Statistical Analysis Plan for Protocol CRN00808-03 (ACROBAT EDGE)

An open label exploratory study to evaluate the safety, pharmacokinetics and efficacy of CRN00808 in patients with acromegaly treated with somatostatin analogue based treatment regimens

(ACROBAT EDGE)

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Protocol Version and Date:	Version 3.0, 07 June 2019
Phase:	Phase 2
Methodology:	Single arm, Open-Label
Sponsor:	Crinetics Pharmaceuticals, Inc. 10222 Barnes Canyon Road, Building #2 San Diego, CA 92121
Analysis Plan Date:	01 October 2020
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APPROVAL PAGE

Statistical Analysis Plan for Protocol CRN00808-03 (ACROBAT EDGE)

Analysis Plan Date: 01 October 2020

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
ACTH	adrenocorticotropic hormone
[redacted]	[redacted]
AE	adverse event
ANCOVA	analysis of covariance
[redacted]	[redacted]
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
C	Celsius
CI	confidence interval
cm	centimeter
CMH	Cochran-Mantel-Haenszel
COVID-19	corona virus disease 2019
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOB	date of birth
DOIC	date of informed consent
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EoT	End of Treatment
[redacted]	[redacted]
FDA	Food and Drug Administration
FP	Follow up Period
FSH	follicle stimulating hormone
fT3	free triiodothyronine hormone
fT4	free thyroxine hormone
G	(NCI CTCAE) grade
GH	growth hormone
H	High
HBV	Hepatitis B virus
HCV	Hepatitis C virus

Abbreviation	Term
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IGF-1	insulin-like growth factor 1
[redacted]	[redacted]
IMP	investigational medicinal product
in	inches
ITT	Intent-to-Treat
kg	kilogram
L	liter or low (context dependent)
lb	pounds
LH	luteinizing hormone
LLOQ	less than the limit of quantitation
m	meter
m^2	meters squared
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/dL	milligrams per deciliter
min	minimum or minute (context dependent)
mITT	modified Intent-to-Treat
mL	milliliters
mm	millimeters
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
msec	milliseconds
NCI	National Cancer Institute
ng	nanogram
ng/L	nanograms per liter
PD	pharmacodynamics
PE	physical examination
PGI	Physician Global Impression
PGI-I	Physician Global Impression of Improvement

Abbreviation	Term
PGI-S	Physician Global Impression of Severity
PK	pharmacokinetic
PT	preferred term
QoL	quality of life
QT	measure of time between start of Q wave and end of T wave
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	standard international unit
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	treatment-emergent adverse event
temp	temperature
TFL	tables, figures, and listings
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VAS	Visual Analogue Scale
vs	versus
WHO	World Health Organization

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of Study CRN00808-03 (ACROBAT EDGE) data collected within the scope of the Crinetics-sponsored protocol. The purpose of this plan is to provide details on analysis populations and on how the variables will be derived, how missing data will be handled, as well as details on statistical methods to analyze the safety and efficacy data. If there are any deviations from protocol planned analyses, these are documented in Section **Error! Reference source not found.**, and the SAP takes precedence.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file prior to database lock and unblinding. Any deviations from this statistical analysis plan will be documented in the clinical study report (CSR).

This SAP is written with consideration of the recommendations outlined in the International Council on Harmonisation (ICH) E9 (Addendum 1) guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."

A detailed description of the planned tables, figures, and listings (TFLs) to be presented in the CSR is provided in an accompanying TFL shell document.

2. INFORMATION FROM THE STUDY PROTOCOL

2.1. Study Objectives

- To evaluate the efficacy of CRN00808 in acromegaly subjects treated with somatostatin analogue based treatment regimens;
- To evaluate the safety and tolerability of CRN00808 in acromegaly subjects;
- To evaluate the pharmacokinetics (PK) of CRN00808 in acromegaly subjects.

2.2. Study Design

2.2.1. Overall Study Design

This is an open label dose blinded exploratory study designed to evaluate the safety, PK and efficacy of CRN00808 in subjects with acromegaly that are treated with somatostatin analogue based treatment regimens. The study will consist of the following periods:

- Screening Period (up to 6 weeks);
- Treatment Period (TP; up to 13 weeks);
- Follow-up Period (FP; up to 4 weeks).

Therefore, the total study duration for the individual subject is up to 23 weeks.

The study design is displayed in Figure 1 and Figure 2.

Figure 1: Screening Period

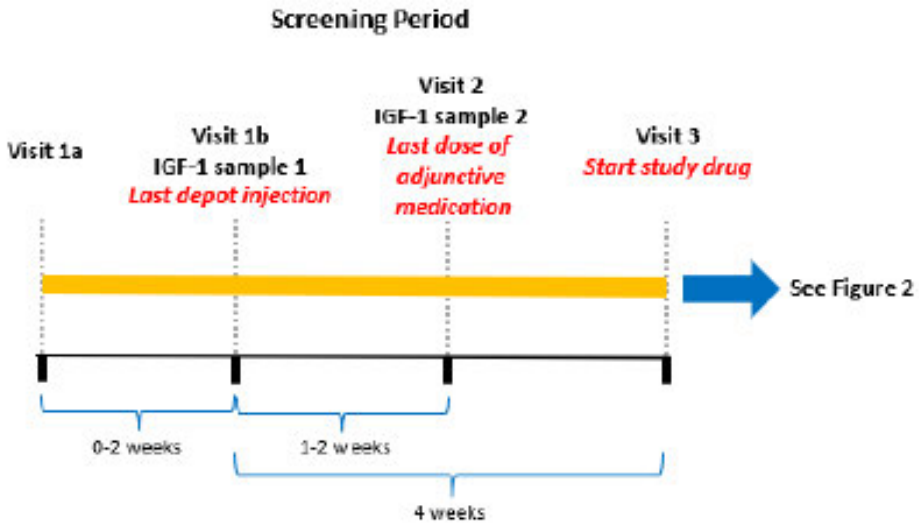
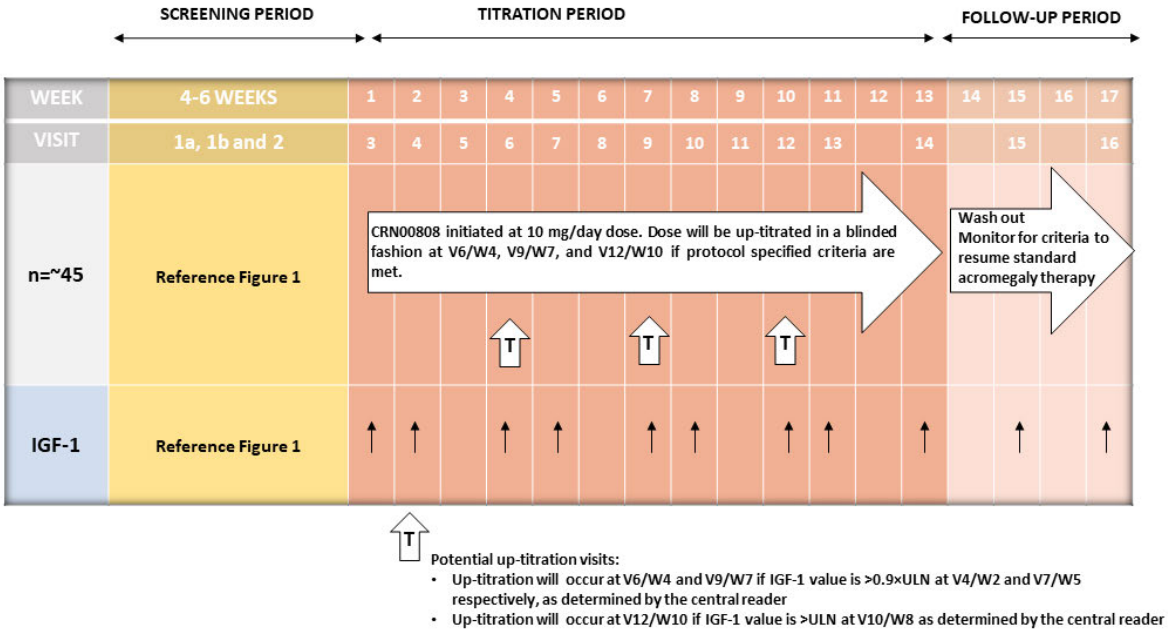


Figure 2: Overall Study Design



See study protocol for complete details. There was a COVID-19 Emergency Amendment to the protocol to specifically address changes to study visit schedule and assessments, changes in subject withdrawal criteria, changes to provision of study drug and study supplies, and IGF-1 measurements and titration.

2.2.2. Study Population

Approximately 45 subjects on stable doses of SSA based pharmacotherapy for the treatment of acromegaly will be recruited for this clinical trial. In order to be eligible to enter the Treatment Period, the Screening IGF-1 measurements (performed by the study central laboratory) must fall into the ranges specified for one of the following groups:

- **Group 1:** Partial responders on a stable treatment of Octreotide LAR or Lanreotide depot (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 2:** Partial responders on a stable combination treatment of SSA (i.e., Octreotide LAR or Lanreotide depot) and a dopamine agonist (Bromocriptine or Cabergoline) (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 3:** Complete responders on a stable combination treatment of SSA (i.e., Octreotide LAR or Lanreotide depot) and a dopamine agonist (Bromocriptine or Cabergoline) (mean of Screening IGF-1 values must be ≤ULN);
- **Group 4:** Complete responders on a stable dose of Pasireotide LAR (mean of Screening IGF-1 values must be ≤ULN);
- **Group 5:** Complete responders on a stable combination treatment of SSA (i.e., Octreotide LAR or Lanreotide depot) and Pegvisomant (mean of Screening IGF-1 values must be ≤ULN).

2.2.3. Study Drug

Study drug consists of CRN00808 or placebo. Placebo was only used for dose-blinding the dose after the first potential up-titration visit and not as a comparator.

CRN00808 is an orally administered nonpeptide somatostatin agonist that is expected to lower serum IGF-1 and GH levels in acromegaly patients. [redacted] is the active pharmaceutical ingredient available as [redacted] ([redacted] Size 2) and [redacted] ([redacted] Size 2) solid dose capsules. Please refer to the protocol for complete product details.

Matching placebo capsules are identical in appearance to CRN00808 (available as [redacted] capsules [[redacted] Size 2]) in order to maintain blinding during dose up-titration.

2.2.4. Treatment Assignment, Blinding, and Randomization Methodology

Subjects who are determined to be eligible to enter the study drug TP will all begin treatment with CRN00808 at [redacted] per day. All subsequent dose changes will be blinded.

The study drug dose is blinded after the first potential up-titration visit and capsules are identical for the study drug and placebo. All instances of unblinding of study drug dose either due to protocol deviation or because of regulatory requirements (i.e., unblinding for purpose of Suspected Unexpected Serious Adverse Reactions [SUSARs] submission) will be documented in the CSR.

2.2.5. Study Procedures

The overall visit schedule is outlined in Table 1 of the study protocol. See study protocol for complete details.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in IGF-1 levels between Baseline and Week 13 / End of Treatment (EoT). The Baseline value will be defined as the mean of the IGF-1 prior to first dose of study drug. If a subject discontinues prior to Week 13, the last on treatment assessment will be used for the Week 13/EoT. Data from the central lab, i.e. the source data will be used for analyses.

See Section 4.7 for definition of visits and Section 8.2 for handling of missing data.

2.3.2. Secondary Efficacy Endpoints

The secondary endpoints are:

2.3.2.1. Proportion of Subjects with IGF-1 ≤ 1.0 × ULN at Week 13/EoT

The secondary endpoint is the proportion of subjects who maintain IGF-1 response, defined as the last assessment prior to end of treatment with IGF-1≤ 1.0 × ULN meet responder criteria. Prior determining response, the IGF-1 value in units of ULN will be rounded to two significant figures. This endpoint will be limited to those subjects in Groups 3, 4, and 5 who start the study with ≤ 1.0 × ULN. For subjects that complete treatment, the Week 13 will be used for each subject. For subjects who do not complete treatment, the last on treatment assessment will be used for each subject. If the IGF-1 value is missing, the subject will be counted as a non-responder.

2.3.2.2. Proportion of Subjects with IGF-1 ≤ 1.5 × ULN at Week 13/EoT

The same responder analysis as specified above in Section 2.3.2.1, but where responder is defined as the last assessment prior to end of treatment with IGF-1 ≤ 1.5 × ULN meet responder criteria. For subjects that complete treatment, the Week 13 will be used for each subject. For subjects who do not complete treatment, the last on treatment assessment will be used for each subject. If the IGF-1 value is missing, the subject will be counted as a non-responder.

2.3.3. Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be evaluated:

2.3.3.1. Biomarkers

2.3.3.1.1. IGF-1

The following change in IGF-1 levels, in units of ULN, will be evaluated:

- Change between each post-baseline timepoint (on treatment and follow up) and Baseline. Baseline is defined as the mean of all IGF-1 assessments prior to first dose of study drug. The change between each post-baseline value and Baseline value will be calculated for each subject.
- Change from end of CRN00808 treatment to 2 and 4 weeks after withdrawal of CRN00808. End of CRN00808 treatment is defined as the Week 13/Visit 14 visit,

therefore, 2 and 4 weeks after withdrawal are defined as visits Week 15/Visit 15 and Week 17/Visit 16 respectively. For subjects who withdraw early and have a follow up visit, the time from last dose to the follow up visit will be calculated and included in the applicable weeks after withdrawal.

The above change endpoints will also be calculated for percent change as well.

Other definitions of response include:

- Response based on percent change from baseline will be defined as percent change from baseline less than or equal to 15%, while a non-responder will be defined as percent change from baseline greater than 15%.
    - The same responder definition, but using 20% instead of 15%.
- Response based on percent change from Week 13/EoT will be defined as percent change from end of CRN00808 treatment greater than 15%, while a non-responder will be defined as percent change from baseline less than or equal to 15%.
    - The same responder definition, but using 20% instead of 15%.

Data from the central lab, i.e. the source data will be used for analyses.

2.3.3.1.2. GH

The proportion of subjects who meet GH responder criteria, defined as the mean the three-serum integrated GH < 5 ng/mL, rounded to two significant figures. For subjects that complete treatment, the mean of the three values obtained at Week 13 will be calculated for subject. For subjects who do not complete treatment, the mean of the last two consecutive on treatment assessments will be calculated for each subject. If any of the three values are missing, the available values will be used. If all three GH values are missing, the subject will be counted as a non-responder.

The same responder analysis will be done, where responder is defined as the mean of the three-serum integrated GH < 2.5 ng/mL, and rounded to two significant figures.

The following change in GH levels will be evaluated:

- Change between Week 13/EoT and Baseline. Baseline is defined as the mean of all available integrated values prior to the first dose of study drug (Visit 1b, Visit 2). For subjects who complete treatment, the Week 13 value will be defined as the mean of the integrated GH values at Week 13. For subjects who do not complete treatment, the mean of the integrated GH values at the last on treatment assessments will be used. If any of the integrated values are missing, the available values will be used. The change between the calculated Week 13/EoT value and Baseline value will be calculated for each subject.
- Change between each post-baseline timepoint including EoT (on treatment and follow up) and Baseline. Baseline is defined as the mean of all available integrated values prior to the first dose of study drug (Visit 1b, Visit 2). At each visit, the mean of the integrated GH values will be used. If any of the integrated values are missing, the available value(s) will be used. The change between each post-baseline value and Baseline value will be calculated for each subject.

- Change from end of CRN00808 treatment to 4 weeks after withdrawal of CRN00808. End of CRN00808 treatment is defined as the Week 13/Visit 14 visit, therefore, 4 weeks after withdrawal are defined as the Week 17/Visit 16. For subjects who withdraw early and have a follow up visit, the time from last dose to the follow up visit will be calculated and included in the applicable weeks after withdrawal.

The above change endpoints will be calculated using SI units and conventional units of GH and for percent change as well.

Data from the central lab, i.e. the source data will be used for analyses.

2.3.3.1.3. [redacted]

All the change endpoints specified above for IGF-1 (Section 2.3.3.1.1) will also be calculated for [redacted].

Data from the central lab, i.e. the source data will be used for analyses.

2.3.3.2. Patient and Investigator Reported Outcomes Endpoints

2.3.3.2.1. [redacted]

[redacted]

- Change between Week 13 and Baseline. The Baseline value will be defined as the mean of the available scores on the 7 days prior to first dose of study drug. The Week 13 value will be defined as the mean of the available scores 7 days prior to their last dose, inclusive of the date of last dose. If any of the 7 days are missing, the available, non-

missing values will be used to calculate the mean. The change between the calculated Week 13 value and calculated Baseline value will be derived for each subject.

- Change from end of CRN00808 treatment to 4 weeks after withdrawal of CRN00808. End of CRN00808 is defined as the Week 13/Visit 14 visit, therefore, 4 weeks after withdrawal is defined as the Week 17/Visit 16 respectively. For subjects who withdraw early and have follow up visit, the value will be included as 4 weeks after withdrawal.
- Change between the Week 17 follow up timepoint and Baseline. The Baseline value will be defined as the mean of the available scores on the 7 days prior to first dose of study drug. The Week 17 value will be defined as the mean of the available scores 7 days prior to the visit. The change between follow up value and Baseline value will be calculated for each subject.
- Change between the Week 17 follow up timepoint and Screening. The Week 17 value will be defined as the mean of the available scores 7 days prior to the visit. The Screening value will be defined as the mean of the available scores between Screening Visit 1b and Screening Visit 2. The change between follow up value and Screening value will be calculated for each subject.

A minimum of 4 days should be available to calculate a mean.

2.3.3.2.2. Investigator Assessed Symptoms of Acromegaly

The investigator assesses symptoms of acromegaly through adverse event monitoring. Initial assessment of symptoms is captured on the Acromegaly Symptoms at Study Entry eCRF. Any significant worsening from the initial assessment are captured on the Adverse Event eCRF as appropriate. Symptoms assessed include headache, excessive sweating (hyperhidrosis), swelling of extremities, joint pain, symptoms of sleep apnea, fatigue, and paresthesia. Each symptom is graded in severity/intensity as mild (Grade=1), moderate (Grade=2), or severe (Grade=3). If the symptom is not present, a grade of 0 will be assigned. The categorical change from study entry (as recorded on the Acromegaly Symptoms at Study Entry eCRF) to Week 13 (Visit 14) will be calculated for each subject (range, -3 to 3).

The most bothersome symptom at study entry is indicated on the Acromegaly Symptoms at Study Entry CRF. Changes in the most bothersome symptom will be calculated in same manner as defined above for the individual symptoms.

2.3.3.2.3. [redacted]

[redacted]

[redacted]

- Change between Week 13/EoT and Baseline. Baseline is defined as the assessments prior to first dose of study drug. For subjects who complete treatment, the Week 13 value will be used. For subjects who do not complete treatment, the last on treatment assessment will be used. The change between the Week 13/EoT value and Baseline value will be calculated for each subject.
- Change between each post-baseline timepoint including EoT (on treatment and follow up) and Baseline. Baseline is defined as the Day 1 (Visit 3) value. The value at each visit will be used for each post-baseline timepoint. The change between each post-baseline value and Baseline value will be calculated for each subject.
- Change between the Week 17 follow up timepoint and end of CRN00808 treatment. For subjects who complete treatment, the Week 13 value will be used. For subjects who do not complete treatment, the last on treatment assessment will be used. The value at each follow up visit will be used. The change between each follow up value and Week 13 value will be calculated for each subject.

2.3.3.2.4. [redacted]

[redacted]

2.3.3.2.5. Patient Global Impression

The Patient Global Impression of Severity (PGI-S) is a single question regarding overall current acromegaly symptom severity scored as none (Score=0), mild (Score=1), moderate (Score=2), and severe (Score=3). The Patient Global Impression of Change (PGI-I) is a single question

regarding overall acromegaly symptom change compared to before study start scored as very much improved (Score=-3), much improved (Score=-2), minimally improved (Score=-1), no change (Score=0), minimally worse (Score=1), much worse (Score=2), and very much worse (Score=3).

The PGI-S change will be calculated as specified above for IGF-1 (Section **Error! Reference source not found.**). Baseline will be defined as the last value prior to first dose of study drug.

The PGI-I scores at Week 13/EoT and follow up Week 17 (Visit 16) will also be presented.

2.3.3.3. Pharmacokinetics (PK)

Plasma CRN00808 concentrations will be measured for each subject throughout the study. Values less than the limit of quantitation (LLOQ) will be included in analyses as LLOQ/2. LLOQ is 1 ng/mL.

Plasma concentrations of Octreotide and Lanreotide is planned to be measured for each subject throughout the study. Because of the small sample size, measurement of Pasireotide concentration will not be performed. Values less than the limit of quantitation (LLOQ) will be included in analyses as LLOQ/2. LLOQ is 100 pg/mL.

2.3.4. Safety Endpoints

Safety and tolerability of CRN00808 as assessed by vital signs; 12-lead ECGs; clinical laboratory tests (hematology, serum chemistry and urinalysis); fT3, fT4, anti-thyroid antibody, TSH, cortisol, ACTH, LH, FSH and prolactin; gall bladder ultrasounds; and group emergent adverse events (TEAEs).

3. SAMPLE SIZE JUSTIFICATION

Approximately 45 subjects are planned to be enrolled in the study. At least 30 subjects from Groups 1 and 2 will be enrolled, i.e., a cap of N=15 is set for the sum of the number of subjects in Group 3 to 5.

The primary objective of this study is to evaluate efficacy (IGF-1 levels) in subjects who are partial responders to somatostatin analogue based treatment regimens. As such, the sample size is chosen to provide sufficient clinical experience to evaluate IGF-1 changes descriptively and is not formally powered for hypothesis testing. Summary statistics for the primary endpoint will be provided.

4. GENERAL STATISTICAL METHODS

4.1. Reporting Conventions

Individual subject data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by subject. The primary data source will be used for all analyses. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate font type, font size, page size, and margin sizes per FDA guidance "Portable Document Format Specifications".

For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Percentages based on frequency counts will be presented to one decimal place, and values less than 0.1% will be presented as "<0.1%." Values less than 100% but greater than 99.9% will be presented as ">99.9%."

For continuous variables, the number of subjects, mean, standard deviation (SD), median, 25th (Q1) and 75th (Q3) quartiles, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean, median, Q1, and Q3 to 1 more decimal place than the raw data, SD to 2 decimal places more than the raw data, and minimum and maximum to the same decimal places as the raw data. In general, the number of decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified, in the table and listing shell.

For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX+1 (e.g., 97.5 will round up to 98), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97).

All statistical tests comparing groups will be conducted at the 2-sided, 0.05 level of significance, unless otherwise specified.

4.2. Computing Environment

All descriptive statistical analyses will be performed using SAS software Version 9.4 or higher, unless otherwise noted. Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary, B3 September 2019.

4.3. Partial Dates

If only a partial date is available and is required for calculation, the following standards will be applied:

- Death Date
    - The last date that each subject was known to be alive will be identified as the greatest date associated with the subject's completed assessments, including telephone contacts at which the subject was confirmed to be alive.
    - For missing day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month as the last known alive date, then the partial date will be imputed to equal the last known alive date.
    - For missing day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the last known alive date, then the partial date will be imputed to equal the last known alive date.
- Diagnosis Date
    - For missing day only – Day will be imputed as the first day of the month (i.e., 1).
    - For missing day and month – Day and month will be imputed as the first day of the year (i.e., 1 January).
- Start Dates (e.g., event date, adverse event [AE] onset date, or start date of medication)
    - For missing start day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as first study drug administration date, then the partial date will be imputed to equal the first study drug administration date being used for the calculation.
    - For missing start day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as first study drug administration date, then the partial date will be imputed to equal the first study drug administration date being used for the calculation.
    - Imputed start dates must be prior to the stop date.
- Stop Dates (e.g., AE resolution date or stop date of medication)
    - For missing stop day only – Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
    - For missing stop day and month – Day and month will be imputed as the last day of the year (i.e., 31 December).
    - Imputed stop dates must be on or after the start date.

All data recorded on the case report form will be included in data listings that will accompany the CSR.

4.4. Data Conventions

The precision of original measurements will be maintained in listings and used in calculations. Derived values greater than 3 decimal places will be rounded to 3 decimal places for display in the listings.

Quantitative laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. In order to retain these values for analysis purpose, the following will be imputed and stored within the analysis datasets:

- For values with <, the imputed value will be the numeric portion × 0.9.
- For values with >, the imputed value will be the numeric portion × 1.1.

Variables with a non-normal distribution that impacts the interpretation or validity of the planned analysis may have a data transformation applied (e.g., ln, $\log_{10}$).

4.5. Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days – A duration expressed in days between one date (*date1*) and another later date (*date2*) will be calculated using the following formulas:

  duration in days = date2 – date1 + 1, where date1 ≥first administration date

  duration in days = date2 – date1, where date1 <first administration date
- Weeks – A duration expressed in weeks is calculated as the number of days divided by 7
- Months – A duration expressed in months is calculated as the number of days divided by 30.4375
- Years – A duration expressed in years between one date (*date1*) and another date (*date2*) is calculated using the following formulas:

  duration in years = (date2 – date1 + 1)/365.25, where date1 ≥first administration date

  duration in years = (date2 – date1)/365.25, where date1<first administration date
- Height – Height entries made in inches (in) are converted to centimeters (cm) using the following formula:

  height (cm) = height (in) × 2.54
- Weight – Weight entries made in pounds (lb) are converted to kilograms (kg) using the following formula:

  weight (kg) = weight (lb) / 2.205
- Temperature – Temperature entries in degrees Fahrenheit are converted to degrees Celsius using the following formula:

temp (degrees Celsius) = 5 / 9 × (temp [degrees Fahrenheit] – 32)

- Body Mass Index (BMI) – BMI is calculated using height (cm) and weight (kg) using the following formula:

  BMI (kg/m^2) = weight (kg) / ([height (cm)/100]^2)

- Change– Change will be calculated as:

  Change = later value – earlier (i.e. baseline) value

- Percent change– Percent change will be calculated as:

  Percent change = ([Change] / earlier (i.e. baseline) value) × 100

4.6. Treatments

Unless otherwise specified, summaries will be presented by the following groups:

- Group 1
- Group 2
- Group 3
- Group 4
- Group 5
- Total

Group 1 is equivalent to the Efficacy Analysis Set and will be noted as such in applicable summary tables.

Some summaries, where specified, may be broken out by dose, where doses will be presented in ascending order as Paltusotine (CRN00808) [redacted], Paltusotine (CRN00808) [redacted], Paltusotine (CRN00808) [redacted], Paltusotine (CRN00808) [redacted], Paltusotine (CRN00808) [redacted], and Total.

4.7. Visits

4.7.1. Windows

Each visit will be denoted by its visit "Week". The first dose day is denoted as Day 1. In data listings, the relative study day of all dates from first dose will be presented.

In the event of unscheduled visits or EoT assessments, these will be reassigned to a scheduled visit for analysis purposes according to Table 1 and Table 2 for on treatment assessments and Table 3 for assessments after last dose. This includes combined visits due to COVID-19, any combined visits will be assigned to the nearest appropriate window as defined by the tables below. If multiple assessments occur within a single visit window, after reassignment of unscheduled visits and EoT assessments, then the assessment closest to the target day of the visit window will be used in the analysis. If there is a tie, the later assessment will be used in the analysis. Summaries of Screening visits will use the nominal, scheduled visit from the eCRF.

Table 1: Treatment Period Visit Windows Excluding PGI-S

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	See Section **Error! Reference source not found.**	
Week 2	8	2	15
Week 4	22	16	24
Week 5	29	25	36
Week 7	43	37	45
Week 8	50	46	57
Week 10	64	58	68
Week 11	71	69	78
Week 13	91	79	95

[a] Study day will be calculated from ***first*** dose of CRN00808.

[b] Baseline is defined in Section 4.7.3.

Table 2: Treatment Period Visit Windows PGI-S Only

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
Baseline[b]	1	See Section **Error! Reference source not found.**	
Week 2	8	2	11
Week 3	15	12	18
Week 4	22	19	25
Week 5	29	26	32
Week 6	36	33	39
Week 7	43	40	46
Week 8	50	47	53
Week 9	57	54	60
Week 10	64	61	67
Week 11	71	69	78
Week 13	91	79	95

[a] Study day will be calculated from ***first*** dose of CRN00808.

[b] Baseline is defined in Section 4.7.3.

Table 3: Follow Up Visit Windows

Target Scheduled Visit	Target Day [a]	Analysis Window Day [a]	
		Low	High
2 Weeks Withdrawal of CRN00808	14	7	21
4 Weeks Withdrawal of CRN00808	28	≥22	

[a] Study will be calculated from ***last*** dose of CRN00808.

4.7.2. Repeat or Unscheduled Assessments

The IGF-1 results were evaluated for anomalous values. Values determined to be anomalous were re-assayed. Appendix 1 describes the decision tree for which re-tested values are included in analyses.

Repeat assessments occur when the original vital signs or ECG result requires confirmation. Repeat assessments are labelled as "Repeat" in the vital signs or ECG listings.

All results not taken at a scheduled timepoint are unscheduled. Unscheduled assessments are labelled as 'Unscheduled' in the listings.

In data listings, the relative study day from first dose of all dates will be presented.

4.7.3. Definition of Baseline(s)

For IGF-1 and IGBP-3, Baseline is defined as the mean of all available values prior to the first dose of study drug (Visit 1b, Visit 2, Visit 3). For GH, Baseline is defined as the mean of all available integrated values prior to the first dose of study drug (Visit 1b, Visit 2). For ASD, Baseline will be defined as the mean of the available scores on the 7 days prior to first dose of study drug. For baseline characteristics, safety assessments and other efficacy assessments, Baseline is as the last non-missing value prior to the first dose of study drug.

Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. In addition, non-missing results from unscheduled and repeat assessments prior to first dose of study drug may also be considered in the calculation of baseline observations.

4.7.4. Definition of End of Treatment (EoT)

The End of Treatment value is defined as the last on treatment assessment. In many cases the V16/ET CRF is to be populated, however, in cases where that is not possible, the last value obtained on treatment will be determined.

5. ANALYSIS SETS

The following subject Analysis Sets will be evaluated and used for presentation and analysis of the data:

- The Efficacy Analysis Set will include all subjects in Group 1 who received at least one dose of study drug. The Efficacy Analysis Set will be the primary analysis population used for all efficacy analyses.
- The Full Analysis Set will include all subjects (all groups) who received at least one dose of the study drug. The Full Analysis Set will be the secondary analysis population used for all efficacy analyses.
- The Completers Analysis Set will include all Full Analysis Set subjects who complete 13 weeks of treatment. The Completers Analysis Set will be the tertiary analysis population used for all efficacy analyses. The Completers Analysis Set will be used for supportive efficacy analyses if it differs from the Full Analysis Set by more than 5 subjects total.
- The Per Protocol (PP) Analysis Set will include all subjects from the Full Analysis Set having no major protocol deviations affecting treatment efficacy. The PP Analysis Set will be used for supportive efficacy analyses if it differs from the Full Analysis Set by more than 5 subjects total.
- The Safety Analysis Set is equivalent to the Full Analysis Set. The Safety Analysis Set will be used for all safety analyses.

6. EXAMINATION OF SUBGROUPS

Subgroups will be defined based on Baseline values, unless otherwise specified. Frequencies of categorizations for the below characteristics will be summarized by group and total.

General baseline subgroups of interest are as follows:

- Age categories: <65 vs ≥65 years
- Sex: Male vs Female
- Race: White vs All Other Races (Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Geographic Region: North America (USA) vs Europe (United Kingdom, Germany, Hungary, Romania, Slovakia, Italy, Poland, Serbia) vs Rest of World (Brazil, Australia, New Zealand)

Efficacy baseline subgroups of interest are as follows:

- Duration (months) of acromegaly from informed consent: <Median vs ≥Median
- Group 1 only: Lanreotide vs Octreotide pretrial acromegaly treatment
- Duration (months) of pre-trial acromegaly treatment: <Median vs ≥Median
- Prior pituitary surgery: Yes vs No

Where the median is specified as the cut point, the median of the specified group at Baseline will be used.

The primary, secondary, and select exploratory efficacy endpoints will be analyzed for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set. During the CSR preparation, additional subgroup analyses may be performed. Those analyses will be considered as ad-hoc analyses and will be presented and discussed in the CSR.

Subgroup analyses related to COVID-19 may be considered after review of blinded data. Any analyses will be documented in the CSR.

7. STUDY POPULATION

7.1. Subject Disposition

Subject disposition will be tabulated and will include the number of subjects screened, the number screened but not dosed with reasons for screen failure, the number treated in the TP, the number in each Analysis Set, the number who withdraw from the study prior to completing the treatment and reason(s) for withdrawal, and the number who discontinued treatment early and reason(s) for discontinuation of treatment. If a subject discontinues to due COVID-19 logistical reasons, instead of summarizing as part of Other, it will be separated out on the summary table. Similarly if a subject discontinues due to an adverse event of COVID-19, this will be presented as a subcategory of Adverse Event, combining the preferred terms of Corona virus infection and/or Coronavirus test positive as COVID-19.

The number and percentage of subjects enrolled by geographical region and study site will be summarized by group and for all subjects for the Full Analysis Set.

By-subject data listings of all the above study disposition data including study completion and any reasons for premature treatment and/or study withdrawal will be presented. Also, by-subject listings of informed consent, re-consent, and eligibility criteria details will be presented.

7.2. Demographics and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent including the subgroups defined in Section 6.
- Sex
- Race
- Ethnicity

Other baseline characteristics, from Baseline, will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2) including frequency of the following subgroup: <30, ≥ 30 kg/m^2
- Ring size
- UGT1A1 genotype and phenotype

Frequencies of categorizations for the above characteristics as defined in Section 6 will also be summarized.

Demographics and baseline characteristics will be presented by group and total for the Full and Completers Analysis Sets. The PP Analysis Set may be presented if it differs from the Full Analysis Set by more than 5 subjects total.

No inferential statistical comparisons will be performed.

All demographic and baseline characteristics data will be presented in by-subject data listings.

7.3. Baseline Acromegaly Disease Characteristics

The following disease characteristics will be summarized:

- Duration (months) since diagnosis (from informed consent)
- Tumor size (mm) prior to pituitary surgery
- Prior pituitary surgery: Yes vs No
- For those with pituitary surgery, IGF-1 (nmol/L) value at least 3 months after surgery
- Pre-trial acromegaly treatments administered at Visit 1b (SSA) or prior to Visit 3 (dopamine agonist or GH receptor blocker): Octreotide LAR, Lanreotide depot, Pasireotide LAR, Bromocriptine, Cabergoline, Pegvisomant
    - Doses pre-trial acromegaly treatments administered at Visit 1b (SSA) or prior to Visit 3 (dopamine agonist or GH receptor blocker) recorded on the Concomitant Medications eCRF. Octreotide LAR, Lanreotide depot, and Pasireotide LAR doses will be summarized as monthly dose, Cabergoline as weekly, and Bromocriptine and Pegvisomant as weekly. If a subject has more than one of these treatments recorded, the last observation, as determined by start date, consistent with treatment recorded on the Administration of Pre-Trial Acromegaly Treatment eCRF, will be used.

Frequencies of categorizations for the above characteristics as defined in Section 6 will also be summarized.

Baseline disease characteristics will be presented by group and total for the Full Analysis Set and Completers Analysis Sets. The PP Analysis Set may be presented if it differs from the Full Analysis Set by more than 5 subjects total. No inferential statistical comparisons will be performed.

Baseline disease characteristics will be presented in by-subject data listings.

7.4. Acromegaly Symptoms at Study Entry

The number and percentage of subject with each acromegaly symptom at study entry and the most bothersome symptom will presented by group and total for Full Analysis Set. In addition, summaries by grade will be presented for each symptom and the most bothersome symptom.

Acromegaly symptoms at study entry will be presented in a by-subject data listing.

7.5. General Medical History

Medical history will be summarized by SOC, PT, and group using the Full Analysis Set. Summaries will be ordered by descending order of total incidence of SOC and PT within each SOC. Any medical history of COVID-19 will appear as per their MedDRA SOC Infections and infestations and PTs of either Coronavirus infection and/or Coronavirus test positive.

General medical history will be presented in a by-subject data listing.

7.6. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without prior notification to the Sponsor (or designee) as described in the protocol.

Important protocol deviations that could potentially affect the efficacy conclusions of the study will be identified prior to database lock and unblinding of individual subject dose information. Important protocol deviations include, but are not limited to

- Subjects who entered the study, even though they did not satisfy the entry criteria.
- Subjects who received incorrect dose.
- Subjects who received a prohibited concomitant treatment.

All protocol deviations and separately only important protocol deviations will be summarized by deviation category and group using the Full Analysis Set. Protocol deviations specific to COVID-19 will be summarized separately in the same manner.

All protocol deviations and separately only important protocol deviations will be presented in a by-subject data listing. A separate listing for COVID-19 specific protocol deviations will be presented.

7.7. Pretreatment, Prior, and New Concomitant Medications or Non-Pharmacological Treatments

Pretreatment medications are those medications with start and stop prior to the first administration of study drug. Prior concomitant medications are those medications/treatments started prior and continued after the first administration of study drug. New concomitant medications are those medications/treatments that were started on or after the first administration of study drug. If it cannot be determined whether the medication/treatment was a new concomitant medication due to a partial start or stop date or if the medication/treatment is taken on the same date as the first administration of study drug, then it will be counted as a new concomitant medication.

Pretreatment medications and non-pharmacological treatments will only be listed. Prior and new concomitant medications will be summarized for each treatment by WHO ATC level 2, WHO ATC level 4, and preferred name using the Full Analysis Set. Prior and new concomitant medications treatments will also be summarized separately. These summaries will present the number and percentage of subjects using each medication/treatment. Subjects may have more than one medication/treatment per ATC level and preferred name. At each level of subject summarization, a subject is counted once if he/she reported one or more medications/treatments at that level. Each summary will be ordered by descending order of the total incidence of ATC level and preferred name within each ATC level. A separate table for all medications with an indication of acromegaly will be presented.

8. EFFICACY ANALYSES

All efficacy analyses will use the Efficacy or the Full Analysis Sets. Select analyses will also be repeated using the Completers Analysis Set. If the total number of subjects in the Full and PP Analysis Set differ by more than 5 subjects, efficacy analyses may be repeated for the PP Analysis Set for relevant primary, secondary, and select exploratory efficacy endpoints.

Statistical analysis of all efficacy endpoints will be considered nominal and descriptive.

All efficacy endpoints, recorded and derived, will be presented in by-subject data listings.

8.1. Adjustments for Covariates

Not Applicable.

8.2. Handling of Dropouts or Missing Data

The following methods will be implemented to address missing data for relevant primary, secondary, and select exploratory efficacy endpoints.

8.2.1. Responder Endpoints

For categorical efficacy endpoints in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable at each visit, any subject who does not provide an assessment at the specified time point for the response definition will be considered as a non-responder.

Sensitivity analyses will use "observed cases," where subjects who do not provide an assessment at the specified time point for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

8.2.2. Biomarker Endpoints

As described within each endpoint definition in Section 2.3, subjects who do not complete treatment will have their last on treatment assessment imputed for the Week 13/EoT value for the purposes of continuous summaries of IGF-1 and GH. Additional analyses will be conducted using observed cases only.

8.2.3. Patient or Investigator Reported Outcomes

Missing data will not be imputed for patient or investigator reported outcomes.

8.3. Interim Analyses and Data Monitoring

8.3.1. Interim Analysis

No interim analyses are planned for this study. Note however, this is an open-label, exploratory study and there may be ongoing review of data during study conduct.

8.4. Multicenter Studies

The number and percentage of subjects randomized by geographical region and study site will be summarized by group and for all subjects. No other summaries or analyses by site or region will be performed.

8.5. Use of an "Efficacy Subset" of Patients

Not Applicable.

8.6. Multiple Comparisons/Multiplicity

Not Applicable.

8.7. Primary Efficacy Analysis

The primary efficacy analysis will test the following hypothesis:

- H_0: The median IGF-1 change from Baseline to Week 13 is equal to zero.
- H_1: The median IGF-1 change from Baseline to Week 13 is different than zero.

The primary efficacy analyses, using the Efficacy Analysis Set, will evaluate change from Baseline to Week 13, at alpha level of 0.05, using Wilcoxon Signed Rank test. Descriptive statistics (Section 4.1) of values and change from Baseline by group and total will be presented including 95% CI for the arithmetic mean and geometric mean with associated 95% CI.

8.7.1. Additional Analyses of the Primary Endpoint

The primary endpoint will be analyzed for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set.

Sensitivity analyses using observed cases will be presented.

Sensitivity analyses using the Full, PP, and Completers Analysis Sets will be presented.

8.8. Secondary Efficacy Analyses

Secondary efficacy endpoints are described in Section 2.3.2.

8.8.1. Proportion of Subjects with IGF-1 ≤ 1.0 × ULN at Week 13/EoT

The secondary efficacy analysis will test the following hypothesis:

- H_0: The proportion of IGF-1 responders at Week 13/EoT is equal to 0.50.
- H_1: The proportion of IGF-1 responders at Week 13/EoT is different than 0.50.

The number and percentage, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category (response, nonresponse) will be presented by group and total for the Full Analysis Set, limited to Groups 3, 4 and 5 only, including a nominal p-value from an exact binomial test.

Sensitivity analyses using the PP and Completers Analysis Sets will be presented.

8.8.2. Proportion of Subjects with IGF-1 ≤ 1.5 × ULN at Week 13/EoT

The secondary efficacy analysis will test the following hypothesis:

- H_0: The proportion of IGF-1 responders at Week 13/EoT is equal to 0.50.
- H_1: The proportion of IGF-1 responders at Week 13/EoT is different than 0.50.

The number and percentage, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category (response, nonresponse) will be presented by group and total for the Full Analysis Set, including a nominal p-value from an exact binomial test.

This endpoint will also be analyzed for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set.

Sensitivity analyses using the PP and Completers Analysis Sets will be presented.

8.9. Exploratory Efficacy Analyses

Exploratory efficacy endpoints are described in Section 2.3.3.

8.9.1. Biomarker Endpoint Analyses

8.9.1.1. IGF-1

Changes in IGF-1 levels specified in Section 2.3.3.1.1 will presented and analyzed in the same manner specified for the primary endpoint (Section 8.7) for the Full, PP, and Completers Analysis Sets. Changes in IGF-1 levels will also be analyzed for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set.

Additional analyses of IGF-1 rate of change will be evaluated using a general linear mixed effects model to evaluate the slope for the Full Analysis Set. Rate of change will be evaluated from Baseline to end of CRN00808 treatment and separately from end of CRN00808 treatment to last assessment. The model will fit a random intercept and slope for each subject and will include fixed effects for group, time, and group × time interaction. Time will be expressed in weeks as a continuous variable and will include all assessments. An unstructured covariance structure will be used to model the within-subject errors. If the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR (1)], AR (1), heterogeneous compound symmetry (HCS), and compound symmetry (CS). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. Estimates of the slope will be presented by group along with corresponding 95% CIs.

As doses are allowed to be titrated, if sufficient data exist, a dose response analysis may be conducted evaluating the change between the following weeks: Week 4 (prior to any dose titration), Week 7 (after 1st potential dose titration), and Week 10 (2nd potential dose titration) for the Full Analysis Set.

Response rates based on percent change from baseline and percent change from end of CRN00808 treatment will be presented using the same methods specified for the IGF-1

secondary endpoints (Sections 8.8.1 and 8.8.2) for the Full and Completer Analysis Sets. Response rates will also be analyzed for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set.

8.9.1.2. GH

The proportion of subjects who achieve a serum GH<5.0 ng/mL, and separately GH<2.5 ng/mL, at Week 13 will be analyzed using the same methods specified in Section **Error! Reference source not found.**. for the Full, PP, and Completers Analysis Sets. GH response rates will also be analyzed for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set.

Changes in serum GH as specified in Section 2.3.3.1.2 will be presented and analyzed in the same manner specified for the primary endpoint (Section 8.7) for the Full, PP, and Completers Analysis Sets. Changes in serum GH will also be analyzed for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set.

The same dose response analysis specified for IGF-1 (Section 8.9.1.1) may be conducted for GH for the Full Analysis Set.

8.9.1.3. [redacted]

Changes in [redacted] levels as specified in Section 2.3.3.1.3 will presented and analyzed in the same manner specified for the primary endpoint (Section 8.7).

8.9.2. Patient and Investigator Reported Outcome Endpoint Analyses

8.9.2.1. Patient Assessed Symptoms of Acromegaly: [redacted]

[redacted]

8.9.2.2. Investigator Assessed Symptoms of Acromegaly

The number and percentage of subjects with each symptom present study entry is presented in Section 7.4. The number of and percentage of subjects whose symptom reduced in severity/grade, resolved, increased in severity/grade, or new occurrence will be presented at each visit by group and total for the Full Analysis Set.

The same summary will be presented for the most bothersome symptom specified at study entry.

8.9.2.3. [redacted]

[redacted]

8.9.2.4. [redacted]

[redacted]

8.9.2.5. Patient Global Impression

The number and percentage of subjects with each PGI-S score for each scheduled visit and the change in PGI-S scores will be presented by group and total for the Full Analysis Set and for the Group 1 Lanreotide vs Octreotide subgroup using the Efficacy Analysis Set.

In addition, responder analyses will be presented for the Full Analysis Set, where a responder is defined as PGI-S / PGI-I Score of very much improved or much improved and a non-responder as all other responses.

8.9.3. Pharmacokinetic (PK) Analyses

Plasma CRN00808 concentrations and elapsed time from the last CRN00808 dose taken will be listed. A summary of concentrations by CRN00808 dose for each timepoint will be presented. In addition, the percent change in CRN00808 concentration from end of CRN00808 treatment will be calculated for each subject.

Residual plasma concentration levels of Octreotide and Lanreotide will be presented in by-subject data listings. The percent change in concentration from Screening Visit 2 and separately the percent change from Week 13 (Visit 11) will be calculated for each subject.

PK concentrations will be reported to 3 significant figures.

9. SAFETY ANALYSES

Safety analyses will be conducted using the Safety Analysis Set.

No inferential comparison of safety endpoints will be performed, unless otherwise specified.

9.1. Extent of Exposure

The number and percentage of subjects exposed to each dose of CRN00808 will be presented for the Safety Analysis Set.

Duration of exposure is defined in days as the last date study drug administration – the first date study drug administration + 1. Duration of total CRN00808 exposure and exposure to each dose level will be summarized with descriptive statistics by CRN00808 dose using the Safety Analysis Set. In addition, duration of exposure will be summarized categorically for subjects exposed to CRN00808 by week, i.e. ≥1 week, …, ≥12 weeks, ≥13 weeks.

Treatment compliance will be calculated based on on-site/diary dosing and separately based on study drug accountability. Compliance based on the on-site dosing and at home dosing diary will be calculated as 100 x (total number of days with dosing / (last dose date – first dose date + 1)). Compliance based on study drug accountability will be calculated as 100 x ((total number of capsules dispensed – total number of capsules returned – 72 capsules [the dispensed overage]) / total number of capsules dispensed). Treatment compliance will be summarized with descriptive statistics using the Safety Analysis Set.

Compliance with fasting conditions will be presented in the data listings.

9.2. Adverse Events

An adverse event (AE) is any undesirable sign, symptom or medical condition, whether or not considered drug related and occurring after the moment of signing ICF. Pretreatment AEs are those AEs with a start date prior to the first administration of study drug. All AE summaries will be restricted to TEAEs, which are defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of study drug. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such.

Each summary will be presented by group and total. Separate summaries will be presented by each CRN00808 dose and total. TEAEs will be determined to have occurred on a specific dose based on the adverse event start date and dose titration dates. For example, if the adverse event starts on or after the first dose, before any dose titration, the adverse event will be counted as occurring on [redacted]; or if the adverse event starts on or after the first dose titration, before the second dose titration, the adverse event will be counted as occurring on [redacted] if the subject was up-titrated or [redacted] if the subject was not up-titrated. A similar process will be followed for all up and down titrations to assign an adverse event to a dose.

Any adverse events of COVID-19 will appear as per their MedDRA SOC Infections and infestations and PTs of either Coronavirus infection and/or Coronavirus test positive. Separate summary tables will not be produced.

Summaries that are displayed by SOC and PT will be ordered by descending order of total incidence of SOC and PT within each SOC. Summaries of the following types will be presented:

- Overall summary of AEs including the number and percent of subjects with at least one of the following:
  - Any TEAE
  - Severe TEAE
  - Serious TEAE
  - Fatal TEAE
  - Treatment-related TEAE
  - Treatment-related severe TEAE
  - Treatment-related serious TEAE
  - Treatment-related fatal TEAE
  - TEAE leading to study drug discontinuation or withdrawal from study
    - TEAE leading to study drug discontinuation
    - TEAE leading to withdrawal from study
- Subject incidence of TEAEs by MedDRA PT.
- Subject incidence of TEAEs by MedDRA SOC and PT.
- Subject incidence of TEAEs by maximum severity, MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Subject incidence of severe TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Subject incidence of related TEAEs by MedDRA SOC and PT. Related is defined as Relationship to IMP of “Possibly”, “Probably”, or “Definitely”. At each level of subject summarization, a subject is classified according to the closest relationship to study drug if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of related, severe TEAEs by MedDRA SOC and PT. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity will be considered severe for this summary. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs by MedDRA SOC and PT.
- Subject incidence of TEAEs leading to study drug discontinuation or withdrawal from study by MedDRA SOC and PT. This is a subset of the AEs where Discontinuation from the study due to AE? = “Yes” or Action Taken to IMP = “Drug Discontinued”.

All of the above tables will be repeated only for MedDRA PT, excluding MedDRA SOC.

The following listings will be presented by group and subject:

- All AEs
- SAEs (this is a subset of the AEs where serious is marked as "Yes")
- Severe AEs (this is a subset of AEs where severity is marked as Severe)
- Related AEs (this is a subset of the AEs where relationship marked as Possibly, Probably, or Definitely Related)
- AEs leading to study drug discontinuation or withdrawal from study by MedDRA SOC and PT. (this is a subset of the AEs where Discontinuation from the study due to AE? = "Yes" or Action Taken to IMP = "Drug Discontinued".
- Fatal AEs (this is a subset of the AEs where outcome is indicated as "Fatal")

9.3. Clinical Laboratory Evaluations

All laboratory assessments are given in protocol section 6.1.8. The data from the central lab is uploaded to the EDC to assist with safety review and assignment of clinical significance. Data from the central lab, i.e. the source data will be used for analyses. Laboratory parameters will be summarized in standard international (SI) system of units.

All clinical laboratory data will be presented in by-subject data listings.

9.3.1. Serum Chemistry, Hematology, and HbA1c

Quantitative serum chemistry, hematology, and HbA1c results for each scheduled visit, baseline through Week 17, and changes from Baseline will be summarized by group and total.

9.3.2. Shifts in CTCAE Grade

Quantitative laboratory tests will be assigned grades based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5, where applicable. Shifts in CTCAE grade from Baseline to worst on-treatment value, worst follow-up value, and worst on-study post- Baseline value will be presented by group and total. Denominators for percentages will be the number of subjects with non-missing data at the specific visit and Baseline.

In addition, for each laboratory test the number and percent of subjects with a lab value with CTCAE grade ≥3 and the number and percent of subjects with a CTCAE shift of ≥2 grades will be presented. Listings will be presented for any subject with a post- Baseline CTCAE grade 3 or 4 laboratory value. Normal ranges provided by the central laboratory will be presented in a separate listing.

Where applicable, if the quantitative criteria for grading are equivalent for two grades, only differentiated by clinical interventions, the clinical intervention will be ignored and the highest CTCAE grade will be used. If a value fits into multiple grades, the worst grade will be assigned.

9.3.3. Shifts in Normal Range

In addition, for laboratory tests that cannot be graded via CTCAE, shift tables (i.e., low-normal-high at baseline versus low-normal-high at post-baseline visit in a 3-by-3 contingency table) from Baseline to worst on-treatment value, worst follow-up value, and worst on-study post-Baseline value will be presented by group and total. Denominators for percentages will be the number of subjects with non-missing data at the specific visit and baseline.

9.3.4. Hormones

Hormone levels will be summarized at Baseline and Week 13 by group and total. In addition, change and percent change from Baseline will be presented.

9.3.5. Genotyping

The UGT1A1 genotype will be summarized with baseline characteristics (Section 7.2) and provided in a separate by-subject data listing.

9.4. Vital Signs

Vital sign parameters including systolic and diastolic pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), and body temperature (C) will be presented in a data listing.

Summaries of vital sign parameter results for each scheduled visit, baseline through Week 17, and changes from Baseline will be summarized by group and total. If a subject has repeat assessments at a specified visit, the last value will be used to calculate the change.

9.5. Ring Size, Weight and BMI

Ring size (mm), weight (kg) and BMI (kg/m^2) will be summarized at Baseline and each post-baseline visit through Week 17 by group and total. In addition, change and percent change from Baseline will be presented.

9.6. 12-Lead Electrocardiograms (ECGs)

ECGs measurements will be made in triplicate and assessed by a central reader. The data from the central reader is uploaded to the EDC to assist with safety review and assignment of clinical significance. Data from the central reader, i.e. the source data will be used for analyses. For summary purposes the mean of the three measurements will be used. If any of the three measurements are not available or additional measurements are available, the available measurements will be used. If one of the triplicates is the same date and time as first dose, the triplicate will be included in the calculation of TP Baseline.

ECG parameters including heart rate, PR interval, QRS duration, QT (uncorrected) interval, and QT interval corrected by the Fridericia's formula [QTcF] will be summarized from Baseline through Week 17 by group and total. In addition, change from baseline will be presented.

A categorical summary of the following abnormal QTcF values will be presented: >450 msec, >480 msec, and >500 msec. Change summaries will also be presented for measurements that represent a change of >30 msec and >60 msec. Categorical analyses will be presented from Baseline through Week 17 by group and total.

A separate listing for those subjects with any QTcF >450 msec or a QTcF change from Baseline >30 msec, based on the average of the triplicates, will be presented. All of the subject's values will be included in the listing and the observation(s) meeting criteria for inclusion will be flagged in the listing.

The investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant. Subjects whose interpretation shifts from normal to abnormal clinically significant or not clinically significant will be listed separately including description of the abnormality and any associated comments.

All ECG results will be presented in by-subject data listings.

9.7. Gall Bladder Ultrasound

The number and percentage of subjects with gallstones absent or present at Baseline and Week 13 will be presented by group and total. Any changes from Baseline to Week 13 will also be summarized as Newly Appeared and No Longer Present. Similar summaries will be presented for gall bladder sludge.

9.8. Other Safety Assessments

The following additional data will be provided in by-subject listings only:

- Physical examination findings based on body systems entered on the eCRF
- Screening outpatient Holter data collection details
- Pregnancy Testing including reproductive status
- Serology (HBV, HCV, HIV testing)
- Urine drug screen
- Head MRI/CT Scan
- Urinalysis
- Study drug dispensing and accountability
- Confirmation of tolerability for potential dose up-titration and potential dose titration CRF details

10. CHANGES TO PROTOCOL PLANNED ANALYSES

The Efficacy Analysis Set was modified to include on Group 1 subjects, excluding Group 2. Group 1 subjects may differ from Group 2 in terms of IGF-1/GH responses to switching from respective pre-trial medication regimens to paltusotine monotherapy. For this reason, the safety and efficacy profile should be considered separately by group.

The secondary endpoint of proportion of subjects with IGF-1 ≤ 1.0 × ULN at Week 13/EoT was clarified to only include subjects who start the study with IGF-1 ≤ 1.0 × ULN, i.e. limited to Groups 3, 4, and 5.

For both secondary endpoints of proportion of subjects with IGF-1 ≤ 1.0 × ULN at Week 13/EoT and proportion of subjects with IGF-1 ≤ 1.5 × ULN at Week 13/EoT, these were clarified to only use Week 13/EoT assessments and not use the mean of last two consecutive assessments. The mean of last two consecutive assessments (Week 11 and Week 13) will not be used as subjects who titrate to the full dose ([redacted]), may not be stabilized at the full dose by Week 11.

For endpoints which specified at Week 13, it was clarified the Week 13 value would be used for subject who complete treatment or End of Treatment value would be used for subjects who do not complete treatment.

The protocol specifies 90% CIs of the mean will be presented, instead the SAP includes 95% CIs.

To assess the protocol specified endpoint of the amount of increase in IGF-1 or GH levels 3 or more weeks after withdrawal of CRN00808, the change from end of CRN00808 treatment will be used (Sections **Error! Reference source not found.** and 2.3.3.1.2 respectively).

The protocol specified physical examination at each post-baseline study visit as an endpoint. However, any clinically significant findings are recorded as an AE. Therefore, results from physical examination are listed only.

Additional exploratory efficacy endpoints were added.

APPENDIX 1. DECISION TREE FOR INCLUDING RE-TESTED IGF-1 VALUES