Official Title: A Randomized, Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Nonpharmacologically Treated Acromegaly

NCT Number: NCT05192382

Document Date: Clinical Study Protocol Version 5.0 20 December 2024

Protocol Title:

A RANDOMIZED, CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PALTUSOTINE IN SUBJECTS WITH NON-PHARMACOLOGICALLY TREATED ACROMEGALY

Study Name: PATHFNDR-2: **P**altusotine **A**cromegaly **T**herapy **F**eaturing a **N**on-Invasive **D**aily **R**egimen

Protocol Number: CRN00808-08

Compound: Paltusotine

Study Phase: 3

Sponsor Name: Crinetics Pharmaceuticals, Inc.

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

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Version 5.0 - Approval Date: 20 December 2024

DOCUMENT HISTORY

Document	Date
Version 5.0	20 December 2024
Version 4.0	22 November 2023
Version 3.0	08 July 2022
Version 2.0	26 September 2021
Original Protocol (Version 1.0)	05 May 2021

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

Protocol Number: CRN00808-08

A Randomized, Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Non-pharmacologically Treated Acromegaly

Protocol Version: 5.0

Protocol Date: 20 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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CRN00808-08 SUMMARY OF CHANGES

Version 4.0 to Version 5.0

This Summary of Changes includes changes made from Version 4.0 to Version 5.0.

Underlined text in the table denotes added text; ~~strikethrough~~ denotes deleted text.

The primary reasons for this protocol amendment are as follows:

- Harmonize this version of the protocol with the EU Clinical Trials Regulation (CTR) (EU No 536/2014).
- Update Benefit-Risk Assessment section with side effects identified as adverse drug reactions (ADRs) and associated mitigation strategy in accordance with the paltusotine Investigator's Brochure (IB) Ed 9.0.
- Administrative updates to document information.

Section(s)	Description of Change	Change Rationale
Throughout protocol	Corrected typographical, grammar, spelling, formatting, and definitions of abbreviations at first use Updated administrative information (eg, document version and dates, company address, signatory), tables of contents Updated intra-document section number references/links as needed	Clarification
Cover page	EU CT Number: 2024-511924-15-00	Updated to comply with Clinical Trial Regulation EU No 536/2014
Principal Investigator agreement page	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.	Updated to comply with Clinical Trial Regulation EU No 536/2014
Responsible Medical Officer	**Responsible Medical Officer:** [redacted]	Updated study information
Sponsor's Medical Contact	**Sponsor's ~~Authorized Officer~~Medical Contact:** [redacted]	Updated study information
Site and Principal Investigator acknowledgment page	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	Updated to comply with Clinical Trial Regulation EU No 536/2014

Section(s)	Description of Change	Change Rationale
	Regulation (CTR) (EU No 536/2014) and all applicable regulatory requirements.	
Summary of Changes, all bullets, table replace (not shown)	~~• To extend the open label extension period by 2 years.~~ ~~• Implement ophthalmic monitoring in response to a Health Authority request to collect additional data to facilitate evaluation of the clinical relevance of a phototoxicity study in rodents (see Investigator's Brochure).~~ • Harmonize this version of the protocol with ~~Protocol~~ the EU Clinical Trials Regulation (CTR) (EU No 536/2014).~~Clarification Letter (France) #1, dated 26 September 2022; Protocol Clarification Letter #1, dated 23 June 2023; and Protocol Clarification Letter #2, dated 02 August 2023.~~ • Update Benefit-Risk Assessment section with side effects identified as adverse drug reactions (ADRs) and associated mitigation strategy in accordance with the paltusotine Investigator's Brochure (IB) Ed 9.0. • Administrative updates to document information	Updated text for new protocol version
Synopsis, Overall Design, paragraph 3 (added last sentence)	An End of Study (EOS) Visit will occur approximately 4 weeks after the last dose of study drug.	Text clarification-aligns with 1.6 Schedule of Activities: Open-Label Extension Phase
Synopsis, End of Study, paragraph 1	An End of Study (EOS) Visit will occur, approximately 4 weeks after the last dose of study drug, at Week 228 to collect final safety data and other assessments as detailed in the SOA.	Text clarification-aligns with 1.6 Schedule of Activities: Open-Label Extension Phase

Section(s)	Description of Change	Change Rationale
Synopsis, RC Phase Rescue Criteria (Auxiliary Medicinal Products), paragraph 3 (added)	**RC Phase Rescue Criteria (Auxiliary Medicinal Products)** Octreotide LAR or lanreotide depot monotherapy are considered auxiliary medicinal products. Rescue therapy should be used according to approved marketing authorization or standard clinical practice.	Updated to comply with Clinical Trial Regulation EU No 536/2014
Synopsis, Open-Label Extension Adjunctive Treatments (Auxiliary Medicinal Products), bullet 1	**Open-Label Extension Adjunctive Treatments (Auxiliary Medicinal Products)** The adjunctive medications bromocriptine/cabergoline and pegvisomant are considered auxiliary medicinal products. Use of any adjunctive medications should be discussed with the Medical Monitor and should be used according to approved ~~labels~~marketing authorization or standard practice. Adjunct medications are not provided by the Sponsor.	Updated to comply with Clinical Trial Regulation EU No 536/2014
Table 4 Risk Assessment Table, Side effects, Summary of Data/Rationale for Risk	~~Gastrointestinal (GI) side effects (eg, diarrhea, abdominal discomfort). Additional reported adverse events (AEs) found in IB. Side effects or lack of drug efficacy could result from interactions with concomitant medications.~~ Diarrhea, abdominal pain, nausea, abdominal discomfort, bradycardia (including sinus bradycardia and bradycardia), and cholelithiasis have been identified as ADRs associated with paltusotine. Rationale: These AEs are generally mild or moderate~~. No discontinuations due~~ and did not lead to ~~AEs in Phase 2 studies~~discontinuation.	Updated to align with Paltusotine IB, Ed 9.0
Table 4 Risk Assessment Table, Side effects, Mitigation Strategy	Clinical monitoring, symptomatic measures, study drug interruption if necessary. Regular safety surveillance, including laboratory testing, physical examinations, AE monitoring, pituitary tumor, and gall bladder monitoring, and evaluations for study drug interruption and stopping rules specified per protocol.	Updated to align with Paltusotine IB, Ed 9.0
4.1.4 End of Study	An End of Study (EOS) Visit will occur approximately 4 weeks after the last dose of study drug, at Week 228 to collect final safety data and other	Text clarification-aligns with 1.6 Schedule of

Section(s)	Description of Change	Change Rationale
	assessments as detailed in the SOAs. The EOS is defined as the date of the last visit of the last subject in the study.	Activities: Open-Label Extension Phase
Added new Section: 4.1.5 Patient Input into Study Design	**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.	Updated to comply with Clinical Trial Regulation EU No 536/2014
4.3 Justification for Dose and Treatment Duration, paragraph 2 (added) paragraph 3 (added)	**4.3Justification for Dose and Treatment Duration** Treatment duration is extended up to 228 weeks (approximately 4 1/3 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 open-label extension (OLE) clinical study (CRN00808-05) show that paltusotine lowered and maintained IGF-1 and GH at levels comparable to prior injected somatostatin receptor ligands (SRLs) for up to 103 weeks. Additionally, RC Phase results from a placebo controlled pivotal study (CRN00808-09) show that paltusotine 40 or 60 mg once daily (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.	Updated to comply with Clinical Trial Regulation EU No 536/2014

Section(s)	Description of Change	Change Rationale
paragraph 4 (added)	Paltusotine was well tolerated, with no unexpected safety findings with long-term treatment.	
Added new Section: Section 4.5 Treatment After End of Trial Participation	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.	Updated to comply with Clinical Trial Regulation EU No 536/2014
6.7.3. RC Phase Rescue Procedure – Auxiliary Medicinal Products, paragraph 3 (added last sentence), paragraph 4 (added)	**6.7.3 RC Phase Rescue Procedure – Auxiliary Medicinal Products** Rescue therapy should be used according to approved marketing authorization or standard clinical practice. Long-acting octreotide or lanreotide depot monotherapy are considered auxiliary medicinal products (AxMPs).	Updated to comply with Clinical Trial Regulation EU No 536/2014
6.7.4 OLE Phase Adjunctive Treatments – Auxiliary Medicinal Products, bullet 1 paragraph 2 (added)	**6.7.4 OLE Phase Adjunctive Treatments – Auxiliary Medicinal Products** Use of any adjunctive medications should be discussed with the Medical Monitor and should be used according to approved ~~labels~~marketing authorizations or standard practice. Adjunct medications are not provided by the Sponsor. Adjunctive treatments such as cabergoline and pegvisomant are considered auxiliary medicinal products.	Updated to comply with Clinical Trial Regulation EU No 536/2014
8.4.4 Regulatory Reporting Requirements for SAEs, paragraph 3	Any such SAE due to any cause, whether or not related to the study drug, must be reported on the Crinetics SAE ~~reporting form~~Report 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 Crinetics SAE ~~reporting form~~Report Form should be sent via email.	Specify current form title

Section(s)	Description of Change	Change Rationale
8.4.5 Pregnancy	Female subjects of childbearing potential must have a negative serum pregnancy test at Screening Visit S1. 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 the RC phase, and during the 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 Crinetics Pregnancy Exposure Report Form to the Sponsor's Pharmacovigilance Group at [redacted] within 24 hours of knowledge of the pregnancy. 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 (eg, 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 ~~form~~Report Form to the Sponsor's Pharmacovigilance Group within 24 hours of knowledge of the event.	Specify current form title and include email for submission
Added new Section: Section 8.9 Collection and Storage of Biological Samples	**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).	Updated to comply with Clinical Trial Regulation EU No 536/2014

Section(s)	Description of Change	Change Rationale
	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' CTIS submission.	
10.1.4 Data Protection	~~Subjects~~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 679/2016), 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 ~~be assigned a~~identify participants by their unique identifier ~~by the Sponsor.~~(assigned participant number) generated and assigned by the electronic data capture (EDC) system. Any ~~subject~~participant records or datasets that are transferred to the Sponsor will contain the identifier only; ~~subject~~participant names or any information which would make the ~~subject~~participant identifiable will not be transferred. The ~~subject must~~participant will be informed ~~that his/her~~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 ~~subject~~participant who ~~will~~may be required to give consent for their data to be used as described in the ~~informed~~ICF, including use of their data that may require a separate consent. The ~~subject must~~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.	Updated to comply with Clinical Trial Regulation EU No 536/2014

Section(s)	Description of Change	Change Rationale
	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;	

Section(s)	Description of Change	Change Rationale
	• 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 case report forms 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	

Section(s)	Description of Change	Change Rationale
	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.	
10.1.7 Data Quality Assurance, paragraph 1 paragraph 3	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 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).	Updated to comply with Clinical Trial Regulation EU No 536/2014

Section(s)	Description of Change	Change Rationale
paragraph 6	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~~their personal data 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.	
10.3.3 Recording and Follow-Up of AE and/or SAE, bullet 6	Any SAE occurring after the ICF has been signed and up until 4 weeks after the last dose must be reported on the Crinetics SAE ~~reporting form~~Report Form (see Section 10.3.4).	Specify current form title
10.3.4 Reporting of SAEs	The primary mechanism for reporting a SAE to the pharmacovigilance unit will be via the SAE ~~reporting form~~Report Form. Any such SAE due to any cause, whether or not related to the study drug, must be reported on the Crinetics SAE ~~reporting form~~Report Form immediately (and under no circumstances should this exceed 24 hours of occurrence) or when the Investigator becomes aware of the event. The Crinetics SAE ~~reporting form~~Report Form should be sent within 24 hours of knowledge of the event to: [redacted]. ~~mailto:~~If a site receives updated data on a previously reported SAE, then the site can report the follow-up information on the Crinetics SAE ~~reporting form~~Report Form and send to the pharmacovigilance group via [redacted]	Specify current form title

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Non-pharmacologically Treated Acromegaly

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 (SRL), 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 octreotide long-acting release (LAR) and lanreotide depot are, at present, the most widely used drugs to control acromegaly.

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 (eg, 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.

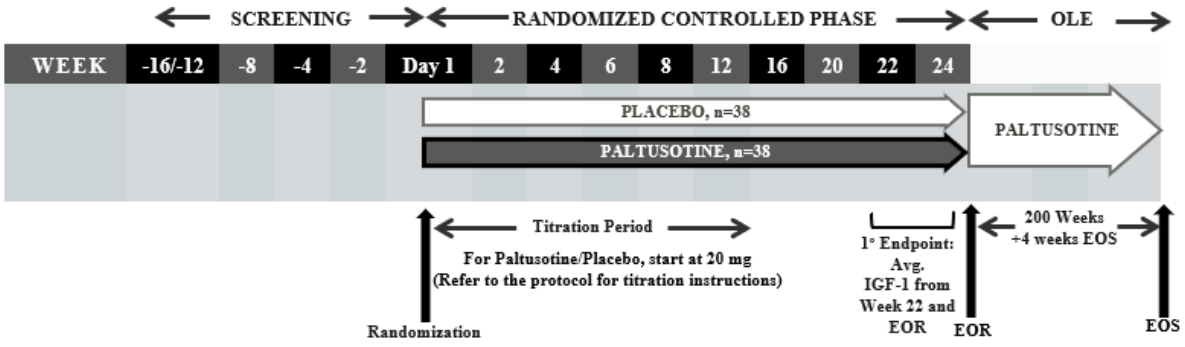
Overall Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study where subjects with nonpharmacologically treated acromegaly will be randomly allocated to receive either paltusotine or placebo. Three groups of subjects will be enrolled: (1) subjects with no prior medical therapy, (2) subjects who last received medical therapy at least 4 months prior to Screening, and (3) subjects who are controlled on medical therapy for at least 3 months but agree to washout prior to beginning study treatment. Groups 1 and 2 constitute Stratum 1 and Group 3 constitutes Stratum 2. The study population will be stratified to ensure equivalent active treatment versus placebo allocations in each stratum.

Approximately 76 subjects will be enrolled. This sample size was generated based on the assumption that there will be an equal number of subjects in each stratum. If this assumption is violated, there could be a reduction in statistical power. Therefore, when [redacted] of the projected 76 subjects (approximately [redacted]) are randomized, enrollment into the strata will be assessed. If there are less than [redacted] subjects in Group 3 (subjects who washout of octreotide or lanreotide during the screening period) at that time, the sample size may be increased (see Section 9.2).

The Screening Period for this study may be approximately 2 to 4, 8, or 12 to 16 weeks, depending on prior treatment. After the Screening Period, subjects will be enrolled in a 24-week Randomized Controlled (RC) phase and randomly assigned in a 1:1 ratio to receive paltusotine or matching placebo, stratified by prior treatment (medically naïve or previously treated versus washout). Rescue criteria are in place for those who require standard acromegaly treatment during the RC Phase. At the End of the Randomized Control Phase (EOR), subjects who, in the opinion of the Investigator, could benefit from treatment with paltusotine, may be enrolled in a long-term open-label extension (OLE) study, during which they will receive paltusotine for up to 200 weeks. An End of Study (EOS) Visit will occur approximately 4 weeks after the last dose of study drug.

Figure 1: Study Schema



EOR=End of Treatment (randomized, controlled phase), EOS=End of Study, IGF-1=insulin-like growth factor-1, OLE=open-label extension, ULN=upper limit of normal

Screening

Subjects ≥18 years of age at the time of Screening who fall into 1 of the following 3 groups are eligible to participate in the study.

- Medically naïve group (Group 1): Those who have not been previously treated with acromegaly medications (including long-acting somatostatin receptor ligands [LA-SRLs]) who at Screening have IGF-1 ≥1.3×the upper limit of normal (ULN) confirmed by the central laboratory test at S1. Group 1 subjects must have had at least 1 pituitary surgery 3 months or more prior to Screening.
- Previously Treated group (no treatment within previous 4 months) (Group 2): Subjects who have last been treated with acromegaly medications at least 4 months prior to Screening and who have IGF-1 ≥1.3×ULN confirmed by the central laboratory test at S1.
- Washout group (Group 3): Subjects at Screening who are receiving stable treatment (no change in dose for 3 months prior to Screening) with octreotide or lanreotide monotherapy, who have IGF-1 ≤1.0×ULN at Screening Visit 1 and are willing to washout of their medication during the Screening Period. Any form of pretrial octreotide or lanreotide monotherapy (long- or short-acting, subcutaneous [SC] or oral) can be washed out and will determine the duration of the Screening Period. After informed consent is provided, the subject should not receive further pretrial

acromegaly medication. IGF-1 must rise from the first Screening visit by at least 30% and be ≥1.1×ULN confirmed by the central laboratory test at S2 or S3 (if needed), to qualify for enrollment.

The Screening Period for the Medically naïve group and the Previously Treated group (no treatment within previous 4 months) should be approximately 4 weeks in duration and will consist of 1 Screening Visit (S1).

For those treated at the time of Screening with long- or short-acting octreotide or lanreotide monotherapy and who are willing to washout, initial eligibility (including IGF-1 ≤1.0×ULN) will be assessed at S1. At that time, subjects will begin washout of their pretrial acromegaly medication. Subjects taking long-acting octreotide or lanreotide will have a Screening Period of approximately 12 to 16 weeks. Subjects taking short-acting octreotide or lanreotide will have a Screening Period of approximately 8 weeks. Documentation of the washout criteria will be confirmed by the central laboratory test at S2. If a second post-washout IGF-1 measurement is needed to confirm eligibility (30% rise from the first Screening visit and IGF-1 ≥1.1× ULN) per the Investigator, the Medical Monitor should be consulted, and a sample collected at S3. S2 should be performed approximately 2 months after last pretrial LA-octreotide or lanreotide injection or approximately 4 weeks after last dose of short-acting (SC or oral) octreotide or lanreotide.

Treatment Period (Randomized, Controlled [RC] 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 The subject will be randomized to treatment on Day 1 of the Treatment Period (Figure 1).

The Treatment Period will be approximately 24 weeks. Subjects will receive their first dose of study drug at Visit 1 (Day 1) (paltusotine or placebo).

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 12, with no dose titrations/adjustments after Week 12. Up-titration after Week 12 should not occur; subjects who require dose up-titration after Week 12 will be considered nonresponders. Down-titration due to unacceptable tolerability is permitted.

If rescue therapy is required during the RC phase, subjects will discontinue paltusotine or placebo, initiate rescue therapy, and should continue the study for the remainder of the 24-week RC phase (see Section 6.7.3 for Rescue Criteria). Rescue therapy with approved SRLs (octreotide LAR or lanreotide depot monotherapy) will be permitted during the study.

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 (SOA) and the subject should return to standard acromegaly treatment as prescribed by the Investigator.

Open-Label Extension Phase

Subjects who complete the 24-week RC phase or who meet rescue criteria and complete the 24-week RC phase with rescue medication can continue participation in the OLE phase if, in the opinion of the Investigator, the subject may benefit from continued participation and treatment with paltusotine, and the subject is willing to participate. At completion of study enrollment,

subjects in the washout group that have entered screening, met initial eligibility criteria at S1, but have not completed S2 and/or S3, may be eligible to directly enroll into the OLE. The OLE Treatment Period is up to 200 weeks plus a 4-week follow-up.

End of Study

An End of Study Visit will occur, approximately 4 weeks after the last dose of study drug, at Week 228 to collect final safety data and other assessments as detailed in the SOA.

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 achieve biochemical response in IGF-1 (≤1.0× the upper limit of normal [ULN]) at the End of the Randomized Control Phase (EOR)
Key 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
Secondary	
• 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 <1 ng/mL at Week 22
• 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 22 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 time to need for rescue treatment of paltusotine versus placebo	• Time from randomization to first dose of rescue treatment
• To evaluate the effect of paltusotine versus placebo on GH response	• Proportion of subjects with GH <2.5 ng/mL at Week 22
• To evaluate the effect of paltusotine versus placebo on tumor volume	• Change from baseline in residual pituitary volume at EOR

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of paltusotine versus placebo	• Incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and TEAEs leading to discontinuation • Change in safety parameters: clinical laboratory tests (hematology, serum chemistry, lipid panel, and hormones), lipid panel, hormones, vital signs, and 12-lead electrocardiogram (ECG) • Incidence of clinically significant changes in abdominal (gallbladder) ultrasound compared with baseline
Pharmacokinetics	
• To evaluate the pharmacokinetic parameters of paltusotine in subjects with acromegaly	• Descriptive summary of concentration data from postdose sparse PK sampling

Table 2: Objectives and Endpoints for the Open-Label Extension

Objectives	Endpoints
Efficacy	
• To evaluate the long-term maintenance of efficacy of paltusotine in subjects with acromegaly	• Change from baseline in IGF-1 and GH levels • Proportion of subjects with IGF-1 ≤1.0×ULN • Proportion of subjects with IGF-1 ≤1.3×ULN • Proportion of subjects who receive permitted adjunctive standard acromegaly treatment • Change from baseline in residual pituitary tumor volume

Objectives	Endpoints
Safety	
• To evaluate the long-term safety and tolerability of paltusotine in subjects with acromegaly	• Incidence of TEAEs, including serious adverse events (SAEs) and TEAEs leading to discontinuation of study drug • Change in quantitative safety parameters: clinical laboratory tests, lipid panel, hormones, vital signs, and 12-lead ECG parameters • Ophthalmic assessments
Pharmacokinetics	
• To evaluate long-term pharmacokinetic parameters of paltusotine in subjects with acromegaly	• Descriptive summary of concentration data from postdose sparse PK sampling

Duration and Intervention Groups

Total Duration of the Study

The Screening Period for this study may be approximately 2 to 4, 8, or 12 to 16 weeks, depending on prior treatment. The RC phase will last 24 weeks for all subjects while those who choose to participate in the OLE will be treated for 200 more weeks. Because there is a 4-week follow-up after completing treatment, the duration may vary from a minimum of approximately 30 to a maximum of approximately 228 weeks.

Study Drug

Paltusotine will be provided as 20 mg tablets. Matching placebo tablets will be identical in appearance to paltusotine and will be administered 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 for subjects who experience worsening acromegaly (see Section 6.7.3 (RC Phase Rescue Procedure) and Section 6.7.4 (OLE Phase Adjunctive Treatments).

Dose Adjustment During the RC Phase

The starting daily dose will be 20 mg (1×20 mg tablet of active paltusotine or matching placebo) for oral self-administration. After confirming tolerability with the subject, the dose should be increased to 40 mg/day (2×20 mg tablet of active paltusotine or matching placebo) at the Week 2 visit.

Beginning with the Week 6 visit and prior to or at the Week 12 visit, further 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

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 12, with no dose titrations/adjustments after Week 12. Up-titration after Week 12 should not occur; subjects who require dose up-titration after Week 12 will be considered nonresponders. Down-titration due to unacceptable tolerability is permitted. If needed, an unscheduled dose titration (DT) 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 patients who are taking P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) inhibitors (see Section 6.7.1).

Protocol specified dose adjustments are summarized in the following table:

Table 3: Dose Titration Options

Dose Titration/Adjustment	IGF-1 Criteria	Tolerability Criteria
20 mg→40 mg	--	Increase required at Week 2 visit if acceptable tolerability on 20 mg
40 mg→60 mg	Week 4 IGF-1 >0.9×ULN or at any time prior to or at the Week 12 visit	Acceptable tolerability on 40 mg
60 mg→40 mg	--	Dose reduction required due to unacceptable tolerability on 60 mg
40 mg→20 mg	--	Dose reduction required due to unacceptable tolerability on 40 mg

If the Investigator determines that a dose titration/adjustment after Week 12 is required, the Investigator should contact the Medical Monitor to ensure that a consistent approach to dose titration/adjustment is applied across the study.

RC Phase Rescue Criteria (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 (eg, significant intervention needed to avert hospitalization or clinically notable increase in frequency or intensity of subject contact required) or substantial clinical deterioration (eg worsening from a mild to severe adverse event (AE) or the onset of an SAE would meet these criteria).

AND

- IGF-1 value ≥1.5×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).

*In a large study of naïve acromegaly patients, octreotide LAR monotherapy achieved mean IGF-1 of 1.5×ULN (Colao 2014) at 3 months of treatment through 12 months.

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 24-week RC phase (see Section 6.7.3 for Rescue Criteria). Only rescue therapy with approved SRLs (octreotide LAR or lanreotide depot monotherapy) will be permitted during the study.

Octreotide LAR or lanreotide depot monotherapy are considered auxiliary medicinal products. Rescue therapy should be used according to approved marketing authorization or standard clinical practice.

Investigators should contact the Medical Monitor about any subject who does not meet the criteria for rescue, but for whom the Investigator recommends discontinuation of study drug and initiation of standard acromegaly medication, in order to discuss the possibility of continuation in the RC phase on standard acromegaly medication, and eligibility for OLE on a case-by-case basis. These situations may include the following: (1) there is worsening of acromegaly symptoms with no improvement from baseline in IGF-1 levels, however IGF-1 is <1.5×ULN; or (2) IGF-1 levels are ≥1.5×ULN without sufficiently worsening acromegaly symptoms.

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 20 mg (1×20 mg tablet), dispensed in an open-label manner; ie, subjects will be given a bottle of paltusotine containing [redacted] tablets and instructed to take 1 tablet per day and then if tolerated, to increase to 40 mg once daily (QD) (2×20 mg tablets) at the Week 26 visit.

Further up-titration 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 QD (3×20 mg tablets). Down-titration due to unacceptable tolerability is permitted.

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 48. If these criteria are met, non-SRL acromegaly treatments, such as cabergoline or GH receptor antagonist (ie, 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. If adjunctive medications are not appropriate or not accessible under local regulations, and the subject is not under acceptable biochemical control while treated with paltusotine monotherapy at the maximal tolerated dose in the opinion of the Investigator, the subject should be discontinued from the OLE portion of the study.

- The adjunctive medications bromocriptine/cabergoline and pegvisomant are considered auxiliary medicinal products (AxMP). 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, 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 cabergoline. If so, the pegvisomant may be added to the paltusotine + cabergoline combination. If there was no evidence of a therapeutic response to combined paltusotine +cabergoline, 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).

Number of Subjects

The primary endpoint assumes the overall rate of response at EOR, defined as IGF-1 ≤1.0×ULN, for paltusotine versus placebo is [redacted] and [redacted], respectively. The study population will be stratified to ensure equivalent active treatment versus placebo allocations in each stratum. Groups 1 and 2 constitute Stratum 1 and Group 3 constitutes Stratum 2. The number of subjects in each stratum is expected to be equally allocated (Melmed, 2010). The responder rates in Stratum 1 are expected to be [redacted] in paltusotine treated subjects and [redacted] in placebo treated subjects. The responder rates in Stratum 2 are expected to be 70% in paltusotine treated subjects and 20% in placebo treated subjects. Through simulations, power was estimated for the comparison of paltusotine versus placebo using an Exact Logistic Regression with strata as a covariate in the model and a 2-sided alpha of 0.05. Power of [redacted] was achieved with 76 subjects (38 per group) which accounts for a [redacted] drop-out rate (treating them as nonresponders).

This sample size was generated based on the assumption that there will be an equal number of subjects in each stratum and a [redacted] drop put rate. If these assumptions are violated, there could be a reduction in statistical power. Therefore, when [redacted] of the projected 76 subjects (approximately 57) are randomized, enrollment into the strata will be assessed. If there are less than [redacted] subjects in Group 3 (subjects who washout of octreotide or lanreotide during the screening period), the sample size may be increased (see Section 9.2).

A sample size of 54 subjects will provide [redacted] power to detect a difference in the key secondary endpoint of change from baseline to EOR in IGF-1 using Wilcoxon rank-sum test under the following assumptions: a difference of [redacted] in the mean change from baseline to EOR in IGF-1 in units of ULN between placebo and paltusotine, a common standard deviation (SD) of [redacted], a 2-tailed alpha of 0.05, and a [redacted] drop-out rate. With 76 subjects enrolled, the power increases to [redacted].

Statistical Methods

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, using an Exact Logistic Regression with a covariate for prior treatment (medically naïve or previously treated versus washout) in the Full Analysis Set (FAS).

The key secondary endpoint of change from baseline in IGF-1 will be analyzed using a worst rank score analysis of covariance (ANCOVA) model including fixed effects for treatment group with prior treatment (medically naïve or previously treated versus washout) as a covariate for the FAS. All other secondary endpoints will be analyzed for the FAS using the same methodology as the primary endpoint.

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. An optional interim analysis may be performed using conditional power to assess futility and for a sample size re-estimation. Further details are in the DMC charter and statistical analysis plan.

1.2. Schedule of Activities: Screening Period for Medically Naïve or Previously Treated Groups (No treatment within previous 4 months)

STUDY PROCEDURES	SCREENING PERIOD	REFs
DAY/WEEK	Week -4 to Day -1 [a] S1	
WINDOW (DAYS)	-	-
Visit to be in-clinic	**X**	-
Visit to be in-clinic or subject's home/suitable alternate location	-	-
Obtain informed consent	X	Section 10.1.3
Register subject in IWRS	X	Section 6.3
Verify eligibility Send Medical Monitor Eligibility Verification Form no later than D1	X	Section 5.1 Section 5.2
Health history, demographics, baseline characteristics	X	Section 8.1
Pretrial acromegaly symptoms	X	Section 8.1
Full physical exam, weight, ring size (height at screening only)	X	Section 8.3.1
Vital signs	X	Section 8.3.2
12-lead ECG (triplicate)	X	Section 8.3.3
Biliary/gallbladder ultrasound Ultrasound may be done at any Screening visit, but results MUST be available to determine eligibility	X	Section 8.3.5
Pituitary MRI MRI may be done at any Screening visit, but results MUST be available to determine eligibility	X	Section 8.3.6
AE monitoring	X	Section 8.4 Appendix 3
Prior & concomitant therapies	X	Section 6.7
Pregnancy test	X	Section 8.4.5 Appendix 2
Clinical laboratory tests (hematology, chemistry, urinalysis)	X	Section 8.3.4 Appendix 2
HbA1c	X	Section 8.3.4 Appendix 2

STUDY PROCEDURES	SCREENING PERIOD	REFs
DAY/WEEK	Week -4 to Day -1 [a] S1	
WINDOW (DAYS)	-	-
Visit to be in-clinic	**X**	-
Visit to be in-clinic or subject's home/suitable alternate location	-	-
Serology (HIV, Hepatitis B and Hepatitis C)	X	Section 8.3.4 Appendix 2
TSH and Free T4	X	Section 8.3.4 Appendix 2
Screening IGF-1	X [b]	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
ASD ASD should be completed by the subject daily at home beginning approximately 2 weeks prior to study drug dosing for the duration of the RC phase	X	Section 8.2.1
[redacted]	X	Section 8.2.4

Notes:

To the extent practical, conduct all study assessments at the same time of day, unless otherwise specified.

MRI and/or ultrasound do not need to be performed on the same day as the screening visit.

[a.] The Screening Period should be approximately 4 weeks in duration, and the S1 visit is to be at least 14 days prior to Day 1 to allow for IGF-1 test results to be obtained.

[b.] The IGF 1 must be ≥1.3× ULN.

Fasting integrated GH consists of 5 samples collected at least 30 minutes apart during a collection period of up to 3 hours. Integrated GH should be measured after at least a 4-hour fast and the subjects should remain fasting during the GH sampling.

AE=adverse event, ASD=Acromegaly Symptoms Diary, D=Day, ECG=electrocardiogram, 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, [redacted], RC=randomized controlled phase, REFs=references, S=Screening, TSH=thyroid-stimulating hormone

1.3. Schedule of Activities: Screening Period for Subjects Washing out of Short-acting Octreotide or Lanreotide (SC or oral)

STUDY PROCEDURES	SCREENING PERIOD			REFs
DAY/WEEK	Week -8 S1	Week -4 S2	Week -2 S3	
WINDOW (DAYS)	**-**	**±2**	**±2**	**-**
Visit to be in-clinic	**X**	**-**	**-**	**-**
Visit to be in-clinic or subject's home/suitable alternate location	**-**	**X**	**X**	**-**
Obtain informed consent	X	-	-	Section 10.1.3
Register subject in IWRS	X	-	-	Section 6.3
Verify eligibility Send Medical Monitor Eligibility Verification Form no later than D1	X	X	X	Section 5.1 Section 5.2
Demographics and Baseline Characteristics				
Health history, demographics, baseline characteristics	X	-	-	Section 8.1
Pretrial acromegaly symptoms	X	-	-	Section 8.1
Safety Assessments				
Full physical exam, weight, ring size (height at screening only)	X	-	-	Section 8.3.1
Vital signs	X	-	-	Section 8.3.2
12-lead ECG (triplicate)	X	-	-	Section 8.3.3
Biliary/gallbladder ultrasound Ultrasound may be done at any Screening visit, but results MUST be available to determine eligibility	X	-	-	Section 8.3.5
Pituitary MRI MRI may be done at any Screening visit, but results MUST be available to determine eligibility	X	-	-	Section 8.3.6
AE monitoring	X	X	X	Section 8.4 Appendix 3
Prior & concomitant therapies	X	X	X	Section 6.7
Laboratory Tests				
Pregnancy test	X	X	-	Section 8.4.5 Appendix 2
Clinical laboratory tests (hematology, chemistry, urinalysis)	X	-	-	Section 8.3.4 Appendix 2

STUDY PROCEDURES	SCREENING PERIOD			REFs
DAY/WEEK	Week -8 S1	Week -4 S2	Week -2 S3	
WINDOW (DAYS)	**-**	**±2**	**±2**	**-**
Visit to be in-clinic	**X**	**-**	**-**	**-**
Visit to be in-clinic or subject's home/suitable alternate location	**-**	**X**	**X**	**-**
HbA1c	X	-	-	Section 8.3.4 Appendix 2
Serology (HIV, Hepatitis B and Hepatitis C)	X	-	-	Section 8.3.4 Appendix 2
TSH and Free T4	X	-	-	Section 8.3.4 Appendix 2
Screening IGF-1	X [a]	X [a]	X [a]	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
Subject-reported Assessments				
ASD ASD should be completed by the subject daily at home beginning approximately 2 weeks prior to study drug dosing for the duration of the RC phase	-	X	-	Section 8.2.1
[redacted]	X	X	-	Section 8.2.4

Notes:

Week -2 Visit (S3) is optional.

To the extent practical, conduct all study assessments at the same time of day, unless otherwise specified.

MRI and/or ultrasound do not need to be performed on the same day as the screening visit.

[a.] IGF-1 value at S1 will be used to determine if the subject is controlled on short-acting octreotide or lanreotide. If the subject is not controlled, the subject will be considered a screen failure. The IGF-1 value at S2 will be used to determine post-washout eligibility (IGF-1 ≥1.1× ULN and 30% rise from S1). If a second post-washout IGF-1 measurement is needed to confirm eligibility (IGF-1 ≥1.1× ULN and 30% rise from S1) per the investigator, the Medical Monitor should be consulted, and a sample collected at S3 (Week -2).

Fasting integrated GH consists of 5 samples collected at least 30 minutes apart during a collection period of up to 3 hours. Integrated GH should be measured after at least a 4-hour fast and the subjects should remain fasting during the GH sampling.

The date and dose level of the most recent short-acting octreotide or lanreotide prior to consent will be recorded as prior medication.

AE=adverse event, ASD=Acromegaly Symptoms Diary, D=day, ECG=electrocardiogram, 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, [redacted] RC=randomized controlled phase, REFs=references, S=Screening, TSH=thyroid-stimulating hormone, ULN=upper limit of normal

1.4. Schedule of Activities: Screening Period for Subjects Washing out of Long-acting Octreotide or Lanreotide

STUDY PROCEDURES DAY/WEEK	SCREENING PERIOD Week -16 to Week -12 S1	 Week -8 to Week -4 S2	 Week -2 S3	REFs
WINDOW (DAYS)	**-**	**-**	**±2**	**-**
Visit to be in-clinic	**X**	**-**	**-**	**-**
Visit to be in-clinic or subject's home/suitable alternate location	**-**	**X**	**X**	**-**
Obtain informed consent	X	-	-	Section 10.1.3
Register subject in IWRS	X	-	-	Section 6.3
Verify eligibility Send Medical Monitor Eligibility Verification Form no later than D1	X	X	X	Section 5.1 Section 5.2
Demographics and Baseline Characteristics				
Health history, demographics, baseline characteristics	X	-	-	Section 8.1
Pretrial acromegaly symptoms	X	-	-	Section 8.1
Safety Assessments				
Full physical exam, weight, ring size (height at screening only)	X	-	-	Section 8.3.1
Vital signs	X	-	-	Section 8.3.2
12-lead ECG (triplicate)	X	-	-	Section 8.3.3
Biliary/gallbladder ultrasound Ultrasound may be done at any Screening visit, but results MUST be available to determine eligibility	X	-	-	Section 8.3.5
Pituitary MRI MRI may be done at any Screening visit, but results MUST be available to determine eligibility An MRI must be done at the end of the washout period.	-	X	-	Section 8.3.6
AE monitoring	X	X	X	Section 8.4 Appendix 3
Prior & concomitant therapies	X	X	X	Section 6.7
Laboratory Tests				
Pregnancy test	X	X	-	Section 8.4.5 Appendix 2

STUDY PROCEDURES DAY/WEEK	SCREENING PERIOD Week -16 to Week -12 S1	 Week -8 to Week -4 S2	 Week -2 S3	REFs
WINDOW (DAYS)	**-**	**-**	**±2**	**-**
Visit to be in-clinic	**X**	**-**	**-**	**-**
Visit to be in-clinic or subject's home/suitable alternate location	**-**	**X**	**X**	**-**
Clinical laboratory tests (hematology, chemistry, urinalysis)	X	-	-	Section 8.3.4 Appendix 2
HbA1c	X	-	-	Section 8.3.4 Appendix 2
Serology (HIV, Hepatitis B and Hepatitis C)	X	-	-	Section 8.3.4 Appendix 2
TSH and Free T4	X	-	-	Section 8.3.4 Appendix 2
Screening IGF-1	X [a]	X [a]	X [a]	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
Subject-reported Assessments				
ASD ASD should be completed by the subject daily at home beginning approximately 2 weeks prior to study drug dosing for the duration of the RC phase	-	X	-	Section 8.2.1
[redacted]	X	X	-	Section 8.2.4

Notes:

Week -2 Visit (S3) is optional.

To the extent practical, conduct all study assessments at the same time of day, unless otherwise specified.

MRI and/or ultrasound do not need to be performed on the same day as the screening visit.

[a.] IGF-1 value at S1 will be used to determine if the subject is controlled on long-acting octreotide or lanreotide. If the subject is not controlled, the subject will be considered a screen failure. The IGF-1 value at S2 will be used to determine post-washout eligibility (IGF-1 ≥1.1× ULN and 30% rise from S1). If a second post-washout IGF-1 measurement is needed to confirm eligibility (IGF 1 ≥1.1× ULN and 30% rise from S1) per the investigator, the Medical Monitor should be consulted, and a sample collected at S3 (Week 2).

Fasting integrated GH consists of 5 samples collected at least 30 minutes apart during a collection period of up to 3 hours. Integrated GH should be measured after at least a 4-hour fast and the subjects should remain fasting during the GH sampling.

The date and dose level of the most recent octreotide or lanreotide prior to consent will be recorded as prior medication.

AE=adverse event, ASD=Acromegaly Symptoms Diary, D=Day, ECG=electrocardiogram, 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, [redacted] REFs=references, S=Sreening, TSH=thyroid-stimulating hormone, ULN=upper limit of normal

1.5. Schedule of Activities: Randomized, Controlled Phase

STUDY PROCEDURES	TREATMENT PERIOD (24 WEEKS)												F/U	
		TITRATION PERIOD				STABLE DOSE				W24				
DAY/WEEK	D1	W2 [a]	W4	W6	W8	W12	W16	W20	W22	EOR	ET	DT [b]	W28	REFS
WINDOW (DAYS)	-	±2	±2	±2	±2	±4	±4	±4	±4	±3	-		±3	-
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	-	-	-	-	-	-
Verify eligibility Send Medical Monitor Eligibility Verification Form no later than D1	X	-	-	-	-	-	-	-	-	-	-	-	-	Section 5.1 Section 5.2
Randomization	X	-	-	-	-	-	-	-	-	-	-	-	-	Section 6.3
Safety Assessments														
Full physical exam, weight, ring size (height at screening only)	X	-	-	-	-	X	-	-	-	X	X	-	-	Section 8.3.1
Symptom-directed physical exam	-	-	X	-	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	Section 8.3.3
Biliary/gallbladder ultrasound	-	-	-	-	-	-	-	-	-	X	X	-	-	Section 8.3.5
Pituitary MRI	-	-	-	-	-	-	-	-	-	X	X	-	-	Section 8.3.6
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4 Appendix 3
Prior & concomitant therapies	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	Section 8.3.4 Appendix 2
Clinical laboratory tests (hematology, chemistry, urinalysis)	X	-	X	-	X	X	-	X	-	X	X	-	X	Section 8.3.4 Appendix 2
HbA1c	X	-	-	-	-	X	-	-	-	X	X	-	-	Section 8.3.4 Appendix 2
Lipid panel (fasting)	X	-	-	-	-	-	-	-	-	X	X	-	-	Section 8.3.4 Appendix 2
TSH and Free T4	X	-	-		-	-	-	-	-	X	X	-	-	Section 8.3.4 Appendix 2
Genotype blood sample (optional)	X [c]	-	-	-	-	-	-	-	-	-	-	-	-	Section 8.6

STUDY PROCEDURES	TREATMENT PERIOD (24 WEEKS)										ET	DT [b]	F/U	REFS
		TITRATION PERIOD				STABLE DOSE				W24				
DAY/WEEK	D1	W2 [a]	W4	W6	W8	W12	W16	W20	W22	EOR			W28	
WINDOW (DAYS)	-	±2	±2	±2	±2	±4	±4	±4	±4	±3	-		±3	-
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	-	-	-	-	-	-
PK (any time)	-	-	-	-	-	-	-	-	-	X	X	-	-	Section 8.5
Fasting Integrated GH 5 samples collected at least 30 minutes apart within a 3-hour period. At W22, collection should be started approximately 1-2 hours after study drug dose	-	-	-	-	-	-	-	-	X	-	X	-	-	Section 8.3.4 Appendix 2
Predose fasting IGF-1 (W24 can be done any time)	X	X	X	X	X	X	-	X	X	X	X	-	X	Section 8.3.4 Appendix 2
Predose fasting PK	-	-	-	X	-	X	-	X	X	-	-	-	-	Section 8.5
Postdose PK, GH, and IGF-1 One sample between 1 and 8 hours postdose	-	X	-	X	-	-	X	-	-	-	-	-	-	Section 8.3.4 Section 8.5 Appendix 2
Drug Administration														
Dispense study drug (via IWRS) (W24 dispensation for subjects continuing into OLE only)	X	X	X	X	X	X	X	X	-	X	-	X	-	Section 6.1
Study drug administration during the visit	X	X	-	X	-	X	-	X	X	X	-	-	-	Section 6.1
Study drug compliance	-	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	-	Section 6.4
Subject-reported Assessments														
ASD	X	X	X	X	X	X	X	X	X	X	X	-	-	Section 8.2.1
[redacted]	X	-	-	-	-	X	-	-	-	X	X	-	-	Section 8.2.2 Section 8.2.3

STUDY PROCEDURES	TREATMENT PERIOD (24 WEEKS)												F/U	
		TITRATION PERIOD				STABLE DOSE				W24	ET	DT [b]		
DAY/WEEK	D1	W2 [a]	W4	W6	W8	W12	W16	W20	W22	EOR			W28	REFS
WINDOW (DAYS)	-	±2	±2	±2	±2	±4	±4	±4	±4	±3	-		±3	-
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	-	-	-	-	-	-
[redacted]	X	X	X	X	X	X	X	X	X	X	X	-	-	Section 8.2.4
[redacted]	-	-	-	-	-	-	-	-	-	X	X	-	-	Section 8.2.4
[redacted] (excluding Medically naïve subjects)	-	-	-	-	-	-	-	-	-	X	X	-	-	Section 8.2.5

Notes:

During the Stable Dose period, down-titration due to unacceptable tolerability is permitted.

To the extent practical, conduct all study assessments at the same time of day, unless otherwise specified. MRI and/or ultrasound do not need to be performed on the same day as the study visit. The pituitary MRI and biliary/gallbladder ultrasound may be performed within ± 2 weeks of the Week 24/EOR visit.

[a.] After confirming tolerability with the subject, the dose should be increased to 40 mg/day (2×20 mg tablet of active paltusotine or matching placebo) beginning at the W2 visit

[b.] 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.

[c.] Genotype blood sample can be drawn at any post-baseline visit in China.

[d.] The [redacted] will not be administered in India due to lack of available validated translations. Fasting integrated GH consists of 5 samples collected at least 30 minutes apart during a collection period of up to 3 hours. Integrated GH should be measured after at least a 4-hour fast and the subjects should remain fasting during the GH sampling. The integrated GH sampling at Week 22 should be started approximately 1-2 hours after study drug dose.

At other indicated visits, single samples for GH will be collected.

The last dose of study drug for the RC phase will be self-administered the day prior to the Week 24/EOR visit. The first dose of the OLE phase will be administered during the Week 24/EOR visit for subjects continuing into the OLE.

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.

Unscheduled visits for octreotide/lanreotide injections may be necessary for subjects who meet criteria for rescue therapy.

Follow-up Visit is to occur approximately 4 weeks after the last dose of study drug for subjects who do not enter the OLE.

[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, IGF-1=insulin like growth factor 1, IWRS= interactive web response system, MRI=magnetic resonance imaging, OLE=open-label extension, [redacted] PK=pharmacokinetics, RC=randomized controlled phase, REFs=references, TSH=thyroid-stimulating hormone, W=Week

1.6. Schedule of Activities: Open-Label Extension Phase

STUDY PROCEDURES	INITIAL OLE PERIOD									2-YEAR EXTENSION				EOS	REFs
WEEK	EOR W24	W26 [a]	W36	W48	W60	W72	W84	W96	W108	W120/ W144 W168 W192 W216	W132/ W156 W180 W204	W224 EOT/ ET	DT [b]	W228	
WINDOW (DAYS)	±3	±4	±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	X	
Visit to be in-clinic or subject's home/suitable alternate location	-	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	-	-	-	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[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	-	-	Section 8.3.5
Pituitary MRI	X	-	-	X	-	-	-	-	-	X[d]	-	X	-	-	Section 8.3.6
Ophthalmic Assessments					X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]			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 [f]	X	-	X	X	X	X	X	X	X	X	X	X	-	X	Section 8.4.5 Appendix 2
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

STUDY PROCEDURES	INITIAL OLE PERIOD									2-YEAR EXTENSION				EOS	REFs
WEEK	EOR W24	W26 [a]	W36	W48	W60	W72	W84	W96	W108	W120/ W144 W168 W192 W216	W132/ W156 W180 W204	W224 EOT/ ET	DT [b]	W228	
WINDOW (DAYS)	±3	±4	±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	X	
Visit to be in-clinic or subject's home/suitable alternate location	-	X	-	X	-	-	-	X	-	X	-	-	-	-	
Lipid panel (fasting)	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[g]		X			Section 8.3.4 Appendix 2
Predose 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 at study site	X	-	-	-	-	-	-	-	-	-	-	-	-	-	Section 6.1
Study drug compliance	X	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
Subject-reported Assessments															
ASD and [redacted]	X	X	X	X	X	X	X	X	X	X	X	X	-	-	Section 8.2.1 Section 8.2.4
[redacted]	X	-	-	-	-	X	-	-	-	X[i]	-	X	-	-	Section 8.2.2 Section 8.2.3
[redacted]	X	-	-	-	-	-	-	-	-	X[i]	-	X	-	-	Section 8.2.4

STUDY PROCEDURES	INITIAL OLE PERIOD									2-YEAR EXTENSION				EOS	REFs
WEEK	EOR W24	W26 [a]	W36	W48	W60	W72	W84	W96	W108	W120/ W144 W168 W192 W216	W132/ W156 W180 W204	W224 EOT/ ET	DT [b]	W228	
WINDOW (DAYS)	±3	±4	±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	X	
Visit to be in-clinic or subject's home/suitable alternate location	-	X	-	X	-	-	-	X	-	X	-	-	-	-	
[redacted] (Excluding Medically naïve subjects)	X	-	-	-	-	-	-	-	-	X[i]	-		-	-	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.

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 W24/EOR visit.

[a.] After confirming tolerability with the subject, the dose should be increased to 40 mg/day (2×20 mg tablet) beginning at the W26 visit.

[b.] One or more optional visits for dose titration and/or safety monitoring (unscheduled safety assessments) may be performed at the discretion of the Investigator. In cases of poor tolerability, the Investigator may reduce dose based on his/her assessment during a telemedicine (phone, video) evaluation.

[c.] Biliary/gallbladder ultrasounds are required at Week 120 and Week 224/ET visits but may be performed at any time if clinically indicated in the opinion of the Investigator.

[d.] Pituitary MRI performed at Week 120 and Week 168 only.

[e] 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.

[f.] 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.

[g] PK sample collections at Week 120, Week 168, and Week 216 only.

[h.] The [redacted] will not be administered in India due to lack of available validated translations.

[i.] [redacted] and [redacted] at Week 120, Week 144, Week 168, and Week 192 only. [redacted] at Week 120 only.

[redacted] AE=adverse event, ASD=Acromegaly Symptoms Diary, DT=dose titration, ECG=electrocardiogram, EQ-5D-5L=EuroQol-5 [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 (SRLs), 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. SRLs octreotide long-acting release (LAR) and lanreotide depot are, at present, the most widely used drugs to control acromegaly. Other treatments for acromegaly that are not widely available and/or used as second line or adjunct therapy include pasireotide, pegvisomant, cabergoline, and an oral formulation of octreotide.

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 (eg subcutaneous [SC], 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.

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.

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).

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Table 4: 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. 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 criteria.
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, adverse events, safety laboratories, GH/IGF-1 monitoring, and protocol defined rescue criteria
Blood draws	Pain, bleeding, infection possible. Rationale: Needed for safety evaluation of study drug	Symptomatic measures

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pituitary magnetic resonance imaging (MRI) scans	Claustrophobia, dizziness, mild nausea, numbness, tingling, muscle twitches, tiny flashing lights in field of vision, or momentary imbalance after leaving the magnet. Possible use of intravenous contrast with associated risk of renal injury (in people with severe kidney disease) or hypersensitivity reaction 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. Rationale: Needed for monitoring gallbladder and biliary ducts	Symptomatic measures
Distance-corrected visual acuity testing Visual field testing	There are no known risks or complications associated with these tests	None needed
Fundus photography Optical coherence tomography of the macula	Some participants may experience some eye dryness or fatigue	Symptomatic measures

ADR=adverse drug reaction, AE=adverse event, CT=computed tomography, ECG=electrocardiogram, MRI=magnetic resonance imaging

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 adverse events (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 achieve biochemical response in IGF-1 (≤1.0× the upper limit of normal [ULN]) at the End of the Randomized Control Phase (EOR)
Key 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
Secondary	
• 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 <1 ng/mL at Week 22
• 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 22 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 time to need for rescue treatment of paltusotine versus placebo	• Time from randomization to first dose of rescue treatment
• To evaluate the effect of paltusotine versus placebo on GH response	• Proportion of subjects with GH <2.5 ng/mL at Week 22
• To evaluate the effect of paltusotine versus placebo on tumor volume	• Change from baseline in residual pituitary tumor volume at EOR

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of paltusotine versus placebo	• Incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and TEAEs leading to discontinuation • Change in safety parameters: clinical laboratory tests (hematology, serum chemistry, lipid panel, and hormones), lipid panel, hormones, vital signs, and 12-lead electrocardiogram (ECG) • Incidence of clinically significant changes in abdominal (gallbladder) ultrasound compared with baseline
Pharmacokinetics	
• To evaluate the pharmacokinetic parameters of paltusotine in subjects with acromegaly	• Descriptive summary of concentration data from postdose sparse PK sampling

3.2. Objectives and Endpoints for the Open-Label Extension

Objectives	Endpoints
Efficacy	
• To evaluate the long-term maintenance of efficacy of paltusotine in subjects with acromegaly	• Change from baseline in IGF-1 and GH levels • Proportion of subjects with IGF-1 ≤1.0×ULN • Proportion of subjects with IGF-1 ≤1.3×ULN • Proportion of subjects who receive permitted adjunctive standard acromegaly treatment • Change from baseline in residual pituitary tumor volume

Objectives	Endpoints
Safety	
• To evaluate the long-term safety and tolerability of paltusotine in subjects with acromegaly	• Incidence of TEAEs, including serious adverse events (SAEs) and TEAEs leading to discontinuation of study drug • Change in quantitative safety parameters: clinical laboratory tests, lipid panel, hormones, vital signs, and 12-lead ECG parameters • Ophthalmic assessments
Pharmacokinetics	
• To evaluate long-term pharmacokinetic parameters of paltusotine in subjects with acromegaly	• Descriptive summary of concentration data from postdose sparse PK sampling

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study where subjects with nonpharmacologically treated acromegaly will be randomly allocated to receive either paltusotine or placebo. Three groups of subjects will be enrolled: (1) subjects with no prior medical therapy, (2) subjects who last received medical therapy at least 4 months prior to Screening, and (3) subjects who are controlled on medical therapy for at least 3 months but agree to washout prior to beginning study treatment. Groups 1 and 2 constitute Stratum 1 and Group 3 constitutes Stratum 2. The study population will be stratified to ensure equivalent active treatment versus placebo allocations in each stratum.

Approximately 76 subjects will be enrolled. This sample size was generated based on the assumption that there will be an equal number of subjects in each stratum. If this assumption is violated, there could be a reduction in statistical power. Therefore, when [redacted] of the projected 76 subjects (approximately [redacted]) are randomized, enrollment into the strata will be assessed. If there are less than [redacted] subjects in Group 3 (subjects who washout of octreotide or lanreotide during the screening period) at that time, the sample size may be increased (see Section 9.2).

The Screening Period for this study may be approximately 2 to 4, 8, or 12 to 16 weeks, depending on prior treatment. After the Screening Period, subjects will be enrolled in a 24-week Randomized Controlled (RC) phase and randomly assigned in a 1:1 ratio to receive paltusotine or matching placebo stratified by prior treatment (medically naïve or previously treated versus washout). At the end of the RC phase (EOR), 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) study, during which they will receive paltusotine for up to 200 weeks.

Subjects who meet rescue criteria in the RC Phase will have treatment with paltusotine or placebo discontinued and be considered nonresponders, 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, and in the opinion of the Investigator, the subject may benefit from continued participation and treatment with paltusotine and the subject is willing to participate. See Figure 1 for the study schema.

4.1.1. Screening

Subjects ≥18 years of age at the time of Screening who fall into 1 of the following 3 groups are eligible to participate in the study.

- Medically naïve group (Group 1): Those who have not been previously treated with acromegaly medications (including long-acting somatostatin receptor ligands [LA-SRLs]) who at Screening have IGF-1 ≥1.3×ULN confirmed by the central laboratory test at S1. Group 1 subjects must have had at least 1 pituitary surgery 3 months or more prior to Screening.
- Previously Treated group (no treatment within previous 4 months) (Group 2): Subjects who have last been treated with acromegaly medications at least 4 months prior to Screening and who have IGF-1 ≥1.3×ULN confirmed by the central laboratory test at S1.

- Washout group (Group 3): Subjects at Screening who are receiving stable treatment (no change in dose for 3 months prior to Screening) with octreotide or lanreotide monotherapy, who have IGF-1 ≤1.0×ULN at Screening Visit 1 and are willing to washout of their medication during the Screening Period. Any form of pretrial octreotide or lanreotide monotherapy (long- or short-acting [subcutaneous (SC) or oral]) can be washed out and will determine the duration of the Screening Period. After informed consent is provided, the subject should not receive further pretrial acromegaly medication. IGF-1 must rise from the first Screening visit by at least 30% and be ≥1.1×ULN confirmed by the central laboratory test at S2 or S3 (if needed), to qualify for enrollment.

The Screening Period for the Medically naïve group and the Previously Treated group (no treatment within previous 4 months) should be approximately 4 weeks in duration and will consist of 1 Screening Visit (S1).

For those treated at the time of Screening with long- or short-acting octreotide or lanreotide monotherapy and who are willing to washout, initial eligibility (including IGF-1 ≤1.0×ULN) will be assessed at S1. At that time, subjects will begin washout of their pretrial acromegaly medication. Subjects taking long-acting octreotide or lanreotide will have a Screening Period of approximately 12 to 16 weeks. Subjects taking short-acting octreotide or lanreotide will have a Screening Period of approximately 8 weeks. Documentation of the washout criteria will be confirmed by the central laboratory test at S2. If a second post-washout IGF-1 measurement is needed to confirm eligibility (30% rise from the first Screening visit and IGF-1 ≥1.1×ULN) per the Investigator, the Medical Monitor should be consulted, and a sample collected at S3. S2 should be performed approximately 2 months after last pretrial LA-octreotide or lanreotide injection or approximately 4 weeks after last dose of short-acting (SC or oral) octreotide or lanreotide.

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. The subject will be randomized to treatment on Day 1 of the Treatment Period (Figure 1).

The Treatment Period will be approximately 24 weeks. Subjects will receive their first dose of study drug at Visit 1 (Day 1) (paltusotine or placebo).

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 12, with no dose titrations/adjustments after Week 12. Up-titration after Week 12 should not occur; subjects who require dose up-titration after Week 12 will be considered nonresponders. Down-titration due to unacceptable tolerability is permitted.

If rescue therapy is required during the RC phase, subjects will discontinue paltusotine or placebo, initiate rescue therapy, and should continue the study for the remainder of the 24-week RC phase (see Section 6.7.3 for Rescue Criteria). Rescue therapy with approved SRLs (octreotide LAR or lanreotide depot monotherapy) will be permitted during the study.

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 24-week RC phase or who meet rescue criteria and complete the 24-week RC phase with rescue medication can continue participation in the OLE phase if, in the opinion of the Investigator, the subject may benefit from continued participation and treatment with paltusotine and the subject is willing to participate. At completion of study target enrollment for the R C Phase, remaining subjects in the washout group who have entered screening and met eligibility criteria may be eligible to directly enroll into the OLE. The OLE Treatment Period is up to 200 weeks plus a 4-week follow-up.

Eligible subjects who enter the OLE following screening will initiate the study at Week 24 of the Schedule of Activities: Open-Label Extension Phase in Protocol Section 1.6. All procedures in this visit will be performed, except for the Pituitary magnetic resonance imaging scans (MRI) and Biliary/gallbladder ultrasound. The Pituitary MRI and Biliary/gallbladder ultrasound performed during screening will be utilized as the subject's baseline assessment.

4.1.4. End of Study

An End of Study (EOS) Visit will occur approximately 4 weeks after the last dose of study drug, at Week 228 to collect final safety data and other assessments as detailed in the SOAs. The EOS is defined as the date of the last visit of the last subject in the study.

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 for subjects who experience worsening acromegaly (see Section 6.7.3 [RC Phase Rescue Procedure] and Section 6.7.4 [OLE Phase Adjunctive Treatments]).

4.3. Justification for Dose and Treatment Duration

The dose rationale and the proposed titration is designed to achieve lower IGF-1 values while minimizing the possibility to experience adverse effects. 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 a 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 SRLs.

Treatment duration is extended up to 228 weeks (approximately 4 1/3 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 a 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.	Subjects ≥18 years of age at the time of Screening who fall into 1 of the following 3 groups are eligible to participate in the study. • Medically naïve group (Group 1): Those who have not been previously treated with acromegaly medications (including LA-SRLs) who at Screening have IGF-1 ≥1.3×ULN (the lower limit for eligibility is IGF-1 of 1.25×ULN when rounded to 2 decimal places) confirmed by the central laboratory test at S1. Group 1 subjects must have had at least 1 pituitary surgery 3 months or more prior to Screening. • Previously Treated group (no treatment within previous 4 months) (Group 2): Subjects who have last been treated with acromegaly medications at least 4 months prior to Screening and who have IGF-1 ≥1.3×ULN (the lower limit for eligibility is IGF-1 of 1.25 when rounded to 2 decimal places) confirmed by the central laboratory test at S1. • Washout group (Group 3): Subjects at Screening who are receiving stable treatment (no change in dose for 3 months prior to Screening) with octreotide or lanreotide monotherapy, who have IGF-1 ≤1.0×ULN (the upper limit for eligibility is IGF-1 of 1.04 when rounded to 2 decimal places) at Screening Visit 1 and are willing to washout of their medication during the Screening Period. Any form of pretrial octreotide or lanreotide monotherapy (long- or short-acting [SC, IM, or oral]) can be washed out and will determine the duration of the Screening Period. After informed consent is provided, the subject should not receive further pretrial acromegaly medication. IGF-1 must rise at least 30% from the first Screening Visit to the last Screening Visit and to ≥1.1×ULN (the lower limit for eligibility is IGF-1 of 1.05 when rounded to 2 decimal places) confirmed by the central laboratory test at S2 or S3, if needed) to qualify for enrollment.
4.	Previous diagnosis of acromegaly confirmed by the Investigator and approved by the Medical Monitor. This requires evaluable documentation of a pituitary adenoma.

Screening and Testing Evaluations	
5.	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	
6.	Females who engage in heterosexual intercourse must be of nonchildbearing potential, defined as either surgically sterile (ie, 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: – Noncyclic, 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 or ligation (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.

7.	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 [ie, 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.	History of ineffectiveness or significant intolerance of octreotide or lanreotide treatment, as determined by the Investigator.
2.	History of pituitary radiation therapy within 3 years of Screening.
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: • Compression of the optic chiasm or invasion of adjacent brain structures (other than sphenoid sinus or cavernous sinus) • History of tumor growth within 1 year after surgery (if performed) or radiation (unless it occurred during a period of medical therapy interruption) • Anticipated requirement for neurosurgical intervention or radiation therapy within the time course of the study. • 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.	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.
10.	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.
11.	Use of the following medications as outlined: • Any history of acromegaly medication use (Group 1 only) • Lanreotide depot or octreotide LAR (within 16 weeks before Screening) (Group 2 only) • Pasireotide LAR (within 24 weeks prior to Screening) • Pegvisomant (within 16 weeks before Screening) • Dopamine agonists (within 16 weeks before Screening) • Any combination of 2 or more acromegaly medications at Screening • Proton pump inhibitors (from start of Screening) until the end of the study 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.
12.	Current use of oral estrogen replacement therapy for <12 weeks prior to Screening.
13.	Current use of medications that are strong inducers of CYP3A4 within 2 weeks prior to Screening (refer to Section 6.7.2 Prohibited Medicine).
14.	Known allergy or hypersensitivity to any of the test materials or related compounds.
Screening Tests and Evaluations	
15.	Active COVID-19 confirmed or suspected based on clinical symptoms.
16.	Symptomatic cholelithiasis.
17.	Clinically significant concomitant disease including but not limited to cardiovascular disease, severe renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m^2), or significant liver disease (including cirrhosis).
18.	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.

19.	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.
20.	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.
21.	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.).
22.	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.
23.	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 (eg, due to hemoglobinopathies).
24.	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.
25.	Known history of, or current alcohol or drug abuse, within the last year.
Other	
26.	An employee or immediate family member of an employee of Crinetics or investigator and clinical site staff.
27.	Participation in any previous clinical study with paltusotine.
28.	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 nonchildbearing potential, defined as either surgically sterile (ie, 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:
  - Noncyclic, 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 [ie, 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 (eg, 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.

5.5. Open-Label Extension Participation

Subjects who complete the 24-week RC phase or for whom rescue is required during the RC phase can continue participation in the study in the OLE phase if, in the opinion of the Investigator, the subject may benefit from continued participation and treatment with paltusotine and the subject is willing to participate.

Investigators should contact the Medical Monitor to discuss 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 pretrial medication and eligibility for OLE on a case-by-case basis. These situations may include the following: (1) when there is worsening of acromegaly symptoms with no improvement from baseline in IGF-1 levels, however IGF-1 is <1.5×ULN or (2) IGF-1 ≥1.5×ULN without sufficiently worsening acromegaly symptoms (see Section 6.7.3).

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 20 mg 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] Drug labels will comply with the legal requirements of each country and will be printed in local language.

The starting daily dose will be 20 mg (1×20 mg tablet of active paltusotine or matching placebo) 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), or another medication will be allowed for at least 1 hour after drug administration.

The last dose of study drug for the RC phase will be self-administered the day prior to the Week 24/EOR visit. The first dose of the OLE phase will be administered during the Week 24/EOR visit for those continuing into the OLE.

Table 5: Study Interventions

Arm Name	**Paltusotine Arm**	**Placebo Arm**
Intervention Name	Paltusotine	Placebo
Type	Drug	Drug (placebo)
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	20 mg	Placebo for 20 mg tablet
Dosage Level(s)	Starting daily dose is 1×20 mg tablet. The dose can be titrated (in 1×20 mg tablet increments) up to 3×20 mg tablets daily. Dose levels may be decreased to 1×20 mg tablet daily.	Starting daily dose is 1×20 mg tablet. The dose can be titrated (in 1×20 mg tablet increments) up to 3×20 mg tablets daily. Dose levels may be decreased to 1×20 mg tablet daily.
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP	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 Dispensing Unit Number (DUN) for drug accountability purposes and traceability. The storage conditions for study drug will be described on the study drug label.

DUN=dispensing unit number; IMP=investigational medicinal product; NIMP= noninvestigational medicinal product

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 (ie, 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. 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-patient shipments of study drug will be allowed in exceptional cases (ie, 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 nonallocated 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 will 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 (ie, 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 (eg, allocation, accountability, tracking, and recording) will be provided in a Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

The study is a double-blind study with subjects, investigators and site staff, and the Sponsor blinded to treatment allocation (paltusotine versus placebo). Subjects will be randomized to study treatment using Suvoda Interactive Response Technology (IRT), 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 Good Clinical Practice.

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 prior treatment (medically naïve or previously treated versus washout).

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 Table 3 for the dose titration schema.

6.5.1. During the RC Phase

The starting daily dose will be 20 mg (1×20 mg tablet of active paltusotine or matching placebo) for oral self-administration. After confirming tolerability with the subject, the dose should be increased to 40 mg/day (2×20 mg tablet of active paltusotine or matching placebo) at the Week 2 visit. At Week 6, the dose should be increased to 60 mg QD (3×20 mg tablets) if the 40 mg dose is acceptably tolerated, and the Week 4 IGF-1 is >0.9×ULN. If the Week 4 IGF-1 is ≤0.9×ULN, the dose will be maintained at 40 mg QD until the end of the RC phase, unless an unscheduled measurement obtained at any time from Week 4 to prior to or at Week 12 shows IGF-1 >0.9×ULN, in which case the dose should be increased from 40 to 60 QD if the 40 mg dose is acceptably tolerated.

A subject's dose may be reduced during the RC phase due to poor tolerability, as evaluated and confirmed by the Investigator. A dose reduction based on tolerability may be necessary for

patients who are taking P-gp (P-glycoprotein) and/or BCRP (breast cancer resistance protein) 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 20-mg increments, if needed, based on protocol specified dose titration criteria to a maximum of 60 mg QD (3×20 mg tablets). See Section 10.3.1 for the definition of a TEAE and Section 10.3.3 for definitions of intensity and causality.

During the RC phase, planned study visits are to occur approximately every 2 to 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 20 mg (1×20 mg tablet), dispensed in an open-label manner; ie, subjects will be given a bottle of paltusotine containing [redacted] tablets and instructed to take 1 tablet per day and then if tolerated, to increase to 40 mg QD (2×20 mg tablets) at the Week 26 visit.

Further up-titration 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 QD (3×20 mg tablets).

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.

If the administration of a prohibited concomitant medication is deemed to be medically necessary for ongoing treatment, the subject will need to discontinue from the study. PPI administration could be allowed for the treatment of a short medical intercurrence, but not for ongoing medical treatment while in the study.

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 nonprohibited 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 current 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. If the administration of a prohibited concomitant medication is deemed to be medically necessary for ongoing treatment, the subject will need to discontinue from the study. Prohibited medications include:

- Proton pump inhibitors;
- Use of famotidine in the evenings;
- Oral estrogen, except for monophasic estrogen-progestin oral contraception or stable estrogen replacement (see Section 5.1 Inclusion Criteria and Section 5.2 Exclusion Criteria);
- 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;
- Octreotide (any form), lanreotide, or pasireotide during the OLE;
- Any other investigational drug, unless approved by the Medical Monitor (eg, COVID-19 therapies).

6.7.3. RC Phase Rescue Procedure – 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.

Criteria for rescue with approved SRLs (injected long-acting octreotide or lanreotide) 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 [eg, significant intervention needed to avert hospitalization or clinically notable increase in frequency or intensity of subject contact required] or substantial clinical deterioration [eg, worsening from a mild to severe AE or the onset of an SAE would meet these criteria])

AND

- IGF-1 value ≥1.5×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)

*In a large study of naïve acromegaly patients, octreotide LAR monotherapy achieved mean IGF-1 of 1.5× ULN (Colao, 2014) at 3 months of treatment through 12 months.

It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 12, with no dose titrations/adjustments after Week 12. Up-titration after Week 12 should not occur; subjects who require dose up-titration after Week 12 will be considered nonresponders. Down-titration due to unacceptable tolerability is permitted. 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 24-week RC phase. Rescue therapy with approved SRLs (octreotide LAR or lanreotide depot monotherapy) will be permitted during the study. Rescue therapy should be used according to approved marketing authorization or standard clinical practice.

Long-acting octreotide or lanreotide depot monotherapy are considered auxiliary medicinal products (AxMPs).

6.7.4. 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 48. If these criteria are met, non-SRL acromegaly treatments, such as cabergoline or GH receptor antagonist (ie, 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. If adjunctive medications are not appropriate or not accessible under local regulations, and the subject is not under acceptable biochemical control while treated with paltusotine monotherapy at the maximal tolerated dose in the opinion of the Investigator, the subject should be discontinued from the OLE portion of the study.

- 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 indicated and it is accessible, 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 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).

Adjunctive treatments such as cabergoline and pegvisomant are considered auxiliary medicinal products.

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 24-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 to confirm that re-initiation of standard SRLs is clinically justified and not the result of poor protocol compliance. Examples of valid clinical reasons to resume standard SRL in the absence of protocol defined rescue criteria would include the following: (1) IGF-1 is not improved from baseline and is ≥1.5×ULN but without sufficiently worsening of acromegaly symptoms as per protocol criteria (see Section 6.7.3), or (2) there is intolerable worsening of acromegaly symptoms, however IGF-1 is <1.5×ULN. Such subjects may benefit from access to paltusotine in the OLE, either because they were randomized to placebo in the RC portion of the study, or, for those randomized to paltusotine during the RC, inadequate efficacy was not clearly demonstrated. Therefore, such cases will be considered for continuation in the RC phase on approved SRLs, and eligibility for the OLE will be decided on a case-by-case basis. Subjects in the OLE portion of the study who require rescue will discontinue both study drug and study participation. (In other words, no subject who after having enrolled in the OLE portion of the study and who subsequently requires rescue with standard acromegaly treatment will remain in the study.)

If a subject discontinues the study early, the Investigator should schedule an early termination 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, 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.

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 (20 mg per day) in the opinion of the Investigator;
4. Other clinically significant potentially drug-related abnormalities (eg, newly developed or worsening hypoglycemia, hyperglycemia, hypersensitivity, symptomatic cholelithiasis, or pancreatitis);
5. Investigator's decision (ie, 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;
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 noncompliance 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 6.7.4).

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 (FDA 2009):

- Detection of Liver Test Abnormalities

  All subjects will have a 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 inquiry 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; nonalcoholic 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 (eg, 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 2-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, eg, 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 (ie, 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 (eg, 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 include but are not limited to the following:

- Inefficacy of the study medication
- Results from ongoing safety monitoring
- Unacceptable changes in the benefit-risk profile of the study medication;
- 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.

Pretrial 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) ASD, (2) [redacted] (3) [redacted], (4) [redacted], (5) [redacted] and (6) [redacted] Questionnaire. 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). A paper questionnaire may be used if an electronic device cannot be utilized or is unavailable.

8.2.1. Acromegaly Symptoms Diary

Subjects will be asked to complete the ASD, a brief symptom diary, daily at home beginning 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]

Note that the [redacted] will not be administered in India due to lack of available validated translations.

8.2.3. [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-directed 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 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. An ultrasound 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 and Serious Adverse Events 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 study drug administration has started will be considered as TEAEs.

Investigators will be asked to assess whether each reported adverse event is a symptom of acromegaly. If adverse events are attributed to acromegaly, they will be reported as adverse events 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 nonleading 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 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 Crinetics SAE Report 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 Crinetics SAE Report 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 (ie, 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.

AEs 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 Visit S1. 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 the RC phase, and during the 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 Crinetics Pregnancy Exposure Report Form to the Sponsor's Pharmacovigilance Group at [redacted] within 24 hours of knowledge of the pregnancy. 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 (eg, 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.

PK samples are not required during the Randomized Controlled Phase for subjects on rescue medication.

To minimize patient burden, only sparse pharmacokinetic (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 and handling 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. Pharmacogenomics

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. Genotype blood sample can be drawn at any post-baseline visit in China.

Direct glucuronidation by [redacted] has been identified as a relevant metabolic pathway that contributes to the systemic clearance of paltusotine. [redacted] is polymorphic, and genotyping has been conducted in selected Phase 1 and both Phase 2 paltusotine studies. Data suggest normal and intermediate metabolizers have similar exposures; however, poor metabolizers have approximately 30% higher exposures than normal/intermediate metabolizers. The pharmacogenomics data collected from this study will be pooled with data from other paltusotine studies for the planned population PK analysis, which will allow for a more quantitative estimate of these effects in healthy volunteers and acromegaly subjects while controlling for other potential covariates (eg, body weight, age).

8.7. Biomarkers

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

For subjects on rescue medication during the Randomized Controlled Phase, IGF-1 and GH samples should still be collected at each of the remaining scheduled visits per the SOA. The terms ‘pre-dose’ and ‘post-dose’ do not apply to these samples, as study medication is no longer being administered.

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 Clinical Trial Regulation (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

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. This section is a summary of the planned statistical analyses of the most important endpoints including primary and 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.

9.1. Statistical Hypotheses

The primary hypothesis:

H_o: $\beta = 0$

H_a: $\beta \neq 0$

Where β is the parameter estimate for treatment group when used in a model with response of IGF-1 ≤1×ULN or IGF-1 >1×ULN and prior treatment (medically naïve or previously treated versus washout) as a covariate in the Exact Logistic Regression model (see Section 9.4.2).

9.2. Sample Size Determination

The primary endpoint assumes the overall rate of response at EOR, defined as IGF-1 ≤1.0×ULN, for paltusotine versus placebo is [redacted] and [redacted], respectively. The study population will be stratified to ensure equivalent active treatment versus placebo allocations in each stratum. Groups 1 and 2 constitute Stratum 1 and Group 3 constitutes Stratum 2. The number of subjects in each stratum is expected to be equally allocated (Melmed, 2010). The responder rates in Stratum 1 are expected to be [redacted] in paltusotine-treated subjects and [redacted] in placebo-treated subjects. The responder rates in Stratum 2 are expected to be [redacted] in paltusotine-treated subjects and [redacted] in placebo-treated subjects. Through simulations, power was estimated for the comparison of paltusotine versus placebo using an Exact Logistic Regression with stratum as a covariate in the model and a 2-sided alpha of 0.05. Power of [redacted] was achieved with 76 subjects (38 per group), which accounts for a [redacted] rate of drop-outs (who are treated as nonresponders).

For subjects in Stratum 1, the expectation is that placebo subjects will have little to no response, based on clinical practice. Assuming that paltusotine and octreotide have similar response rates, the sample size estimate was based on the rates observed in a similar patient population in the registrational trial for pasireotide LAR in which octreotide LAR was used as an active comparator (Colao, 2014). For Stratum 2, the estimates are based on the Phase 2 ACROBAT Edge study (CRN00808-03) with paltusotine, as well as the observed placebo response in a similarly designed clinical study for oral octreotide (Chiasma Inc.; Optimal Study; EudraCT:2017-000737-31).

For the Phase 2 ACROBAT Edge study (CRN00808-03) in subjects with acromegaly previously treated with stable dose octreotide LAR or lanreotide depot, 20/23 patients (87%) who completed the dosing period achieved IGF-1 levels at end of treatment that were within biological variability of the assay (20% of baseline) or lower. The estimated maintenance of baseline response used in PATHFINDR-1 samples size calculation ([redacted]) is considered conservative.

In ACROBAT Edge, all subjects who completed 13 weeks of treatment were washed out of paltusotine and followed for 4 additional weeks. In the primary analysis population, 18% of the patients did not show a meaningful rise in IGF-1 during the washout, consistent with data from the OPTIMAL trial (Samson, 2020), in which 19.4% of patients randomized to placebo maintained normal IGF-1 after 9 months of treatment.

This sample size was generated based on the assumption that there will be an equal number of subjects in each stratum and that [redacted] will drop out. If these assumptions are violated, there could be a reduction in statistical power. Therefore, when [redacted] of the projected 76 subjects (approximately [redacted]) are randomized, enrollment into the strata will be assessed. If there are less than [redacted] subjects in Group 3 (subjects who washout of octreotide or lanreotide during the screening period), the sample size may be increased as follows:

Subjects in Group 3 (Washouts of SRLs)	Minimum Power	New Sample Size
16-22	80%	78
10-15	80%	88
0-9	80%	98

A sample size of 54 subjects will provide [redacted] power to detect a difference in the key secondary endpoint of change from baseline to EOR in IGF-1 using a Wilcoxon-rank sum test under the following assumptions: a difference of [redacted] in the mean change from baseline to EOR in IGF-1 in units of ULN between placebo and paltusotine, a common standard deviation (SD) of [redacted], a 2-tailed alpha of 0.05, and a [redacted] drop-out rate. With 76 subjects enrolled, the power increases to [redacted]

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 pill counts. This PPS will be used as a sensitivity analysis for the primary endpoint. All major protocol violations will be defined prior to unblinding the study.
- 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.

Analysis Sets for Open Label Extension

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

9.4. Statistical Analyses

9.4.1. General Considerations

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

All efficacy and safety will be evaluated at the end of the EOR. A second database lock will occur at the end of the OLE for long-term safety and efficacy evaluation.

9.4.2. Efficacy 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, using an Exact Logistic Regression model with treatment group as a factor and a covariate for prior treatment (medically naïve or previously treated versus washout) 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 collected at Weeks 22 and 24. If only one IGF-1 result is available at Weeks 22 or 24, then that result will be used alone to define response. Nonresponse is defined as an IGF-1 level >1.0×ULN based on the average of the same last 2 measurements at EOR (Weeks 22 and 24) or if a subject has a missing IGF-1 value at both of these time points. Subjects who discontinue treatment for any reason prior to EOR or receive rescue procedures as described in Section 6.7.3 will be considered nonresponders. Subjects who titrate up in dose after Week 12 will also be considered nonresponders.

9.4.2.1. Primary Endpoint

The following sensitivity analyses will be performed on the primary endpoint. 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 will be defined in the SAP.
- LOCF will be used to carry the last IGF-1 value prior to treatment discontinuation due to withdrawal or rescue medication forward. For subjects who dose titrate up after Week 12, the last IGF-1 value prior to this dose titration will be carried forward.
- A completers analysis will be performed to include only FAS subjects who complete 24 weeks of treatment. The same analysis will be performed as described above.
- All primary endpoint analyses will be performed on the PPS in addition to the FAS which will be the primary analysis set.
- The current analysis of the primary endpoint will be performed without treating subjects who dose titrate up after Week 12 as non-responders.

- An exact logistic regression will be used to analyze the primary endpoint for each stratum separately. The stratum will no longer be needed as a covariate in the model.

9.4.2.2. Key Secondary Endpoint:

The key secondary endpoint of change from baseline to EOR in IGF-1 will be analyzed using a worst-rank score analysis of covariance (ANCOVA) model including treatment group as a factor with prior treatment (medically naïve or previously treated versus washout) as a covariate for the FAS. The treatment difference in ranks 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 IGF-1 results captured at 22 and 24 weeks of treatment. If only one IGF-1 result is available at Weeks 22 and 24, then that result will be used alone. EOR for subjects who discontinue treatment, receive prohibited standard acromegaly treatment, or dose titrate up after Week 12 will be assigned a rank based on the reason for the missing data.

A sensitivity analysis for the FAS will also be performed where multiple imputations are used to impute missing data then analyzed using an ANCOVA. Change from Baseline to EOR will be compared between treatment groups after adjusting for prior treatment. Baseline and EOR will be defined in the same manner as above. EOR for subjects who discontinue treatment, receive prohibited standard acromegaly treatment, or dose titrate up after Week 12 will be considered missing and imputed per the multiple imputations.

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

1. A response of IGF-1 <1.3×ULN at EOR will be analyzed for the FAS using the same methodology as the primary endpoint. Response is defined as an IGF-1 level <1.3×ULN based on the average of last 2 measurements collected at EOR (Weeks 22 and 24). If only one IGF-1 result is available at Weeks 22 and 24, then that result will be used alone to define this response. Nonresponse is defined as an IGF-1 level ≥1.3×ULN based on the average of the same last 2 measurements at EOR (Weeks 22 and 24) or if a subject has missing IGF-1 values at these visits. Subjects who discontinue treatment for any reason prior to EOR, receive prohibited standard acromegaly treatment, or dose titrate upward after Week 12 will be considered nonresponders.
2. Growth hormone 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 22. Nonresponse is defined as GH ≥1 ng/mL or missing at Week 22. Subjects who discontinue treatment for any reason prior to Week 22, take prohibited standard acromegaly treatment, or dose titrate upward after Week 12 will be considered nonresponders.
3. Change from baseline in Total ASD score will be analyzed for the FAS using the same methodology specified for the key secondary endpoint of change from baseline in IGF-1.

Exploratory endpoints will include nominal p-values with descriptive statistics. Continuous endpoints will be analyzed using parametric or nonparametric methods as applicable (to be defined in the SAP) and summarized with the number of nonmissing 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. Subgroup analyses will be performed for prior treatment with lanreotide or octreotide and within each strata.

9.4.2.3. Open Label Extension

The OLE is designed to descriptively evaluate long term safety and efficacy of paltusotine for the endpoints that are defined in the randomized controlled phase. Summary statistics defined as the number of subjects, mean, median, standard deviations and range will be presented for continuous endpoints by visit. Change from Baseline will also be summarized by visit during the OLE. The number and percentage of subjects with categorical endpoints will be presented by visit. Shift tables from Baseline to OLE visits may also be evaluated for certain endpoints.

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

9.4.2.4. Multiplicity

All hypothesis testing will be performed using the gatekeeping test strategy based on a fixed sequential method. The primary, key secondary, 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 9.4.2.2. The hypothesis testing of secondary endpoints will be conducted only if the primary efficacy endpoint comparison is statistically significant at the predefined 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. Treatment-emergent AEs by severity and relationship will be summarized as well as and TEAEs leading to discontinuation or death. 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 by treatment group. 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 optional interim analysis for superiority of the primary endpoint may occur when 50% of the subjects complete or withdraw from the RC treatment period. If an interim analysis is performed, a conditional power calculation will be performed to evaluate futility defined as a conditional power of <30%. If futility is not declared, and the conditional power is between 30% and 80%, then a sample size re-estimation will be performed to ensure that the study accrues enough subjects for at least 80% power. The conditional power calculation and sample size re-estimation will be generated by an independent biostatistician and communicated to the Sponsor by the unblinded DMC. Additional details can be found in the SAP and the DMC charter.

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.

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. Note that the Sponsor (or designee) will comply with any local or national requirements that differ from the above (eg, a requirement to submit any amendment regardless of classification for review and 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 679/2016), 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 case report forms 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.

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 their personal data 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 (eg, 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 predefined in the Study Management Plan to identify systematic issues that can impact subject safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report.
- Monitoring details describing strategy (eg, 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 (eg, 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 subject 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 clinical study report. 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 (eg, 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 (eg, 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 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 6: Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Hemoglobin Hematocrit RBC count Platelet count	RBC Indices: Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils 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 • 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 during a collection period of up to 3 hours. Integrated GH should be measured after at least a 4-hour fast and the subjects should remain fasting during the GH sampling. The integrated GH sampling at Week 22 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.

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 (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, 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 preexisting 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 NOT 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 (eg, 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 preexisting 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 preexisting 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

A SAE is defined as any serious event that, at any dose:
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 (eg, 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 the Crinetics SAE Report 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 (eg, 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 (ie, 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 Report Form
The primary mechanism for reporting a SAE to the pharmacovigilance unit will be via the SAE Report Form. Any such SAE due to any cause, whether or not related to the study drug, must be reported on the Crinetics SAE Report Form immediately (and under no circumstances should this exceed 24 hours of occurrence) or when the Investigator becomes aware of the event. The Crinetics SAE Report 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 can report the follow-up information on the Crinetics SAE Report Form and send to the pharmacovigilance group via [redacted].

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
[redacted]	[redacted]
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASD	Acromegaly Symptoms Diary
AST	Aspartate aminotransferase
AxMP	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
CYP	Cytochrome
DMC	Data Monitoring Committee
DPO	Data Protection Officer
DUN	Dispensing unit number
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOR	End of the Randomized Controlled phase
EOS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
ET	Early Termination
EU	European Union
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
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive web response system
LAR	Long-acting release
LA-SRL	Long-acting somatostatin receptor ligand
LDL	Low-density lipoprotein
MRI	Magnetic resonance imaging
NIDDK	National Institute of Diabetes and Digestive and Kidney Disease
NIMP	Non-investigational medicinal product
OLE	Open-label extension
[redacted]	[redacted]
[redacted]	[redacted]
P-gp	P-glycoprotein
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	Randomized, controlled phase
S1, S2, S3	Screening Visit 1, etc.
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation

Abbreviation	Definition
SOAs	Schedules of Activities
SOP	Standard Operating Procedure
SRL	Somatostatin receptor ligand
SS	Safety Set
SST2	Somatostatin receptor 2
TB	Total bilirubin
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
W	Week
WBC	White blood cell

11. REFERENCES

Carroll PV and Jenkins PJ. Acromegaly. In: De Groot LJ, Chrousos G, Dungan K, et al, eds. Endotext. https://www.ncbi.nlm.nih.gov/books/NBK279097. Last updated Sep 2022.

Colao A, Bronstein MD, Freda F. et al. Pasireotide versus octreotide in acromegaly: A head-to-head superiority study. J Clin Endocrinol Metab. 2014; 99(3):791-9.

Katznelson L, Laws Jr ER, Melmed S. et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Nov;99(11):3933-51. doi: 10.1210/jc.2014-2700.

Melmed S and Kleinberg D. Pituitary masses and tumors. Chapter 9. pages 232-299. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology. 13th Edition. Elsevier Inc. Copyright 2016.

Melmed S, Cook, D, Schopohl J, Goth MI, Lam KSL, and Marek J. Rapid and sustained reduction of serum growth hormone and insulin-like growth factor-1 in patients with acromegaly receiving lanreotide Autogel therapy: a randomized, placebo-controlled, multicenter study with a 52 week open extension. Pituitary. 2010;13(1):18-28. doi: 10.1007/s11102-009-0191-1.

NIDDK diseases online health information. Acromegaly. https://www.niddk.nih.gov/health-information/endocrine-diseases/acromegaly. Last accessed Nov 17, 2023.

Samson SL, Nachtigall LB, Fleseriu M, et al. Maintenance of Acromegaly Control in Patients Switching from Injectable Somatostatin Receptor Ligands to Oral Octreotide. J Clin Endocrinol Metab. 2020 Oct 1;105(10):e3785–97.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009.

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