SRLs for up to 103 weeks. Additionally, RC Phase results from this placebo controlled pivotal study (CRN00808-09) show that paltusotine 40 or 60 mg QD provides sustained efficacy in terms of maintenance of disease control for up to 36 weeks in participants with acromegaly, who switched from being controlled on standard of care injectable SRLs. The durability of this clinical meaningful treatment effect was maintained in the OLE with participants continuing to experience clinical benefits.

Paltusotine was well tolerated, with no unexpected safety findings with long-term treatment.

## 4.4. End of Study Definition

The EOS is defined as the date of the last visit of the last subject in the study.

## 4.5. Treatment After End of Trial Participation

After the end of the trial, participants may resume regionally licensed acromegaly treatment as prescribed by their healthcare provider.

# 5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

## 5.1. Inclusion Criteria

| | |
|---|---|
| 1. | Willing and able to provide written informed consent prior to any study-related procedures. |
| 2. | Willing and able to comply with the study procedures as specified in the protocol and comply with the study treatment administration. |
| *Demographics and Medical History* | |
| 3. | Adults ≥18 years of age with medically stable, confirmed-active acromegaly and on an approved, stable monotherapy dose of long-acting octreotide or lanreotide, for at least 12 weeks prior to Screening*. Continuous treatment with octreotide or lanreotide must be at least 24 weeks prior to Screening.<br>*The following prior treatment regimens are allowed for inclusion into this study: long-acting octreotide: 10, 20, 30, 40 mg every 4 weeks or long-acting lanreotide: 60, 90, 120 mg every 4 weeks or 120 mg every 6 or 8 weeks. |
| 4. | Previous diagnosis of acromegaly confirmed by the Investigator and approved by the Medical Monitor. This requires evaluable documentation of a pituitary tumor diagnosed by pituitary imaging or histopathologic confirmation of a pituitary adenoma at least 24 weeks prior to Screening.<br>For subjects who have had pituitary surgery, there must be documentation of IGF-1 concentration ≥1.3×ULN at least 12 weeks after last pituitary surgery. The surgery must have been performed ≥24 weeks prior to Screening. Subjects who have not had pituitary surgery must have documentation of IGF-1 concentration ≥1.3×ULN performed ≥24 weeks prior to Screening. |
| *Screening and Testing Evaluations* | |
| 5. | Screening average IGF-1 levels of ≤1.0×ULN.<br>The upper limit for eligibility is mean IGF-1 of 1.04 (rounded to 2 decimal places) and will be based on 2 or 3 separate measurements in consultation with the Medical Monitor. |
| 6. | Willing and able to undergo biliary/gallbladder ultrasound procedure and pituitary MRI during Screening and during the study. |
| 7. | If currently using thyroid hormone therapy, the subject should be adequately treated based on clinical status and free thyroxine concentration measured during Screening and on a stable dose of thyroid hormone for at least 8 weeks prior to Screening. |

| *Lifestyle Restrictions* | |
|---|---|
| 8. | Females who engage in heterosexual intercourse must be of non-childbearing potential, defined as either surgically sterile (i.e., hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), OR be postmenopausal with at least 1 year of amenorrhea, OR must agree to use either a *highly effective* or a *clinically acceptable* method of contraception from the beginning of Screening until at least 30 days after the last dose of study drug.<br>• Acceptable *highly effective* methods of contraception include:<br>– Non-cyclic, stable dose (monophasic) combined estrogen-progestin oral hormonal contraception associated with consistent inhibition of ovulation. Oral contraceptives containing estrogens should be in stable use for at least 12 weeks prior to Screening.<br>– Desogestrel-based progestin-only contraception associated with consistent inhibition of ovulation; this includes oral, injectable, and implantable methods<br>– Intravaginal and transdermal hormone delivery methods<br>Intrauterine device (with or without hormone elution)<br>– Bilateral tubal occlusion or ligation (must be documented)<br>– Vasectomized partner (must be documented) or<br>– Sexual abstinence (only when it is the usual and preferred lifestyle of the subject)<br>• Clinically acceptable methods of birth control include:<br>– Male or female condom with or without spermicide;<br>Norethindrone-based progestin-only oral contraceptives; or<br>– Cap, diaphragm, or sponge with spermicide.<br>• Withdrawal method (“coitus interruptus”) is not permitted. |
| 9. | If the subject is male, the subject should agree to use a condom when sexually active with a female partner of childbearing potential from Screening until at least 30 days after the last dose of study drug (or be surgically sterile [i.e., vasectomy with documentation]; or remain abstinent [when this is in line with the preferred and usual lifestyle]. Male subjects should also agree to not donate sperm for the duration of the study and until at least 30 days after the last dose of study drug. |

## 5.2. Exclusion Criteria

| *Medical History and Medications* | |
|---|---|
| 1. | Treatment-naïve or treatment-withdrawn acromegaly subjects. |
| 2. | History of pituitary radiation therapy. |
| 3. | Subjects with adrenal insufficiency, diabetes insipidus, or central hypogonadism who are not receiving adequate hormone replacement therapy at the time of Screening, as determined by the Investigator. |
| 4. | High risk pituitary tumor pattern as defined by:<br>• Compression of the optic chiasm or invasion of adjacent brain structures (other than sphenoid sinus or cavernous sinus)<br>• History of tumor growth within 1 year after surgery or radiation (unless it occurred during a period of medical therapy interruption)<br>• Anticipated requirement for neurosurgical intervention or radiation therapy within the time course of the study.<br>• Pituitary carcinoma currently or at any time in the past. |
| 5. | History of major surgery/surgical therapy for any cause within 4 weeks prior to Screening. |
| 6. | Diabetes mellitus treated with insulin for less than 6 weeks prior to the study entry, or with change in total daily insulin dose by >15% within 6 weeks prior to Screening. |
| 7. | History of unstable angina or acute myocardial infarction within the 12 weeks preceding the screening visit or other clinically significant cardiac disease at the time of screening as judged by the Investigator. |
| 8. | Known history of hepatitis B or human immunodeficiency virus, or active hepatitis C infection |
| 9. | Known history of, or current alcohol or drug abuse, within the last year. |
| 10. | Active malignant disease within the last 5 years with exception of basal and squamous cell carcinoma of the skin with complete local excision and resected carcinoma in situ of cervix. |
| 11. | Concomitant mental condition rendering him/her unable to understand the nature, scope, and possible consequences of the study, and/or evidence of poor compliance with medical instructions. |

| | |
|---|---|
| 12. | Use of the following medications as outlined:<br>• Pasireotide LAR (within 24 weeks prior to Screening),<br>• Pegvisomant (within 12 weeks before Screening),<br>• Dopamine agonists (within 12 weeks before Screening), or<br>• Short-acting somatostatin analogs (SA-SSAs) within last 12 weeks before the first dose of study drug.<br>Note: Withdrawal of these medications should be part of the subject's medical care plan prior to Screening; entry into the study should not be the sole reason for withdrawal of a prior medication. |
| 13. | Current use of oral estrogen replacement therapy for <12 weeks prior to Screening. |
| 14. | Current use of medications that are strong inducers of cytochrome (CYP)3A4 within 2 weeks prior to Screening (refer to Section 6.7.2 Prohibited Medicine). |
| 15. | Known allergy or hypersensitivity to any of the test materials or related compounds. |
| *Screening Tests and Evaluations* | |
| 16. | Active COVID-19 confirmed or suspected based on clinical symptoms. |
| 17. | Symptomatic cholelithiasis. |
| 18. | Clinically significant concomitant disease including but not limited to cardiovascular disease, moderate or severe renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 $m^2$), or significant liver disease (including cirrhosis). |
| 19. | Clinically significant abnormal findings during the Screening Period or any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardize the subject's safety or ability to complete the study. |
| 20. | Systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg during Screening. If the initial measurement is out of range, it may be repeated 2 more times after 15 minutes and the last assessment should be used to determine subject's eligibility. |
| 21. | Resting (at least 10 minutes) palpated pulse rate <45 bpm or >105 bpm during Screening. If either of these criteria is met, the assessment should be repeated 2 more times and the last assessment should be used to determine the subject's eligibility. |
| 22. | QT interval corrected using Fridericia's formula (QTcF) >480 msec (or corrected QT [QTc] interval >500 msec in the presence of complete bundle branch block) or PR interval >240 msec during Screening based on a central reading of an average of 3 ECGs each separated in time by approximately 1 minute after the subject has rested quietly in the supine position for at least 10 minutes without significant stimulation (noise, television, etc.). |
| 23. | Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3×ULN and/or total bilirubin >1.5×ULN during Screening. Subjects with previously diagnosed Gilbert's syndrome not accompanied by other hepatobiliary disorders and associated with total bilirubin <3.5 mg/dL (<51.3 µmol/L) will be permitted. |

| | |
|---|---|
| 24. | Poorly controlled diabetes mellitus defined as having a hemoglobin A1c (HbA1c) ≥8.5% (≥ 69 mmol/mol), or estimated HbA1c based on fructosamine if HbA1c is not evaluable (e.g., due to hemoglobinopathies). |
| 25. | Female subjects who are pregnant or lactating. Subjects must have a negative pregnancy test during Screening and prior to the first dose of study drug. |
| 26. | Not applicable; exclusion criterion removed in protocol version 3.0. |
| *Other* | |
| 27. | An employee or immediate family member of an employee of Crinetics. |
| 28. | Participation in any previous clinical study with paltusotine. |
| 29. | Subjects who have received an investigational drug (either approved or not approved) in any prior clinical study within 30 days or 5 half-lives (whichever is longer) prior to Screening. |

## 5.3. Lifestyle Considerations

### 5.3.1. Contraception

Females who engage in heterosexual intercourse must be of non-childbearing potential, defined as either surgically sterile (i.e., hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), OR be postmenopausal with at least 1 year of amenorrhea, OR must agree to use either a *highly effective* or a *clinically acceptable* method of contraception from the beginning of Screening until at least 30 days after the last dose of study drug.

- Acceptable *highly effective* methods of contraception include:
  - Non-cyclic, stable dose (monophasic) combined estrogen-progestin oral hormonal contraception associated with consistent inhibition of ovulation. Oral contraceptives containing estrogens should be in stable use for at least 12 weeks prior to Screening.
  - Desogestrel-based progestin-only contraception associated with consistent inhibition of ovulation; this includes oral, injectable, and implantable methods
  - Intravaginal and transdermal hormone delivery methods
  - Intrauterine device (with or without hormone elution)
  - Bilateral tubal occlusion (must be documented)
  - Vasectomized partner (must be documented) or
  - Sexual abstinence (only when it is the usual and preferred lifestyle of the subject)
- Clinically acceptable methods of birth control include:
  - Male or female condom with or without spermicide;
  - Norethindrone-based progestin-only oral contraceptives; or
  - Cap, diaphragm, or sponge with spermicide.

- Withdrawal method ("coitus interruptus") is not permitted.

If the subject is male, the subject should agree to use a condom when sexually active with a female partner of childbearing potential from Screening until at least 30 days after the last dose of study drug (or be surgically sterile [i.e., vasectomy with documentation]; or remain abstinent [when this is in line with the preferred and usual lifestyle]. Male subjects should also agree to not donate sperm for the duration of the study and until at least 30 days after the last dose of study drug.

## 5.4. Screen Failures

Subjects who fail to meet the eligibility criteria at any point during the Screening Period are defined as screening failures. The reason for each screening failure will be recorded.

Subjects who have failed screening based on findings which the Investigator believes are temporary and not reflective of the usual state of the subject (e.g., HbA1c of ≥8.5% [69 mmol/mol] when the subject is usually well below this value) can be considered for re-screening. These cases should be discussed with the Medical Monitor.

# 6. STUDY DRUG AND CONCOMITANT THERAPY

Study drug is defined as any investigational drug or placebo intended to be administered to a study subject according to the study protocol.

## 6.1. Study Drugs Administered

Paltusotine will be provided as [redacted] tablets in [redacted] Matching placebo tablets will be identical in appearance to paltusotine tablets and will be administered orally according to the randomization scheme, on an identical schedule to those receiving paltusotine. Paltusotine and matching placebo tablets will each be packed in [redacted] containing desiccant. Drug labels will comply with the legal requirements of each country and will be printed in local language.

The starting daily dose will be paltusotine 40 mg (or matching placebo) QD for oral self-administration. Study drug will be swallowed in the morning, with at least 8 ounces (237 mL) of water, after an overnight fast of at least 6 hours. No food or drink (except for water) will be allowed for at least 1 hour after drug administration, including time for study drug administration. The last dose of study drug for the RC phase will be self-administered the day prior to the W36/EOR visit. The first dose of the OLE phase will be administered during the W36/EOR visit for those continuing into the OLE.

**Table 4: Study Interventions**

| **ARM Name** | **Paltusotine Arm** | **Placebo Arm** |
|---|---|---|
| **Intervention Name** | Paltusotine | Placebo |
| **Type** | Drug | Drug (placebo) |
| **Dose Formulation** | Tablet | Tablet |
| **Unit Dose Strength(s)** | [redacted] | Placebo for [redacted] tablet |
| **Dosage Level(s)** | Starting dose is [redacted] tablets daily. The dose can be titrated up to [redacted] tablets daily. Dose levels may be decreased to [redacted] tablet daily. | Starting dose is [redacted] tablets daily. The dose can be titrated up to [redacted] tablets daily. Dose levels may be decreased to [redacted] tablet daily. |
| **Route of Administration** | Oral | Oral |
| **Use** | Experimental | Placebo |
| **IMP and AuxMP** | IMP | IMP |
| **Sourcing** | Provided centrally by the Sponsor | Provided centrally by the Sponsor |

| ARM Name | Paltusotine Arm | Placebo Arm |
|---|---|---|
| **Packaging and Labeling** | Sponsor will package and label the study drug. Drug labels will comply with the legal requirements of each country and will be printed in the local language. The labels will supply no information about the subjects. Each bottle or pack will have a unique Dispensing Unit Number (DUN) for drug accountability purposes and traceability. The storage conditions for study drug will be described on the study drug label. | Sponsor will package and label the study drug. Drug labels will comply with the legal requirements of each country and will be printed in the local language. The labels will supply no information about the subjects. Each bottle or pack will have a unique DUN for drug accountability purposes and traceability. The storage conditions for study drug will be described on the study drug label. |

IMP=investigational medicinal product, AuxMP=auxiliary medicinal product
Note: AuxMPs are described in Section 6.8.

## 6.2. Preparation/Handling/Storage/Accountability

The appointed team members will be identified at each center whose role in the study will be handling of the study drugs (i.e., they will be responsible for the receipt and accountability of the study drug). Furthermore, other tasks can be delegated to them in a clear manner by the Investigator and that will be documented and completed in the *Study Staff Signature and Delegation Log*.

The Investigator must ensure the availability of proper storage conditions. Study staff at the study site will take all steps to maintain adequate records and will ensure that the study drug is stored as specified on the medication labels, in a strictly controlled, secure area, at appropriate temperature and in accordance with the protocol and any applicable regulatory requirements. Direct-to-subject shipments of study drug will be allowed in exceptional cases (i.e., where subjects would not be able to attend on-site visits and would risk continued access to study drug). Study drug will be provided by the Sponsor and are to be dispensed only in accordance with the protocol. Study drug must not be dispensed to any person not enrolled in the study.

An accurate inventory and accountability records of the study drug will be kept by the appointed team member. Drug accountability must be performed for all delivered DUNs. Returned study drug (partly used or unused including empty packaging material) must be stored separately from non-allocated study drug. The storage temperature should be monitored by recording the actual, minimum, and maximum temperatures using a calibrated thermometer or thermocouple, or by continuous recording using a qualified temperature monitoring system. The temperature should be evaluated and documented at least on working days on a temperature log. This log must be included in the Investigator Site File upon study termination.

The appointed study staff must contact the site monitor in case of temperature deviations outside the acceptable range.

Paltusotine tablets and matching placebo tablets will each be packed in [redacted]. Bottles of tablets should be stored at the study site at [redacted]

Paltusotine and matching placebo will be provided by the Sponsor and the logistics of supply would be managed by the Sponsor/appropriate designee.

All study drugs should be stored and inventoried according to applicable state and federal regulations and study procedures.

At the end of the study (i.e., close-out visit) and following reconciliation and documentation by the site monitor, all study drugs and related materials will be either returned to the Sponsor or a designee or destroyed locally following the review and approval of the site's destruction procedures.

The study drugs (sufficient to last until the next planned visit) will be dispensed by the appointed study staff to the subjects at relevant study visits.

Subjects will be instructed to store the study drug [redacted] in the original packaging and out of reach of children. The storage conditions will be carefully described to the subjects.

If the Investigator, the site staff, or the site monitor suspect that the study drug is defective or potentially defective, Crinetics Pharmaceuticals or designee should be contacted immediately. Full details concerning study drug handling e.g., allocation, accountability, tracking, and recording will be provided in a Pharmacy Manual.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

Subjects will be randomized to study treatment, using an interactive, automated system which has been validated for the intended use under the International Society of Pharmaceutical Engineers Good Automated Manufacturing Practice guidelines, 21 CFR 11 (FDA regulation for Electronic Records and Electronic Signatures) and the International Council for Harmonization (ICH) Guidance E6 for Industry on GCP.

Randomization will be performed using a fixed-block randomization scheme. The randomization scheme will be generated prior to the initiation of the study by an independent statistician/programmer who will not be a member of the study team; all Investigators and the study team will not be aware of the block size of the randomization scheme. Randomization will be stratified by IGF-1 level ($<0.86\times$ULN, $\geq 0.86\times$ULN) and prior treatment (lanreotide or octreotide).

Study drug will be dispensed at the study visits summarized in the SOAs.

Returned study drug should not be re-dispensed to the subjects.

The Interactive Voice Response System/Interactive Web Response System will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a subject's intervention assignment unless this could delay emergency treatment of the subject. If a subject's intervention assignment is unblinded, the Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

Sponsor safety staff or designee may unblind the intervention assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

## 6.4. Study Drug Compliance

Subject randomization, study drug allocation, and dose titration must be performed in the interactive, automated system.

When subjects are dosed during a study visit, they will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered during the visit will be recorded in the source documents.

When subjects self-administer study drug at home, compliance will be assessed at each visit. Compliance will be assessed by either direct questioning and/or counting returned tablets during the site visits and documented in the source documents and relevant forms. Deviations from the prescribed dosage regimen should be recorded.

A record of the quantity of study drug dispensed to and administered by each subject must be maintained and reconciled with study drug and compliance records. Study drug start and stop dates, including dates for study drug delays, drug interruptions and/or dose reductions, will also be recorded.

Further details are provided in the Pharmacy Manual and relevant monitoring plan.

Subjects will be instructed to return all used and unused study drugs at each study visit during the Treatment Period. All returned study drug and study drug materials should be stored, inventoried, reconciled, and returned according to applicable local regulations and study procedures.

## 6.5. Dose Modification

See Figure 2 for the dose titration schema.

### 6.5.1. During the RC Phase

The dose of study drug can be titrated up to 60 mg QD. Dose levels may increase from 40 mg [redacted] tablets) to 60 mg ([redacted] tablets) based on IGF-1 response. It is anticipated that the study drug dose will be stable and titration completed prior to or at Week 24, with no dose titrations/adjustments after Week 24. Up-titration after Week 24 should not occur; subjects who require dose up-titration after Week 24 will be considered non-responders. Down-titration will be allowed based on tolerability.

Dose up-titration will be based on 2 criteria:

- Acceptable tolerability at the current dose, as evaluated by the Investigator,

  **AND**

- The subject's most recent IGF-1 result is >0.9×ULN

If needed, an unscheduled dose titration Visit may be performed. The study drug dose may be decreased at any time during the study if study drug toleration is unacceptable in the judgment of the Investigator. A dose reduction based on tolerability may be necessary for subjects who are taking P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) inhibitors (see Section 6.7.1). In general, a TEAE of severe intensity for which there is a reasonable possibility it is caused by (related to) study drug would be expected to result in study drug dose reduction. If tolerance improves following a dose reduction, the Investigator may increase the dose in [redacted] increments, if needed, based on protocol specified dose titration criteria to a maximum of 60 mg [redacted] tablets). See Section 10.3.1 for the definition of a TEAE and Section 10.3.3 for definitions of intensity and causality. When, in the Investigator's judgment the study medication is not tolerated, the study medication may be interrupted for up to a total of 14 days per year, but no more than 7 consecutive days per year, during the study followed by resumption of the study medication at the same or reduced dose as appropriate.

During the RC phase, planned study visits are to occur approximately every 4 weeks; however, unscheduled visits may be required for more frequent monitoring, dose titration, and to assess rescue criteria.

### 6.5.2. During the OLE

The starting daily dose regimen for all subjects who participate in the OLE will be paltusotine 40 mg QD, dispensed in an open-label manner. The first dose of the OLE phase will be administered at the W36/EOR visit. Subjects will be given bottles of paltusotine containing [redacted] tablets and instructed to take 2 tablets daily until their next visit.

Dose escalation in the OLE will generally occur once the first IGF-1 result is available. At that time, the Investigator can determine whether the dose can be up-titrated to 60 mg.

The study medication may be held for up to a total of 14 days, but no more than 7 consecutive days per year in the OLE. If the study drug has to be stopped for longer due to appropriate medical care for the subject, the medical monitor should be contacted.

## 6.6. Treatment of Overdose

There are no clinical data available on effects associated with overdose. No documented incidents of overdose have occurred with paltusotine to date. Preclinical animal studies indicate bradycardia or hypertension may result from overdose. The recommended treatment of overdose with paltusotine would include supportive and symptomatic measures employed in the management of overdose with a drug with potential cardiovascular events.

## 6.7. Concomitant Therapy

### 6.7.1. Permitted Medicine

Concomitant medications allowed in this study are those non-prohibited medications used during Screening to control existing medical conditions and/or those initiated during the study if medically needed. All concomitant medications will be recorded in the subject's electronic case report form (eCRF). If a new medication should become necessary for any reason during the course of the study, the subject is required to inform the Investigator immediately, who will record the drug, the dose, start and stop dates, indication, route, and frequency. The Investigator

is responsible for ensuring the new medication is not prohibited by the protocol and to contact the Medical Monitor for any questions.

Caution should be used when co-administering permitted concomitant medications that have the potential to interact with drug metabolizing enzymes or drug transporters shared with or affected by paltusotine (see IB and Paltusotine Guidance on Concomitant Medications reference document for Investigators). In addition, caution should be used with concomitant medications that have been associated with QT prolongation/Torsades de Pointes or may be associated with significant heart rate slowing. For a regularly updated list of drugs with known and possible risk for Torsade des Pointes, refer to www.crediblemeds.org.

### 6.7.2. Prohibited Medicine

Any questions regarding prohibited medications should be discussed with the Medical Monitor or appropriate designee. Prohibited medications include:

- Oral estrogen, except for monophasic estrogen-progestin oral contraception;
- Strong inducers of the drug metabolizing enzyme CYP3A4, including but not limited to: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort (because these medicines may decrease the concentration of paltusotine in the systemic circulation);
- Any standard acromegaly drug that is not used as a rescue medication during the RC phase of the study or an allowed adjunctive medication in the OLE;
- Any other investigational drug, unless approved by the Medical Monitor (e.g., COVID-19 therapies).

## 6.8. Auxiliary Medicinal Products

### 6.8.1. RC Phase Rescue Medication (Auxiliary Medicinal Products)

During the RC phase, acromegaly treatments other than study drug are prohibited, unless the subject meets criteria for rescue therapy as described below.

Criteria for rescue with approved SRLs (injected long-acting octreotide or lanreotide [auxiliary medicinal products (AuxMPs)]) consist of the following:

- Significant worsening of 1 or more acromegaly symptoms or the development of a new acromegaly symptom, at the highest dose (60 mg) for at least 2 weeks, as assessed by the Investigator. Symptoms should be attributed to uncontrolled acromegaly in the opinion of the Investigator and could include, but are not limited to, the following: headache, arthralgia, fatigue, hyperhidrosis, or soft tissue swelling. ("Significant worsening" in the opinion of the Investigator may be defined as symptoms requiring a substantial increase in level of clinical care [e.g., significant intervention needed to avert hospitalization or clinically notable increase in frequency or intensity of subject contact required] or substantial clinical deterioration [e.g., worsening from a mild to severe AE or the onset of an SAE would meet these criteria]).

  **AND**

- IGF-1 value ≥1.3×ULN at the highest dose (60 mg) measured at 2 successive planned visits or at an unscheduled visit if an earlier result is needed (as evaluated by the Investigator).

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 24, with no dose titrations/adjustments after Week 24. Up-titration after Week 24 should not occur; subjects who require dose up-titration after Week 24 will be considered non-responders. If rescue therapy is required during the RC phase, subjects will discontinue paltusotine or placebo, initiate rescue therapy, and should continue the visits and surveillance in the study for the remainder of the 36-week RC phase. Rescue therapy should be used according to approved marketing authorization or standard clinical practice.

Once rescue therapy is administered during the RC Phase, the subject will be considered as non-responder.

### 6.8.2. OLE Phase Adjunctive Treatments (Auxiliary Medicinal Products)

If there is evidence of paltusotine efficacy and at 6 months, subjects have not reached therapeutic target goals, adjunctive treatment may be initiated if clinically appropriate beginning at Week 60. If these criteria are met, non-SRL acromegaly treatments, such as cabergoline or GH receptor antagonist pegvisomant are permitted and may be initiated as an adjunct when a subject has experienced at least 2 consecutive elevated IGF-1 (≥1.3×ULN) measurements at the highest paltusotine dose level (60 mg), or otherwise not at the subject's therapeutic target in the judgement of the Investigator.

- Use of any adjunctive medications should be discussed with the Medical Monitor and should be used according to approved marketing authorizations or standard practice. Adjunct medications are not provided by the Sponsor.
- If it is determined that adjunctive medication is required, then use of cabergoline would be the expected first-line adjunct, as clinically appropriate. If after an adequate period of assessment, study medication combined with cabergoline does not achieve therapeutic targets, then pegvisomant may be added as a second-line adjunct, if clinically appropriate (Katznelson, 2014). In this situation, the Investigator should assess if there was evidence of an IGF-1 lowering response from cabergoline. If so, the pegvisomant may be added to the paltusotine + cabergoline drug combination. If there was no evidence of a therapeutic response to combined paltusotine + cabergoline, the cabergoline should be stopped and pegvisomant added to paltusotine therapy.
- Short- and long-acting somatostatin receptor agonists (other than paltusotine) remain prohibited and are not permitted during the study (subjects will be discontinued from the study if these are needed and an ET Visit will be scheduled prior to resuming these treatments).

# 7. DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Treatment/Participation

All subjects will be informed that they have the right to withdraw from the study at any time, for any reason, without prejudice, and without having to justify their reasons or decisions. Additionally, the Investigator may discontinue a subject's participation at any time if he/she considers that to be in the subject's best interest or if the Investigator determines that continuing participation would result in a significant safety risk for that subject. A discontinuation of treatment occurs when an enrolled subject discontinues participation in the study, regardless of the circumstances, prior to completion of the study. However, every effort should be made to observe subjects who have been enrolled until the scheduled end of their observation without study discontinuation, even if they discontinue early from the study drug treatment, if clinically appropriate. A subject who discontinues from study drug early by meeting protocol criteria for rescue with approved SRLs and completes the 36-week RC phase may be eligible for participation in the OLE portion of the study. Subjects who do not meet criteria for rescue, but for whom the Investigator recommends discontinuation of study drug and resumption of approved SRLs should be discussed with the Medical Monitor. Such cases will be considered for continuation in the RC phase on approved SRLs and eligibility for the OLE on a case-by-case basis.

If a subject discontinues the study early, the Investigator should schedule an ET visit, particularly to ensure collection of AE follow-up data (if applicable) and to collect samples for laboratory evaluations. This visit should be documented as appropriate. The Investigator will record the reason for the study discontinuation and provide or arrange for appropriate follow-up and ensure return to standard acromegaly treatment for such subjects. In addition, the Investigator will report the subject's withdrawal to the responsible Medical Monitor within 24 hours. In case of occurrence of adverse reactions the Investigator will ensure that adequate follow-up measures are in place to monitor the outcome of the adverse reaction itself.

Reasons for a subject to discontinue the study treatment and/or participation in this clinical study include, but are not limited to:

1. Withdrawal of informed consent by the subject;
2. Occurrence of AEs for which study treatment and/or study participation discontinuation is desired by the subject or considered necessary by the Investigator or the Medical Monitor;
3. Unacceptable tolerability of the lowest study drug dose ([redacted] per day) in the opinion of the Investigator;
4. Other clinically significant potentially drug-related abnormalities (e.g., newly developed or worsening hypoglycemia, hyperglycemia, hypersensitivity, symptomatic cholelithiasis, or pancreatitis);
5. Investigator's decision (i.e., if in the Investigator's opinion it is not in the best medical interest for the subject to continue participation in the study for reasons other than AEs);
6. Need for administration of a prohibited concomitant medication (Section 6.7.2);

7. Any other protocol deviation that may result in a significant risk to the subject's safety or protocol deviations that will interfere with assessment of the efficacy endpoints of this study, including subject's non-compliance with the study procedures/study protocol;
8. Pregnancy;
9. Lost to follow-up (the subject stopped coming for visits, and study personnel are unable to contact the subject);
10. Inability to fulfill study requirements and procedures;
11. Death.
12. After 6 months of treatment during the OLE phase, cabergoline and pegvisomant may be used as adjuncts to maximal dose paltusotine as clinically appropriate. Subjects who need to resume standard injected SRLs because paltusotine or paltusotine in combination with allowed adjuncts do not achieve adequate control of acromegaly will be discontinued from the study (see Section 6.8.2).

### 7.1.1. Liver Chemistry Abnormality Monitoring and Study Drug Stopping Criteria

Closely monitoring abnormalities of liver tests and discontinuation for evidence of liver injury will be performed according to the following process (DHHS DILI 2009):

- Detection of Liver Test Abnormalities

  All subjects will have a serum chemistry panel as per the SOAs. Confirmation of detected liver test abnormalities is required for any subject with 1 or more of the following:

  – ALT or AST >3×ULN (for subjects with ALT and AST <ULN at baseline);
  – ALT or AST >3×ULN and >2×Baseline (for subjects with ALT or AST >ULN at Baseline);
  – Total bilirubin (TB) >2×ULN (for subjects with TB <ULN at baseline);
  – TB >2×ULN and >2×Baseline (for subjects with TB >ULN at baseline);
  – Alkaline phosphatase (ALP) >3×ULN (for subjects with ALP <ULN at baseline);
  – ALP >3×ULN and >2×Baseline (for subjects with ALP >ULN at baseline).

- Confirmation of Detected Liver Test Abnormalities

  If any of the above-listed liver test abnormalities are detected, they should be followed by repeat testing within 48 to 72 hours (of ALT, AST, ALP, and TB) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiries made about symptoms.

  If the above-listed liver test abnormalities (and/or related symptoms) persist or worsen, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening over time. (See Close Observation recommendations below.) If close monitoring is not possible, the drug should be discontinued.

- Close Observation of Any Subject with Detected Liver Test Abnormalities.

  Close observation includes:

  – Repeating ALT, AST, ALP, and TB tests 2 to 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic;

  Obtaining a more detailed history of symptoms and prior or concurrent diseases;

  – Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets;

  – Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.

  – Obtaining a history of exposure to environmental chemical agents;

  – Obtaining additional tests to evaluate liver function, as appropriate (e.g., international normalized ratio);

  – Considering gastroenterology or hepatology consultations.

Discontinuation of study drug for abnormal liver tests is required when a subject meets 1 of the conditions outlined below:

- ALT or AST >8×ULN;
- ALT or AST >5×ULN for more than 2 weeks;
- ALT or AST >3×ULN and TB >2×ULN or INR >1.5;
- ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

### 7.1.2. Amylase or Lipase Study Drug Stopping Criteria

The Medical Monitor should be contacted promptly if amylase or lipase levels increase from baseline by more than two-fold and exceed 3×ULN. Testing should be repeated within 1 week and if the amylase or lipase elevation persists, study drug should be stopped. The Medical Monitor and Investigator will determine together the appropriateness of continued study participation.

### 7.1.3. Cardiac Study Drug Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline [average of triplicate ECGs] in QTcF after enrollment), the Investigator or qualified designee will determine if the subject can continue in the study and if any change in subject management is needed. Any new clinically relevant finding should be reported as an AE.

Cardiology consultation should be obtained within 7 days for new clinically important symptoms or findings judged by the Investigator to be reasonably likely to be of cardiac origin, e.g., evidence for new arrhythmia, significant chest discomfort/pain, presyncope or syncope.

Discontinuation of study drug is required when a subject meets 1 of the clinically significant cardiac symptoms or findings as outlined below:

- Based on the average of triplicate ECGs, QTcF >500 msec (or QTc >530 msec in subjects with a bundle branch block) repeated on a second set of ECGs at least 2 hours apart and confirmed by a stat central ECG reading;
- Any ventricular tachyarrhythmia associated with symptoms of hemodynamic response;
- Sustained ventricular tachycardia (lasting >30 seconds) irrespective of symptoms;
- Torsades de pointes;
- Cardiac arrest;
- Pause >5 seconds;
- Type 2 second degree block or third degree atrioventricular block;
- New occurrence of clinically significant, symptomatic bradycardia;
- Based on the average of triplicate ECGs, an increase in QTcF >60 msec with an absolute QTcF <500 msec repeated on a second set of ECGs at least 2 hours apart and confirmed by a stat central ECG reading;
- Any supraventricular tachyarrhythmia associated with symptoms of hemodynamic response.

The Medical Monitor and Investigator will determine the appropriateness of any further study drug dosing after stabilization of any of the above events.

## 7.2. Lost to Follow up

If a subject fails to attend scheduled assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

For subjects who are lost to follow-up (i.e., subjects whose status is unclear because they fail to appear for the study visits without stating an intention to withdraw), the Investigator should document in the source documents all steps taken to contact the subject (e.g., dates of telephone calls, registered letters, etc.).

## 7.3. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may include, but not limited to, the following:

- Inefficacy of the study medication;
- Results from ongoing safety monitoring;
- Other medical or ethical reasons.

Regulatory Authorities/Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) also have the right to terminate the study for any reason.

In the event the study is terminated, the IRBs/IECs and Competent Authorities will be notified of the relevant decision.

# 8. STUDY ASSESSMENTS AND PROCEDURES

## 8.1. Demographics and Baseline Characteristics

Demographics will include age, sex, ethnicity, and race. Baseline characteristics will include acromegaly history, medical history, and concomitant medications.

Pre-trial acromegaly symptoms including assessment of the most bothersome symptom will be recorded.

## 8.2. Subject-reported Assessments

Planned time points for all subject-reported assessments are provided in the SOAs. When these assessments are done at the same visit, the order will be as follows: (1) Acromegaly Symptoms Diary, [redacted] These assessments will be completed using an electronic device (either through an application on the subject's electronic device or by a device provided by the Sponsor).

### 8.2.1. Acromegaly Symptoms Diary

Subjects will be asked to complete the ASD, a brief symptom diary, daily at home beginning at least approximately 2 weeks prior to study drug dosing for the duration of the randomized controlled phase. Sparse periodic administrations at home or at study visits will be performed during the OLE. The ASD should be completed at approximately the same time of day, as consistently as possible. Site staff will review subject compliance with ASD completion at each study visit. Responses to the ASD will not be reconciled with AE data.

The ASD consists of 9 items (headache pain; joint pain; sweating; fatigue; weakness in legs; swelling; numbness or tingling; difficulty sleeping; and a question on short-term memory), each ranked in intensity from 0-10. The total ASD score will be computed by adding the individual symptom intensities for headache pain; joint pain; sweating; fatigue; weakness in legs; swelling; and numbness or tingling, therefore total ASD score can range from 0-70. All individual item scores, including difficulty sleeping and the question on short-term memory will be collected and analyzed in individual item scoring.

### 8.2.2. [redacted]

[redacted]

### 8.2.3. [redacted]

[redacted]

[redacted]

**8.2.4.** [redacted]

[redacted]

**8.2.5.** [redacted]

[redacted]

## 8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SOAs.

### 8.3.1. Physical Examinations

A complete physical examination includes assessment of head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system, ring size, and, where appropriate, other body systems. Symptom-related physical examinations (with weight measurement as appropriate) will also be performed.

Physical examination will include height measurement at Screening and weight measurement at certain study visits. The study site must use calibrated equipment with subjects required to remove their shoes and heavy objects from their clothing prior to height and weight measurement, respectively.

Any confirmed clinically significant physical examination abnormalities occurring after the moment of signing informed consent form (ICF) are to be recorded as AEs.

### 8.3.2. Vital Signs

Vital signs (blood pressure at rest, pulse rate, respiratory rate, and oral (or equivalent) body temperature) will be assessed as per standard practice at relevant study visits. When possible, vital signs should be performed while fasting after the study drug dosing.

Blood pressure (resting) should be measured with calibrated digital equipment after resting quietly for 5 minutes.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Blood pressure and pulse rate measurements will be repeated at the Investigator's discretion. Any confirmed clinically significant vital sign measurements occurring before signing the ICF are to be designated as medical history.

### 8.3.3. Electrocardiograms

A standard 12-lead ECG will be performed in triplicate (approximately 1 minute apart) after the subject has rested quietly in the supine position for at least 10 minutes without significant stimulation (noise, television, etc.). When possible, the ECGs should be performed while fasting after the study drug dosing. The ECG parameters that will be assessed include a summary of findings as well as measurement of the heart rate, QT, QTcF, and PR intervals, and QRS duration based on the ECG machine readings.

All ECG assessments will be initially assessed by the Investigator for any findings that require immediate medical attention and will also be read by an ECG central reader. The clinical significance of any ECG findings will be determined by the Investigator, including after the central reading result is available. Only the Investigator's assessment will be recorded in the eCRF. Any potentially significant outlier values should be confirmed by the central ECG reader. Any ECG measurement determined to be clinically significant (occurring after signing the ICF) will be noted as an AE on the appropriate eCRF page(s). Such abnormalities will be monitored until the end of the study or until resolution if considered related to the study drug.

Refer to Section 7.1.3 for cardiac withdrawal criteria and any additional QTc readings that may be necessary.

### 8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the SOAs for the timing and frequency.

All analyses must be done with the minimally required blood amount and the number of needle insertions should be minimized during the blood collection.

Laboratory management and shipping details are described in a Laboratory Manual.

After sampling, blood collection tubes will be labelled and handled as defined in the Laboratory Manual.

All results (except pharmacokinetics [PK] and genotyping) will be reported to the Investigator after completion of analyses.

All laboratory reports received must be reviewed, assessed for clinical significance, signed, and dated by the Investigator or delegated sub-Investigator. A legible copy of all reports must be filed in a subject medical record (source document) for that visit. Any laboratory test result (occurring after the moment of signing ICF) considered by the Investigator to be clinically significant will be recorded as an AE and will be managed as described in Section 8.4.

### 8.3.5. Biliary/Gallbladder Ultrasound

Biliary/gallbladder ultrasound will be performed according to the study site procedures for the evaluation of presence or absence of lithiasis or sludge or other significant biliary abnormalities.

The ultrasounds can be performed at any time if clinically indicated in the opinion of the Investigator. An ultrasound is required for all subjects, including those that have had surgical removal of the gallbladder (cholecystectomy). The ultrasound does not need to be performed on the same day as the study visit. Ultrasounds may be performed within ± 2 weeks of the study visit. The results will be recorded.

### 8.3.6. Magnetic Resonance Imaging

Pituitary MRI should be performed locally and does not need to be performed on the same day as the study visit. MRIs may be performed within ± 2 weeks of the study visit. Tomography is not permitted as a replacement for MRI. Image acquisition standards will be provided and must be followed to allow proper evaluation of tumor volume. All MRI assessments will be assessed by the Investigator for any findings that require immediate medical attention and will also be read by an MRI central radiologist. The clinical significance of any MRI findings will be determined by the Investigator, including after the central reading result is available. However, only MRI results provided by the local report will be recorded in the eCRF. Management of subjects prior to and during the MRI should follow standard local procedures.

### 8.3.7. Ophthalmic Assessments

Ophthalmic assessments will be conducted on all subjects. Initial ophthalmic testing should be performed as soon as practical and then at 6-month intervals, preferably associated with scheduled visits whenever possible, through study completion. If the most recent ophthalmic assessment is performed within 3 months of ET, there is no need to repeat at ET. Assessments will be performed at a local facility with appropriate testing equipment and qualified personnel. The following assessments will be conducted:

- Corrected distance visual acuity evaluation
- Threshold visual fields ([redacted])
- Fundus photography of the macula (single photograph centered on macula in each eye) and
- Optical coherence tomography of the macula

Detailed specifications for acceptable instrumentation, data acquisition, data collection, and test results distribution processes will be provided to the investigative sites in separate ophthalmic assessment guidance documents.

Visual acuity and threshold visual field results and images for fundus photography of the macula and optical coherence tomography of the macula will be transferred from the local testing facility to the designated data processing portal accessible by the [redacted]

## 8.4. Adverse Events, Serious Treatment-emergent Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

All medical conditions present prior to the study entry will be documented. However, medical conditions occurring after the moment of signing the ICF or a worsening of a medical condition

present prior to the study entry are to be recorded as AEs. All AEs occurring after the study drug administration has started will be considered as TEAEs.

Investigators will be asked to assess whether each reported AE is a symptom of acromegaly. If AEs are attributed to acromegaly, they will be reported as AEs of special interest.

The Investigator or qualified designee is obliged to interview a subject at every visit and clarify/discuss with him/her any abnormality that may indicate any potential AE/TEAE.

Subjects should be informed that they do not have to wait for scheduled visits to report AEs/TEAEs.

Adverse events related to the study drug that are ongoing at the end of the study will be followed for outcome information until resolution or stabilization.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

### 8.4.1. Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be recorded from after the moment of signing ICF, up to 4 weeks after the last dose of the study drug.

All SAEs will be recorded and reported to the Sponsor or designee immediately (and under no circumstance should this exceed 24 hours) of knowledge of the event, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on TEAEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

### 8.4.2. Method of Detecting AEs

Care will be taken not to introduce bias when screening for AEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE or TEAE occurrences.

### 8.4.3. Follow-up of AEs

After the initial AE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts.

Any AE that occurs in the course of a clinical study must be monitored and followed up until either:

- it has resolved,
- laboratory abnormalities have returned to normal, OR
- steady state of the symptoms has been achieved.

If none of these alternatives apply, then the subject must be asked about the evolution of the AE at the follow-up visit 4 weeks after the last dose of study drug. The status must be reported in the Case Report Form (CRF), and this ends the follow-up process for this AE.

It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

Further information on follow-up procedures is provided in Appendix 3.

### 8.4.4. Regulatory Reporting Requirements for SAEs

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to both expedited and periodic safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Any SAE occurring after the ICF has been signed and up until 4 weeks after the last dose of study drug must be reported to the designated Pharmacovigilance group.

Any such SAE due to any cause, whether or not related to the study drug, must be reported on the SAE reporting form immediately (and under no circumstances should this exceed 24 hours of occurrence) or when the Investigator becomes aware of the event. A properly completed SAE reporting form should be sent via email.

Pharmacovigilance Group e-mail: [redacted]

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be provided whether or not the Investigator considers the event to be related to the study drug.

Appropriate measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all available additional follow-up information to the Pharmacovigilance Group within 24 hours. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

Suspected unexpected serious adverse reactions (SUSARs, i.e., unexpected SAEs considered drug related as assessed by the Investigator/Sponsor/authorized person) will qualify for expedited reporting and cross reporting to the IRB/IEC, Competent Authorities, and participating Investigators by Crinetics Pharmaceuticals, Inc. In the EU, Crinetics Pharmaceuticals, Inc. will act in compliance with the CTR EU No 536/2014.

SAEs occurring after the study termination must be reported only if considered study drug-related per Investigator judgment.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed until its resolution or stabilization.

### 8.4.5. Pregnancy

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening. All other pregnancy tests will be urine tests. If the result of a urine test is positive the result will be confirmed with a serum pregnancy test. Urinary pregnancy tests will be performed monthly at Screening, during RC phase, and during OLE phase when the duration between the visits is longer than 4 weeks. Pregnancy tests may also be obtained at any time during the study as an unscheduled test if clinically appropriate. Subjects must discontinue study drug immediately in the event of pregnancy in a female subject. Any pregnancy will be reported by telephone (optional) and by emailing a completed Pregnancy Exposure Report form to the Sponsor's Pharmacovigilance Group within 24 hours of knowledge of the pregnancy at [redacted]. The pregnancy will not be processed as a SAE. However, the Investigator will follow-up with the subject or female partner of the male subject (after obtaining informed consent, as appropriate) until completion of the pregnancy and must determine the outcome of the pregnancy in the shortest possible time. The Investigator should notify the Sponsor's Pharmacovigilance Group of the pregnancy outcome by submitting a follow-up Pregnancy Exposure Report form. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by telephone (optional) and by e-mailing a completed SAE Report form to the Sponsor's Pharmacovigilance Group within 24 hours of knowledge of the event.

## 8.5. Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentration of study drug as specified in the SOAs.

To minimize patient burden, only sparse PK samples are to be collected at various study visits. Plasma paltusotine concentrations and elapsed time from the last paltusotine dose taken will be listed. A summary of concentrations by paltusotine dose for each timepoint will be presented.

In addition, PK concentration data from this study will be pooled with data from other paltusotine studies for the planned population PK analysis to assess relevant intrinsic and extrinsic factors on paltusotine PK dispositions.

Instructions for the collection, handling, and storage of biological samples will be provided by the Sponsor in the Laboratory Manual. The actual date and time (24-hour clock time) of collection of each sample will be recorded. The actual date and time of last dose of study drug prior to each sample collection will also be recorded.

## 8.6. Genetics

On Day 1, blood may be drawn for genotyping for the determination of the [redacted] genotype. This is optional for subjects and consent will be obtained before the blood sample is collected.

## 8.7. Biomarkers

Blood will be drawn at the time points on the SOAs to measure IGF-1 and GH.

## 8.8. Immunogenicity Assessments

Antidrug antibodies are not evaluated in this study.

## 8.9. Collection and Storage of Biological Samples

The Sponsor will comply with the applicable rules for the collection, storage, and future use of biological samples from clinical trial subjects. The Sponsor will comply with national requirements including those set in the CTR (EU) No 536/2014, Article 7.1 (h).

A description of the arrangements to comply with CTR (EU) No 536/2014, Article 7.1 (h) is provided in the form ‘Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)’ submitted as a Part 2 document of this trials Clinical Trials Information System (CTIS) submission.

# 9. STATISTICAL CONSIDERATIONS

## 9.1. Statistical Hypotheses

The primary hypothesis:

$H_o$: $\pi_{placebo} = \pi_{Paltusotine}$

$H_a$: $\pi_{placebo} \neq \pi_{Paltusotine}$

Where $\pi_{placebo}$ is the proportion of subjects at EOR with IGF-1 ≤1×ULN while on placebo and $\pi_{Paltusotine}$ is the proportion of subjects at EOR with IGF-1 ≤1×ULN while on paltusotine.

## 9.2. Sample Size Determination

The primary endpoint assumes that IGF-1 ≤1×ULN rates for paltusotine versus placebo are 70% and 20%, respectively. Based on a 2-sample Fisher's Exact test at a 2-sided alpha=0.05 level of significance, a total sample size of 52 subjects (26 in the paltusotine arm, 26 in the placebo arm) will provide 93.6% power to achieve superiority of paltusotine over placebo.

The estimates used for the power are based on Phase 2 data with paltusotine as well as the observed placebo response in similarly designed clinical study of oral octreotide (Chiasma Inc.; Optimal Study; EudraCT: 2017-000737-31). In the Phase 2 paltusotine acromegaly studies, the drop-out (discontinuation) rates were approximately 10%. These study discontinuation rates are accounted for in the estimates of overall non-response seen in a in similarly designed clinical study of oral octreotide (Chiasma Inc.; Optimal Study; EudraCT: 2017-000737-31) where 68% of the placebo group either dropped out or were on rescue medications defining them as a non-responder.

## 9.3. Analysis Sets

The following analysis sets will be evaluated and used for presentation and analysis of the data in this study:

- The Full Analysis Set (FAS) is defined from the intention-to-treat principle and will include all randomized subjects. The FAS will be the primary analysis set used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Per Protocol (PPS) Analysis Set is defined as all randomized dosed subjects assigned to the treatment received, with no major protocol violations that would affect efficacy, and at least 75% treatment compliance based on tablet counts. This PPS will be used as a sensitivity analysis for the primary endpoint.
- The Safety Analysis Set (SS) will include all subjects who received study drug with treatment assignment based on the treatment received. If a subject receives any amount of paltusotine then the subject will be assigned to the paltusotine group. The SS will be the primary analysis set used for safety analyses.

<u>Analysis Sets for Open-Label Extension</u>

- The OLE SS will include all subjects who received any amount of paltusotine in the OLE.

## 9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to the interim analysis (if undertaken), and it will include a more technical and detailed description of the statistical analyses described in this section. The SAP will also provide additional information about procedures for accounting for missing, unused, data, and will explain how to record and report any deviation from the original statistical plan. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

There will be 2 formal database locks of all data, 1 at the end of the EOR and the other at the end of the OLE.

### 9.4.1. General Considerations

All continuous endpoints will be summarized showing the N, mean, median, standard deviation (SD), minimum and maximum values. Discrete endpoints will be presented showing the N and percentage.

### 9.4.2. Efficacy Analyses

#### 9.4.2.1. Analyses

The primary efficacy analyses will test for superiority in IGF-1 response rates at EOR between placebo and paltusotine, at a 2-sided alpha level of 0.05, an Exact Logistic Regression with covariates of baseline IGF-1 groups (<0.86×ULN, ≥0.86×ULN) and baseline prior treatment groups lanreotide, octreotide) in the FAS. Response is defined as an IGF-1 level ≤1.0×ULN (rounded to 2 significant figures based on the average of last 2 measurements at Week 34 and Week 36 (EOR). If only one measurement is available at Weeks 34 and 36, then just this one measurement will be used to define response. Nonresponse is defined as an IGF-1 level >1.0×ULN based on the average of the last 2 measurements or with IGF-1 missing at both Week 34 and Week 36. Subjects who discontinue treatment for any reason prior to EOR, receive prohibited standard acromegaly treatment, or titrate up in dose after Week 24 will be considered non-responders. The following sensitivity analyses will be performed on the primary endpoint:

- Multiple imputations will be used to impute missing values. The same analysis will be performed as described above. Additional details defined in the SAP.
- A completers analysis will be performed to include only FAS subjects who complete a minimum of 34 weeks of treatment. The same analysis will be performed as described above.
- The primary endpoint analysis where subjects are not considered non-responders for titrating up in dose after Week 24.
- All primary endpoint analyses will be performed on the PPS in addition to the FAS which will be the primary analysis set.

Secondary endpoints in order of clinical importance along with their corresponding analyses are as follows:

- Change from baseline in IGF-1 will be analyzed using a rank analysis of covariance (ANCOVA) model including fixed effects for treatment group with the ranked IGF-1

baseline group and baseline prior treatment group included as a covariate for the FAS. The Hodges-Lehman estimate of the median treatment difference with associated 95% confidence interval (CI) will also be presented. Baseline IGF-1 will be defined as the average of the measurements taken on Day 1 of first dose of study drug and the last IGF-1 value measured just prior to this day. EOR will be defined as the average of the last 2 assessments at Week 34 and Week 36 (EOR) for subjects who complete 36 weeks of treatment. If IGF-1 values are not available for both of these visits, then only the one available IGF-1 values will be used to define EOR. If IGF-1 is missing at both of these visits, subjects discontinue treatment, receive prohibited standard acromegaly treatment, or titrate up in dose after Week 24 then they will be assigned a rank based on the reason for missing data. Subjects will be ranked as follows, ordered from worst to best:

1. Subjects who died prior to EOR where time to death is used to rank earlier deaths worse than later deaths;
2. Subjects who are missing EOR and vital status is unknown at EOR;
3. Subjects who are missing EOR because the subject physically cannot perform the test, due to physical incapacity, hospitalization, or other reason;
4. Subjects who are missing EOR, known to be alive, took a prohibited standard acromegaly treatment where time to start of the prohibited treatment is used to rank earlier worse than later;
5. Completed subject's values will be ranked from worst (largest change) to best (smallest change).

- Growth hormone maintenance of response will be analyzed for the FAS using the same methodology as the primary endpoint. Response is defined as GH <1 ng/mL at Week 34, in the subgroup of subjects with GH <1 ng/mL at baseline. Non-response is defined as GH ≥1 ng/mL or missing at Week 34. Subjects who discontinue treatment for any reason prior to EOR, take prohibited standard acromegaly treatment, or titrate up in dose after Week 24 will be considered non-responders.
- Change from baseline in Total ASD score will be analyzed for the FAS using the same methodology specified for the change from Baseline in IGF-1.

Exploratory endpoints will include nominal p-values with descriptive statistics. Continuous endpoints will be analyzed using parametric or non-parametric methods as applicable (to be defined in the SAP) and summarized with the number of non-missing observations, mean, SD, median, minimum, and maximum. Binary endpoints will be analyzed using the same methodology as specified for the primary endpoint and summarized using the number and percentage of subjects for each category. Where applicable, 95% CIs will also be calculated. Time to event endpoints will be analyzed using Kaplan-Meier methods with a Cox regression model hazard ratio to evaluate the magnitude of effect.

#### 9.4.2.2. Open-Label Extension

The endpoints and analyses for the OLE will be defined in the SAP.

#### 9.4.2.3. Multiplicity

All hypothesis testing will be performed using the gatekeeping test strategy based on a fixed sequential method. The primary and secondary efficacy analyses will have an overall 2-sided level of significance at an alpha of 0.05. The secondary endpoints will be tested in the order they are listed in Section 9.4.2.1. The hypothesis testing of secondary endpoints will be conducted only if the primary efficacy endpoint comparison is statistically significant at the pre-defined alpha level of 0.05. If this comparison is not statistically significant, then the comparison of secondary efficacy endpoints will be considered nominal, descriptive, and exploratory.

### 9.4.3. Safety Analyses

The subject incidence of TEAEs, SAEs, and TEAEs leading to discontinuation will be summarized overall by system organ class and preferred term, and similarly by dose level. TEAEs will also be summarized by those on paltusotine monotherapy and paltusotine plus adjunctive therapy.

Vital signs, clinical laboratory results (including lipid panel and thyroid hormone levels), and ECG data will be summarized descriptively. Subject level listings for all safety endpoints (including ophthalmic assessments) will be provided.

### 9.4.4. Protocol Deviations

Protocol deviations are defined as any variation from the protocol, including enrollment of a subject who did not meet all inclusion and exclusion criteria and failure to perform the assessments and procedures within the required time frame. Protocol deviations will be categorized as major or minor based on Sponsor review.

The Sponsor or designee will be responsible for producing the final protocol deviation file, in collaboration with the data monitoring group as applicable. This file will be finalized prior to database lock.

## 9.5. Interim Analysis

An interim futility analysis may be conducted for the primary analysis of the primary endpoint when 50% of subjects have completed or withdrawn from the Treatment Period of the RC phase.

If patient recruitment completes rapidly, there could arise a situation in which the results of the interim analysis cannot be made available in time to have a meaningful impact prior to study completion. This is a scenario in which the Sponsor may not perform the interim analysis. The limited conditional power calculation for potential interim assessment of futility will be evaluated by the unblinded Data Monitoring Committee (DMC). If conditional power is less than 30% then the DMC will recommend that the study stop for futility. Otherwise, the DMC will recommend that the study continue as planned. No hypothesis testing will be performed for this analysis.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 54, 56, and 312 of Title 21 of the CFR, in compliance with GCP guidelines, and per all applicable local regulatory guidelines and Directive of the European Parliament, guidelines set out in Volume 10 of the publications "The rules governing medicinal products in the European Union" and other applicable European Medicines Agency regulations.

Declaration of Helsinki and amendments can be accessed via the website of the World Medical Association at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the Clinical Study Protocol, IB, protocol amendments, ICFs, and subject information sheets.

Amendments to the Clinical Study Protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of subjects or the conduct of the study will be classified as administrative amendments and will be submitted to the IRB/IEC and Regulatory Authorities for information only. The Sponsor (or designee) will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

Should protocol deviations that affect subject safety occur, the Sponsor must be informed as soon as possible. Important protocol deviations will be included in the Clinical Study Report (CSR). Reporting of protocol deviations to IRBs/IECs will be performed in accordance with applicable Regulatory Authority mandates and IRB/IEC policies.

All subjects must meet all eligibility criteria in order to participate in the study. Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If during the course of a subject's post-enrollment participation in the trial it is discovered that the subject did not meet all eligibility criteria, the subject will be discontinued.

### 10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

For each study subject, written informed consent will be obtained prior to any protocol-related activities. An ICF must be signed and dated personally by the subject and by the Investigator and/or the study team member designated by the Investigator to conduct the informed consent procedure.

As part of this procedure, the Investigator or 1 of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study is aware of the potential risks, inconveniences, or adverse effects that may occur. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and ICH guidelines. The subject must provide free and willing consent to enroll in the study. (Note that the Sponsor does not consider persons who are housed in an institution under a court or official order capable of providing free and willing consent.) The Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC approved ICF prior to the start of the study.

### 10.1.4. Data Protection

The Sponsor, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 2016/679), its subsequent amendments and any additional national laws on Data Protection, recommendations, and guidelines as applicable.

To maintain participant privacy, data capture tools, study drug accountability records, study reports, and communications will identify participants by their unique identifier (assigned participant number) generated and assigned by the electronic data capture (EDC) system. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant will be informed both verbally and in written form (ICF) that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who may be required to give consent for their data to be used as described in the ICF, including use of their data that may require a separate consent. The participant will also be informed that his/her medical records may be examined by Clinical Quality Assurance auditors, Monitors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, the Sponsor has implemented and maintains the following measures:

- restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel and approved visitors;
- ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial;

- implementing the pseudonymisation and encryption of personal data, as appropriate;
- implementing the ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services;
- implementing network, application, and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks;
- means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident;
- logging of security events/incidents in information systems;
- implementing procedures that cover reporting, analysis, monitoring and resolution of security incidents;
- ensuring that information systems, computers and software involved in the performance of the services provided in the Study are backed up;
- a process for regularly testing, assessing and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing;
- implementing procedures to capture within a reasonable time any personal data breaches;
- implementing procedures and practices for the destruction of paper documents containing personal data;
- implementing business continuity procedures ensuring continued provision of services through operational interruption

All locations, personnel and information systems that are used to perform services for the Study will be covered. The Sponsor will ensure the technical and organizational security measures described above are regularly reviewed and updated considering any evolution of technological developments.

The Sponsor may apply additional specific statutory requirements, where applicable in national laws, and will implement the necessary security measures even if they are not expressly listed above.

In addition to the already mentioned technical and organizational measures, the Sponsor by means of internal measures and imposed standard contractual clauses to the selected contractors, service providers, vendors, or sub-contractors (collectively, “Representatives”), ensures the confidentiality of records and personal data of subjects.

With exception of activities in the scope of on-site monitoring, the name of the patient will neither be asked for, nor recorded by Sponsor. An identification number will be allocated to each patient registered in the Study. This number will identify the patient and will be included on all CRFs and corresponding material and data associated with the patient.

Monitors acting on behalf of Sponsor will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for mandatory source data verification, including ICH-GCP obligations, applicable to the conduct of the Study. Staff involved in the

performance of this task are bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

The Sponsor has implemented a functional process for reporting of any data breach occurring at Crinetics' or its Representatives' facilities and premises. Investigators must promptly report to the Sponsor's Data Protection Officer (DPO) any suspected data breaches relevant to personal study-related data the Sponsor holds about the participants. If there is a suspected breach related to data that the Sponsor holds, the Sponsor's DPO will be responsible for investigating suspected data breaches and notifying authorities, where appropriate. In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach. In addition, in case of a high-risk data breach, subjects will be informed by the Sponsor.

Investigators must promptly report to the Sponsor's DPO any participant request to know what personal study-related data the Sponsor holds about the participant.

### 10.1.5. Data Monitoring Committee

An unblinded DMC comprising independent subject matter experts will be established to evaluate the underlying disease and to assess the risk versus benefit of the interventions during the trial. The DMC will meet at intervals as specified in the DMC charter and may convene for ad hoc meetings if there are immediate safety concerns identified during the study. In the event an interim futility analysis is undertaken when 50% of subjects have completed the Treatment Period of the RC phase, the DMC will be responsible for evaluating those data.

### 10.1.6. Dissemination of Clinical Study Data

Once the study is completed and the CSR written, appropriate information will be provided for the clincialtrials.gov or clinicaltrialsregister.eu websites as required. All IRBs/IECs will receive appropriate documentation with study results.

### 10.1.7. Data Quality Assurance

The study will be conducted according to GCP (as outlined by ICH topic E6, step 5 guidelines) and in compliance with applicable local legislation including the EU CTR (EU No 536/2014). The contract research organization maintains a quality assurance system with written Standard Operating Procedures (SOPs) to ensure that clinical trials are conducted, and data are generated, documented, and reported in compliance with the Clinical Study Protocol, GCP, and applicable regulatory requirements.

The Sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the Clinical Study Protocol, SOP, GCP, and all applicable local regulatory requirements including the EU CTR (EU No 536/2014). Audits will

be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at the study sites and during data management to assure that safety and efficacy data are adequate and well documented.

Investigators/Institution will permit trial related audits, IRB/IEC review, and regulatory inspections, providing direct access to source data/documents.

Study records and source documents must be preserved for at least 25 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region or as per local requirements, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Directive 95/46/EC: Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data and in a form satisfactory to the Sponsor.

- All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Electronic CRF completion guidance will be provided to Investigators.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined in the Study Management Plan to identify systematic issues that can impact subject safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for the specified period of time after study completion as applicable per local and national regulations or institutional policies retention period require. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 10.1.8. COVID-19 Procedures

Investigators and clinical sites are expected to follow their country, local, and site requirements and guidance with respect to COVID-19 monitoring and detection procedures. Only approved and/or registered diagnostic tests (per local country requirements) should be used for the detection of COVID-19.

The following preventive and protective safety measures will be in effect until local governments lift COVID-19 pandemic restrictions and subjects, monitors, and research staff can safely complete study procedures according to the protocol:

- Site staff to inform study subjects of changes to the study conduct prior to implementation and obtain written consent prior to implementation. In regions where permitted, verbal consent approved for use and in such cases, the consent process and patient consent must be documented in the study records, including follow-up written consent.
- In-clinic visits may be missed for COVID-19 related reasons at the discretion of the Investigator. Missed visits/procedures will be classified as protocol deviations due to COVID-19 and will be documented. The impact of deviations will be discussed in the final CSR. Subjects will not be discontinued from the study due to missed visits or procedures as a result of COVID-19. In order to minimize missed visits, home health care nursing may be used if available per country regulations. Note that not all countries allow home visits. In such countries, all visits must take place at the clinic site.
- Site staff to contact each subject by phone at least once monthly, in place of projected in-clinic study visits, to assess their status, safety and compliance. These phone calls will be captured as Unscheduled Visits due to COVID-19.
- Study subjects will be supplied with an adequate supply of study drug to guarantee continuous treatment. If COVID-19 related inability to conduct visits at sites, all subjects will be re-supplied with an additional supply of study drug, to allow continued treatment. If local regulations allow, study drug will be shipped directly to a subject's home. Detailed instructions will be provided in the Guideline to Investigators for IMP Shipment from Site to Subject's Home. In such cases, subjects must first provide informed consent (verbal or written as permitted/required by regional requirements) to share their personal contact information (e.g., name, address, and phone number) with the courier service. This consent will be documented as described above.
- On-site Monitoring Visits by study monitors will be cancelled until it is safe for monitors to return to the study site and resume their regular monitoring activities, including complete drug accountability. If necessary (e.g., for SAEs) and permitted by country regulations, review of data will be performed remotely with consideration made to minimize site staff burden. All country and local laws, regulations, and guidance must be followed with respect to handling and processes of remote source data.

### 10.1.9. Source Documents

The study will be monitored to ensure that it is conducted and documented properly according to the Clinical Study Protocol, GCP, and all applicable regulatory requirements.

Before the study begins at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and the eCRF with the Investigators and their staff.

During the study, on-site monitoring visits will be made at appropriate times. Site monitors will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRF, the adherence to the Clinical Study Protocol and to GCP, the progress of enrollment, the completeness of the IRB records and the Investigator Site File, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the site monitor during these visits.

The Investigator must give the site monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables will be checked. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

### 10.1.10. Publication Policy

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this Clinical Study Protocol, subject to the terms of any such agreement. To facilitate such ownership, Investigators will be required to assign all such inventions directly to the Sponsor as will be set forth in the clinical study agreement.

## 10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in below will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

### Table 5: Protocol-Required Safety Laboratory Tests

| Laboratory Tests | Parameters | | | |
|---|---|---|---|---|
| Hematology | Hemoglobin<br>Hematocrit<br>RBC count<br>Platelet count | RBC Indices:<br>Mean corpuscular volume<br>Mean corpuscular hemoglobin<br>Mean corpuscular hemoglobin concentration | WBC count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical Chemistry | Total protein | Sodium | Phosphate | Aspartate aminotransferase |
| | Blood urea nitrogen | Potassium | Magnesium | Alkaline phosphatase |
| | Creatinine | Chloride | Albumin | Amylase |
| | Uric acid | Calcium | Total, direct, and indirect bilirubin | Lipase |
| | Fasting lipid panel: total cholesterol, LDL, HDL, and triglycerides | | Alanine aminotransferase | Glucose |
| Thyroid Hormones and HbA1c | Free T4, and TSH | | HbA1c | |
| IGF-1 and GH | IGF-1 and growth hormone* | | | |
| Pregnancy testing | Serum and urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) | | | |
| Routine Urinalysis | Specific gravity and appearance<br>White blood cells, protein, bilirubin, nitrites, ketones, blood, and pH, by dipstick | | | |
| Other Screening Tests | Serology (HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody) | | | |

Notes:
Investigators must document their review of each laboratory safety report.
*Fasting integrated GH consists of 5 samples collected at least 30 minutes apart over 3 hours. Integrated GH should be measured after at least a 4-hour fast and the subjects should remain fasting during the 3 hours of GH sampling. The integrated GH sampling at Week 34 should be started approximately 1-2 hours after study drug dose.
Fasting blood samples (unless otherwise indicated) should be collected after an overnight fast of at least 6 hours.
Subjects receiving pegvisomant as an adjunctive medication during the OLE portion of the study will not have growth hormone results analyzed while receiving this agent.
GH=growth hormone; HDL=high-density lipoprotein; HIV=human immunodeficiency virus, IGF-1=insulin-like growth factor-1; LDL=low-density lipoprotein OLE=open-label extension; RBC=red blood cell; TSH=thyroid-stimulating hormone; WBC=white blood cell

# 10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## 10.3.1. Definition of AE

**AE Definition**

- An AE is any untoward medical occurrence in a clinical study subject, temporally associated with study participation, whether or not considered related to the study intervention.
- NOTE: A TEAE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated in either intensity or frequency) that is temporally associated with the use of study drug.

**Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- New conditions initially detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction between a concomitant medication and study drug.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose in the absence of clinical sequelae will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

**Events <u>NOT</u> Meeting the AE Definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe or increased in frequency than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

**A SAE is defined as any serious event that, at any dose:**

**a. Results in death**

**b. Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Significant Medical Event:**

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

### 10.3.3. Recording and Follow-Up of AE and/or SAE

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/ SAE information in the eCRF and on appropriate forms for the reporting of SAEs.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the pharmacovigilance unit in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the pharmacovigilance unit. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Any SAE occurring after the ICF has been signed and up until 4 weeks after the last dose must be reported on SAE reporting form (see Section 10.3.4).

**Assessment of Intensity**

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe.

**Assessment of Causality**

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship using the following descriptors: not related, unlikely related, possibly related, probably related, and definitely related.

**NOT RELATED:** This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

**UNLIKELY:** This category applies to those AEs that are judged to be unrelated to the IMP, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to the IMP if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the IMP; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the IMP; or (4) it does not reappear or worsen when the IMP is re-administered.

**POSSIBLY:** This category applies to those AEs for which a connection with the IMP administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of IMP; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the IMP.

**PROBABLY:** This category applies to those AEs that the investigator feels with a high degree of certainty are related to the IMP. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IMP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the IMP, yet drug-relatedness clearly exists (e.g., as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the IMP.

**DEFINITELY:** This category applies to those AEs that the investigator feels are incontrovertibly related to the IMP. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IMP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to the IMP (if re-challenge occurs); and (4) it follows a known pattern of response to the IMP.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE has occurred, and the Investigator has minimal information to include in the initial report to the pharmacovigilance unit. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the pharmacovigilance unit.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements. Possibly, probably, or definitely related will be recorded as related for regulatory reporting purposes.

**Follow-up of AEs and SAEs**

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the pharmacovigilance unit to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.

- Adverse event outcomes will be recorded as 1 of the following: Recovered/Resolved, Recovering/Resolving, Not Recovered/Not Resolved/Ongoing, Recovered/Resolved with sequelae, Fatal, Unknown.

| |
|---|
| **Recovered/Resolved** - One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated. The subject recovered from the AE. Record the AE stop date. |
| **Recovering/Resolving** - One of the possible results of an adverse event outcome that indicates that the event is improving. No AE stop date should be recorded. |
| **Not recovered/Not resolved/Ongoing** - One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated. No AE stop date should be recorded. |
| **Recovered/Resolved with sequelae** - One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE stop date. The AE stop date will represent the date the AE stabilized with no change in event outcome anticipated. |
| **Fatal** - The AE directly caused death. Record the date of death as the AE stop date. |
| **Unknown** - There is an inability to access the subject or the subject's records to determine the outcome (i.e., subject withdraws consent or is lost to follow-up). No AE stop date should be recorded. |

- The Investigator will submit any updated SAE data to the pharmacovigilance unit within 24 hours of receipt of the information.

### 10.3.4. Reporting of SAEs

**SAE Reporting to the pharmacovigilance unit via SAE Reporting Form**

- The primary mechanism for reporting a SAE to the pharmacovigilance unit will be an SAE reporting form. Any such SAE due to any cause, whether or not related to the study drug, must be reported on the SAE reporting form immediately (and under no circumstances should this exceed 24 hours) of occurrence or when the Investigator becomes aware of the event.

The SAE reporting form should be sent within 24 hours of knowledge of the event to: [redacted]

- If a site receives updated data on a previously reported SAE, then the site must report this follow-up information on the SAE reporting form and send to the pharmacovigilance group via [redacted]

## 10.4. Appendix 4: Abbreviations

| Abbreviation | Definition |
|---|---|
| [redacted] | |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| ASD | Acromegaly Symptoms Diary |
| AST | Aspartate aminotransferase |
| AuxMP | auxiliary medicinal product |
| BCRP | breast cancer resistance protein |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CSR | Clinical Study Report |
| CTIS | Clinical Trials Information System |
| CTR | Clinical Trials Regulation |
| CYP | Cytochrome |
| DPO | Data Protection Officer |
| DMC | Data Monitoring Committee |
| DT | Dose titration |
| DUN | Dispensing unit number |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | electronic data capture |
| EOR | End of the Randomized Control Phase |
| EOS | End of study |
| EOT | End of treatment |
| [redacted] | |
| ET | Early termination |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| GH | Growth hormone |
| HbA1c | Hemoglobin A1c |

| Abbreviation | Definition |
|---|---|
| HDL | High-density lipoprotein |
| HIV | Human immunodeficiency virus |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonization |
| IEC | Independent Ethics Committee |
| IGF-1 | Insulin-like growth factor-1 |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| IWRS | Interactive web response system |
| LAR | Long-acting release |
| LDL | Low-density lipoprotein |
| MRI | Magnetic resonance imaging |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Disease |
| OLE | Open-label extension |
| [redacted] | |
| [redacted] | |
| P-gp | P-glycoprotein |
| PK | Pharmacokinetic |
| PPS | Per Protocol Set |
| QD | Once daily |
| QTc | Corrected QT interval |
| QTcF | QT interval corrected using Fridericia's formula |
| QTL | Quality tolerance limits |
| RBC | Red blood cell |
| RC Phase | Randomized, controlled phase |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SA-SSA | Short-acting somatostatin analog |
| SD | Standard deviation |
| SOAs | Schedules of Activities |
| SOP | Standard Operating Procedure |
| SRL | Somatostatin receptor ligand |

| Abbreviation | Definition |
|---|---|
| SS | Safety Set |
| SST2 | Somatostatin receptor 2 |
| SUSAR | Suspected unexpected serious adverse reactions |
| TB | Total bilirubin |
| TEAE | Treatment-emergent adverse event |
| TSH | Thyroid-stimulating hormone |
| [redacted] | [redacted] |
| ULN | Upper limit of normal |
| W | Week |
| WBC | White blood cell |

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