Statistical Analysis Plan for Protocol CRN00808-02 (ACROBAT EVOLVE)

A double-blind, placebo-controlled, randomized withdrawal study to evaluate the safety, pharmacokinetics and efficacy of CRN00808 in patients with acromegaly that are responders to octreotide LAR or lanreotide depot (ACROBAT EVOLVE)

Investigational Product:	CRN00808
US IND Number:	137912
ClinicalTrials.gov Identifier:	NCT03792555
EudraCT Number:	2018-001833-42
Protocol Version and Date:	Version 3.0, 06 June 2019
Phase:	Phase 2
Methodology:	Double-Blind, Placebo-Controlled, Randomized Withdrawal Study
Sponsor:	Crinetics Pharmaceuticals, Inc. 10222 Barnes Canyon Road, Building #2 San Diego, CA 92121
Analysis Plan Date:	08 September 2020
Analysis Plan Version:	Final, Version 1.0

APPROVAL PAGE

Statistical Analysis Plan for Protocol CRN00808-02 (ACROBAT EVOLVE)

Analysis Plan Date: 08 September 2020

Analysis Plan Version: Final, Version 1.0

See last page for electronic signature manifestation	
Authored by: [redacted], DrPH [redacted] **Crinetics Pharmaceuticals, Inc.**	**Date**
Approved by:	
See last page for electronic signature manifestation	
[redacted], MD [redacted] **Crinetics Pharmaceuticals, Inc.**	**Date**
See last page for electronic signature manifestation	
[redacted], PhD [redacted] **Crinetics Pharmaceuticals, Inc.**	**Date**
See last page for electronic signature manifestation	
[redacted], MS [redacted] **Crinetics Pharmaceuticals, Inc.**	**Date**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
ACTH	adrenocorticotropic hormone
[redacted]	[redacted]
AE	adverse event
ANCOVA	analysis of covariance
ASD	Acromegaly Symptom Diary
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
EQ	EuroQol
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
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Term
[redacted]	[redacted]
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
RWP	Randomized Withdrawal Period
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
TP	Treatment Period
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 CRN00808-02 (ACROBAT EVOLVE) 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 10, 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 that are complete responders to parenteral octreotide LAR or lanreotide depot monotherapy;
- 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 double-blind, placebo-controlled, randomized withdrawal study is designed to evaluate the safety, PK and efficacy of CRN00808 in subjects with acromegaly that are responders to octreotide LAR or lanreotide depot and will consist of the following periods:

- Screening Period (4-6 weeks);
- Treatment Period (TP; up to 13 weeks);
  - Titration Period (9 weeks)
  - Randomized Withdrawal Period (RWP; 4 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

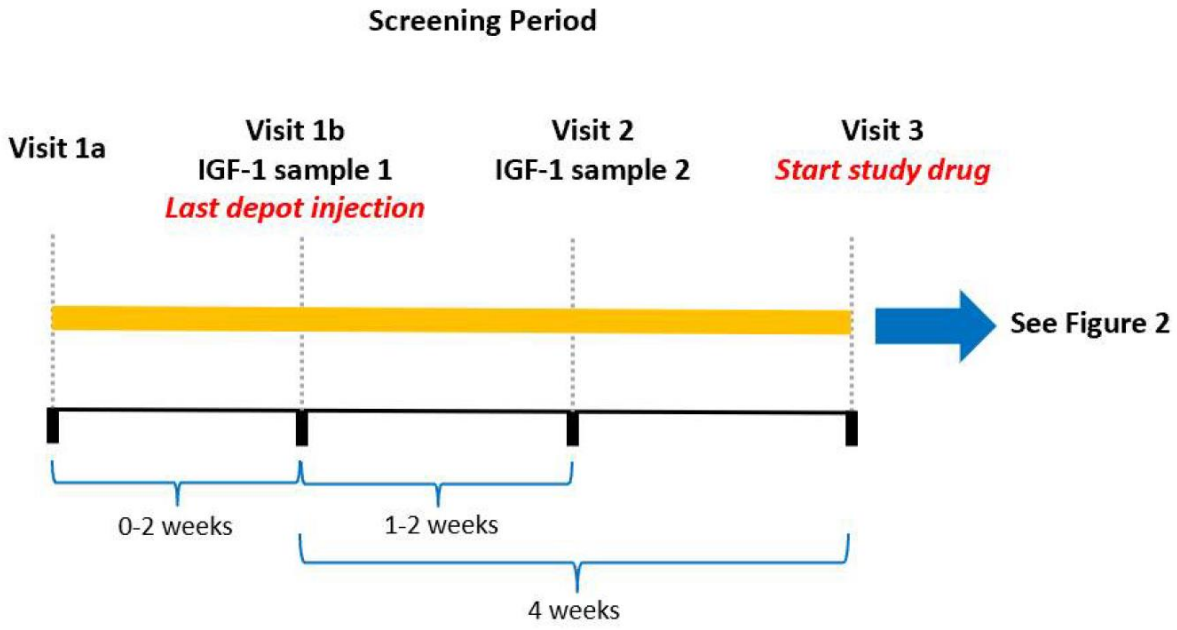
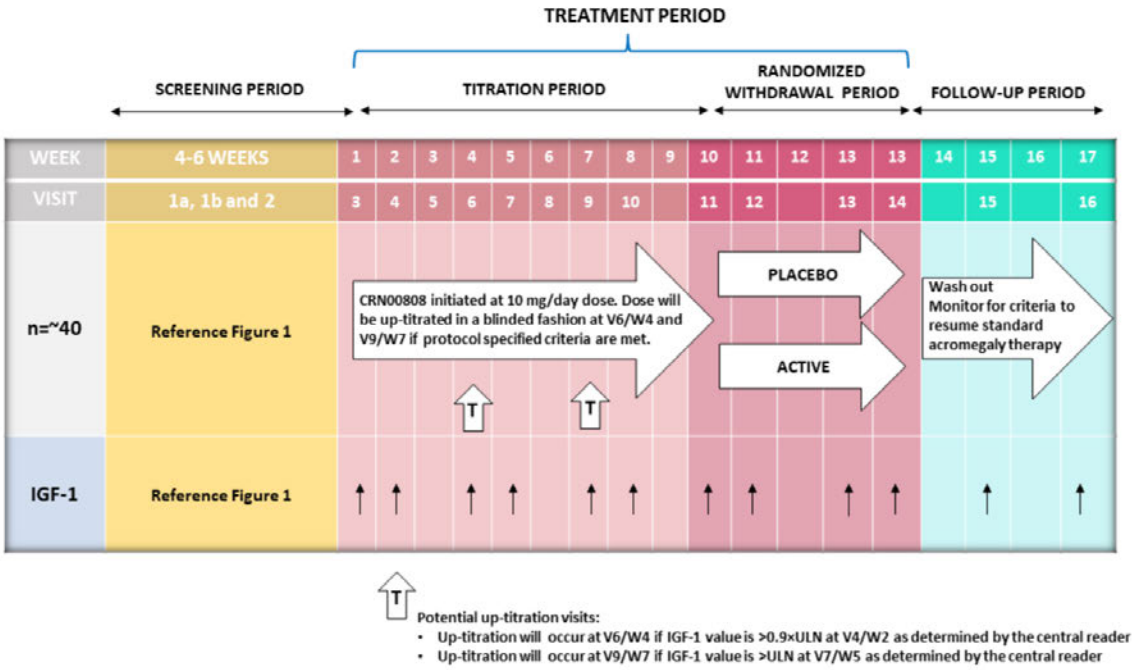


Figure 2: Overall Study Design



Approximately 40 subjects on stable doses of octreotide LAR or lanreotide depot for the treatment of acromegaly were to enter the TP in order to have approximately 36 randomized at Week 10 (Visit 11). However, a business decision was made to stop recruiting activity for this study as of 31MAR2020. The final number of subjects dosed in the TP will be 13. It is unknown how many will end up completing the RWP at the time of writing this document.

2.2.2. Study Population

Approximately 13 adult subjects entered into the TP because they meet all the inclusion and none of the exclusion criteria.

2.2.3. Study Drug

Study drug consists of CRN00808 or placebo.

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] and [redacted] capsules [[redacted] Size 2]) and will be orally administered in a double-blinded manner according to the randomization scheme on an identical schedule to those receiving CRN00808.

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. At Week 10 (Visit 11), subjects who are eligible for randomization will be randomly assigned, in a ratio 1:1 to one of the two treatment arms: CRN00808 or placebo. The assignments will be based on a pre-generated permuted-block randomization schedule. Randomization will be stratified based on pre-trial somatostatin therapy (i.e., octreotide LAR or lanreotide depot). Approximately 50% of the randomized subjects will have been treated with lanreotide depot prestudy.

Blinding will be assured by restricting access to the treatment codes to only those authorized to distribute blister card numbers to sites and to the central IGF-1 reader. The study drug is blinded and is provided in identical packaging for the study drug and placebo treatments. All instances of unblinding 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 endpoint is the proportion of subjects who meet IGF-1 responder criteria, defined as the mean of two consecutive IGF-1 measurements ≤ULN at Week 13 (Visit 13 and Visit 14). The mean of the IGF-1 values at Visit 13 and Visit 14 will be calculated for each subject, and rounded to two significant figures. If the mean is ≤ULN, the subject will be counted as a responder, otherwise if the mean is >ULN, the subject will be counted as a non-responder. If either Visit 13 or Visit 14 value is missing, the individual value (instead of the mean) will be used. If both Visit 13 and Visit 14 IGF-1 values are missing, the subject will be counted as a non-responder. Data from the central lab, i.e. the source data will be used for analyses.

2.3.2. Secondary Efficacy Endpoints

The secondary endpoints, in order of priority are:

2.3.2.1. Change in IGF-1 Levels between Week 10 and Week 13

The first key secondary endpoint is the change in IGF-1 levels between RWP Baseline / Week 10 and Week 13. The RWP Baseline / Week 10 value is the value taken prior to dosing in the RWP. The Week 13 value will be defined as the mean of the IGF-1 values at Visit 13 and Visit 14. If either the Visit 13 or Visit 14 value is missing, the individual value will be used instead of the mean. The change between the calculated Week 13 value and RWP Baseline / Week 10 value (Week 13 – Week 10) will be calculated for each subject. Data from the central lab, i.e. the source data will be used for analyses.

2.3.2.2. Change in GH Levels between Week 8 and Week 13

The second key secondary endpoint is the change in GH levels between RWP Baseline / Week 8 and Week 13. The RWP Baseline / Week 8 and Week 13 values will be defined as the mean of the three values obtained at the specified visit. If any of the three values are missing, the available values at the specified visit will be used to calculate the mean for that subject. The change between the calculated Week 13 value and calculated RWP Baseline / Week 8 value (Week 13 – Week 8) will be derived for each subject. Data from the central lab, i.e. the source data will be used for analyses.

2.3.2.3. Change in Patient Assessed Symptoms of Acromegaly as Measured by Total ASD Score between Week 10 and Week 13

The Acromegaly Symptom Diary (ASD) consists of 9 items (headache pain; joint pain; sweating; fatigue; weakness in legs; swelling; numbness or tingling; sleeping; short term memory), where the subject ranks the intensity from 0 – 10. The short term memory item was not part of the ASD in previous versions of the protocol (Version 1 and 2). In addition, previous versions of the protocol referenced swelling in the "hands, arms or legs", while the current protocol generally refers to swelling. Response to the sleeping item changed from previous versions of the protocol to the current protocol, from 0 = No difficulty sleeping and 10 = Worst possible difficulty sleeping to remove the word "sleeping" from the response for consistency with other item responses. For the purposes of analyses within this SAP, no adjustment for differences in question or response wording will be accounted for.

The total ASD score will be computed by adding each of the individual symptom intensities (headache pain; joint pain; sweating; fatigue; weakness in legs; swelling; numbness or tingling), therefore, the total ASD score can range from 0 - 70. If more than one diary is entered on a single day, the worst (i.e. the highest) score will be used in analyses. In the current protocol (Version 3), subjects are to complete the ASD daily beginning the day after Screening Visit 1b through Week 1/Day 1/Visit 3; daily beginning the day after Week 8/Visit 10 through Week 10/Visit 11; daily beginning the day after Week 11/Visit 12 through Week 13/Visit 14; and daily beginning the day after Week 15/Visit 15 through Week 17/Visit 16. The previous version of the protocol (Version 2), collected ASD daily after Screening Visit 1b. Only visits based on the current protocol (Version 3) will be considered for summaries, while all data will be listed.

The third key secondary endpoint is the change in the total ASD score between RWP Baseline / Week 10 and Week 13. The RWP Baseline / Week 10 value will be defined as the mean of the available total ASD score values on the 7 days prior to first dose in the RWP. The Week 13 value will be defined as the mean of the available total ASD score values 7 days prior to their last dose, inclusive of the date of last dose. Assessments used in the definition of Week 13 must be greater than 10 days after randomization. If there are only assessments in the first 10 days after randomization, then no imputation of missing data will be performed. If any of the 7 days are missing, the available, non-missing values will be used to calculate the mean. A minimum of 4 days should be available to calculate a mean. The change between the calculated Week 13 value and calculated Week 10 value (Week 13 – Week 10) will be derived for each subject.

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 calculated for each subject:

- In addition to the key secondary endpoint, change between RWP Baseline / Week 10 and each RWP scheduled visit value (i.e. Week 11, Week 13/Visit 13, and Week 13/Visit 14). The RWP Baseline / Week 10 value is the value taken prior to dosing in the RWP.
- Change between the TP Baseline value and each scheduled TP scheduled visit value through Week 13/Visit 14, and the mean of the last Week 13 visits (Visit 13 and Visit 14). TP Baseline is defined as the mean of all available values prior to first dose of study drug (Visit 1b, Visit 2, Visit 3).
- Change from end of CRN00808 treatment to 1, 2, 3, 4, 6, and 8 weeks after withdrawal of CRN00808. End of CRN00808 treatment for subjects randomized to placebo in the RWP is defined as the Week 10 visit, therefore, 1 week after withdrawal is defined as the Week 11 visit, 3 weeks after withdrawal is defined as the first Week 13 (Visit 13) visit, 4 weeks after withdrawal is defined as the second Week 13 (Visit 14) visit, and 6 and 8 weeks after withdrawal is defined as Week 15/Visit 15 and Week 17/Visit 16 respectively. End of CRN00808 treatment is defined as the Week 13/Visit 14 visit for those subjects who were not randomized into the RWP and continued treatment or those randomized to CRN00808 in the RWP, 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.

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

2.3.3.1.2. GH

The following changes in GH will be calculated for each subject:

- Change between the TP Baseline value and each scheduled TP scheduled visit value through Week 13/Visit 14. TP Baseline is defined as the mean of all available integrated values prior to the first dose of study drug (Visit 1b, Visit 2). TP visit values will be defined as the mean of the three values obtained at the specified visit. If any of the three values are missing, the available values at the specified visit will be used.
- Change from end of CRN00808 treatment to 4 and 8 weeks after withdrawal of CRN00808. End of CRN00808 treatment for subjects randomized to placebo in the RWP is defined as the Week 10 visit, therefore, 4 weeks after withdrawal is defined as the second Week 13 (Visit 14) visit, and 8 weeks after withdrawal is defined as Week 17/Visit 16 respectively. End of CRN00808 treatment is defined as the Week 13/Visit 14 visit for those subjects who were not randomized into the RWP and continued treatment or those randomized to CRN00808 in the RWP, therefore 4 weeks after withdrawal is defined as 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 be calculated using SI 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 changes in IGF-1 endpoints specified above for IGF-1 (Section 2.3.3.1.1) will also be calculated for [redacted] at applicable visits. Data from the central lab, i.e. the source data will be used for analyses.

2.3.3.2. Patient and Investigator Assessed Reported Outcomes Endpoints

2.3.3.2.1. Patient Assessed Symptoms of Acromegaly

The ASD is described in Section 2.3.2.3.

The following change in total ASD score and the change in each of the 9 individual ASD scores will be calculated for each subject (in addition to the key secondary endpoint):

- Change between the RWP Baseline/Week 10 and calculated TP Baseline value. The RWP Baseline / Week 10 value will be defined as the mean of the available total ASD score values on the 7 days prior to first dose in the RWP. The TP Baseline value will be defined as the mean of the available scores on the 7 days prior to first dose of study drug.
- Change from end of CRN00808 treatment to 4 weeks after withdrawal of CRN00808. End of CRN00808 treatment for subjects randomized to placebo in the RWP is defined as the Week 10 visit, therefore, 4 weeks after withdrawal is defined as the second Week 13 (Visit 14) visit. End of CRN00808 is defined as the Week 13/Visit 14 visit for those subjects who were not randomized into the RWP and continued treatment or those randomized to CRN00808 in the RWP, 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.

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 RWP Baseline/Week 10 and the change from RWP Baseline/Week 10 to RWP 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. Patient Assessed [redacted]

[redacted]

- Change between the Week 13 value and RWP Baseline/Week 10 value. RWP Baseline/Week 10 value is defined as the Visit 11 value. Week 13 value is defined as the Visit 14 value.
- Change between the Baseline/Week 10 value and TP Baseline value. TP Baseline is defined as the Day 1 (Visit 3) value. RWP Baseline/Week 10 value is defined as the Visit 11 value.
- Change from end of CRN00808 treatment to 4 weeks after withdrawal of CRN00808. End of CRN00808 treatment for subjects who do not enter the RWP or subjects randomized to placebo in the RWP is defined as the Week 10 visit. End of CRN00808 treatment for subjects randomized to CRN00808 in the RWP is defined as the Week 13/Visit 14 visit. For subjects randomized to CRN00808 in the RWP and who complete treatment in the RWP or subjects who do not enter the RWP, 4 weeks after withdrawal is defined as the Week 17/Visit 16 respectively. For subjects randomized to placebo in the RWP, 4 weeks after withdrawal is defined as the second Week 13 (Visit 14) visit. For subjects who withdraw early and have follow up visit, the value will be included as 4 weeks after withdrawal.

2.3.3.2.4. Patient Assessed [redacted]

[redacted]

[redacted]

2.3.3.2.5. [redacted]

[redacted]

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 or lanreotide will be measured for each subject throughout the study. Values 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 treatment emergent adverse events (TEAEs).

3. SAMPLE SIZE JUSTIFICATION

The sample size is justified with respect to the number of subjects meeting criteria to be randomized. With 36 randomized subjects, assuming a 60% response rate in the CRN00808 arm and a 10% response rate in the placebo arm (allocation ratio between two arms 1:1), the exact power to conclude superiority of the CRN00808 arm over placebo, applying an exact unconditional score test at a significance level of 5% (two-sided) is 92.2%. No adjustment for dropout rate was made because enrollment will continue until approximately 36 subjects with IGF-1 <ULN are randomized in the RWP. The exact power was computed based on the binomial distribution by evaluating all possible (N1+1) (N2+1) outcomes, weighted by their probability of occurrence for given true R1, R2 response rates in the two arms (0.6 and 0.1, respectively).

Recruiting activity for this study was stopped as of 31MAR2020. The final number of subjects dosed in the TP will be 13. At the time of writing this document, it was unknown how many subjects completed the RWP.

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. Summary statistics for each treatment will be presented, as well as two-sided 95% CIs comparing groups will be provided.

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 the 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 the 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.

Dates will be presented on the listing as recorded, without imputation. 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.

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 treatment groups:

- Paltusotine (CRN00808): To be used for ITT, mITT, and Safety summaries
- Placebo: to be used for mITT and Safety summaries
- Total: to be presented for all summaries except efficacy summaries

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], and Total.

4.7. Visits

4.7.1. Windows

Nominal, scheduled visits will be used for all by-visit analyses, visit windows will not be calculated for scheduled visits. Each visit will be denoted by its visit "Week " and "Visit" number, e.g. Week 2 (Visit 4). 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 for on treatment assessments and

Table 2 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. Any unscheduled visits assessments during screening, i.e. prior to the first dose of CRN00808, will not be windowed.

Table 1: Treatment Period Visit Windows, Except [redacted]

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
TP Baseline (Visit 3)[b]	1	See Section 4.7.3	
TP Week 2 (Visit 4)	8	2	15

Target Scheduled Visit	Target Study Day [a]	Analysis Window Study Day [a]	
		Low	High
TP Week 4 (Visit 6)	22	16	24
TP Week 5 (Visit 7)	29	25	36
TP Week 7 (Visit 9)	43	37	45
TP Week 8 (Visit 10)[c]	50	46	57
RWP Baseline / Week 10 (Visit 11) [b, d]	64	58	68
RWP Week 11 (Visit 12)	71	69	78
RWP Week 13 (Visit 13)	85	79	86
RWP Week 14 (Visit 14)	91	87	95

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

[b] Baseline is defined in Section 4.7.3.

[c] Also the RWP Baseline for GH.

[d] Only includes assessments PRIOR to randomization.

[e] Also used for assessments only obtained at Visit 14. Visits used for Week 13, must not be used for FP Week 15.

Table 2: 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

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, TP Baseline is defined as the mean of all available values prior to first dose of study drug (Visit 1b, Visit 2, Visit 3). For GH, TP 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, the TP Baseline value 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, TP Baseline is as the last non-missing value prior to the first dose of CRN00808 and RWP Baseline is the last non-missing value prior to the first dose of in the RWP.

For IGF-1 and IGBP-3, the RWP Baseline / Week 10 value is the value taken prior to dosing in the RWP. For GH, the RWP Baseline / Week 8 values will be used for TP Baseline. For ASD, the RWP Baseline / Week 10 value will be defined as the mean of the available total ASD score values on the 7 days prior to first dose in the RWP.

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 study drug administration may also be considered in the calculation of baseline observations.

5. ANALYSIS SETS

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

- The Intent-to-Treat (ITT) Analysis Set will include all subjects who received at least one dose of the study drug. The ITT Analysis Set will be used for analyses of some of the secondary and exploratory efficacy endpoints. During the RWP, subjects will be included in the treatment group to which they were randomized. Data from all subjects dosed prior to RWP, regardless of eligibility to randomize, will be pooled.
- The Modified Intent-to-Treat (mITT) Analysis Set will include all subjects from ITT who were randomized and dosed in the RWP. The mITT Analysis Set will be used for the primary analysis of all efficacy endpoints. Subjects will be included in the treatment group to which they were randomized.
- The Safety Analysis Set will include all subjects who received at least one dose of study drug. The Safety Analysis Set will be used for all safety analyses. Treatment group assignments for safety analyses during the RWP will be based on the treatment that was received (if this differs from the randomized treatment). Data from all subjects dosed prior to RWP, regardless of eligibility to randomize, will be pooled.

The Safety and ITT Analysis Sets are the same with the exception of using the actual treatment (Safety) versus the randomized treatment (ITT), in case a subject receives a treatment different than what he/she was randomized to. If the analysis sets are identical, TFLs will use the ITT Analysis Set.

6. EXAMINATION OF SUBGROUPS

Due to the small sample size, no summaries by subgroup will be presented.

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 randomized with reasons for screen failure, the number treated in the Titration Period of the TP, the number randomized to the RWP, the number randomized and not treated in the RWP, the number in each Analysis Set, the number who withdraw from the study prior to completing the study 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.

By-subject data listings of all the above study disposition data including randomization schedule with stratification factor, 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

The following demographic variables and associated subgroups will be summarized:

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

Other baseline characteristics, from TP 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

Demographics and baseline characteristics will be presented by treatment and overall for ITT, mITT, and Safety Analysis Sets. If the ITT and Safety Analysis Sets are equivalent, only the ITT Analysis Set will be included.

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 and associated subgroups will be summarized:

- Duration (months) since acromegaly diagnosis from informed consent date
    - <Median vs ≥Median
- 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 Treatment (Octreotide LAR vs Lanreotide Depot)
    - Doses pre-trial acromegaly treatments administered as recorded on the Concomitant Medications eCRF. 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.

Where the median is specified as the cut point, the median of the total study population at TP Baseline will be used.

Baseline disease characteristics will be presented by treatment and overall for the ITT, mITT, and Safety Analysis Sets. If the ITT and Safety Analysis Sets are equivalent, only the ITT Analysis Set will be included.

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

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

7.5. General Medical History

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

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 treatment or dose information. Important protocol deviations include, but are not limited to

- Subjects who entered the study, or RWP, even though they did not satisfy the entry criteria.
- Subjects who received the wrong treatment or 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 treatment using the ITT 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.

Non-pharmacological treatments will be listed separately. Pretreatment, prior and new concomitant medications will be listed.

8. EFFICACY ANALYSES

All efficacy analyses will use the mITT Analysis Set. Exploratory analyses will also use the ITT Analysis Set.

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

8.1. Adjustments for Covariates

For comparison of treatment groups with respect to change and percent change, rank analysis of covariance (ANCOVA) models will be used. The corresponding ranked TP Baseline or RWP Baseline/Week 10 value will be used as a covariate in the model.

8.2. Handling of Dropouts or Missing Data

The following methods will be implemented to address missing data for relevant primary, key 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, regardless of treatment group.

8.2.2. Continuous Endpoints

Due to the small sample sizes, a simple approach to imputation of continuous endpoints will be employed. Only end of treatment period visits will be imputed, i.e. Week 8/Visit 10 (GH only), Week 10/Visit 11, and Week 13/Visit 14.

For IGF-1 and GH, subjects who missed a visit will also have their missing visit values imputed using last observation carried forward (LOCF). Visit values will only be carried forward within the same study period.

- Only TP visit values prior to randomization in the RWP will be used for missing visit values after Week 1/Day 1/Visit 3 and before Week 10/Visit 11.
- Only RWP visit values will be used for missing visit values after Week 10/Visit 11 up to Week 13/Visit 14.
- Follow up visit (FP Week 15 and FP Week 17) data will not be imputed.

For analyses using a rank ANCOVA, the value will be imputed using LOCF prior to ranking.

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

8.3. Interim Analyses and Data Monitoring

8.3.1. Interim Analysis

No interim analyses are planned for this study.

8.4. Multicenter Studies

The randomization is not stratified by site. Likewise, analyses of efficacy data will not be stratified by study site. The number and percentage of subjects randomized by geographical region and study site will be summarized by treatment group and for all subjects.

8.5. Use of an "Efficacy Subset" of Patients

Not Applicable.

8.6. Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons will be made due to the small sample size.

8.7. Primary Efficacy Analysis

The primary efficacy analysis will test the following hypothesis:

- H_0: The percentage of IGF-1 responders at Week 13 is equal between placebo and CRN00808.
- H_1: The percentage of IGF-1 responders at Week 13 is different between placebo and CRN00808.

The primary efficacy analyses, using the mITT Analysis Set, will compare placebo and CRN00808 on the distribution of responders at Week 13, at alpha level of 0.05, using the exact unconditional score test for the difference between two binomial proportions. The number and percentage, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category (response, non-response) will be presented by treatment.

8.7.1. Additional Analyses of the Primary Endpoint

Sensitivity analyses using observed cases will be presented.

The number and percentage, with associated two-sided exact (Clopper-Pearson) 95% CIs, of subjects in each category (response, non-response) will be presented by treatment using observed cases at each scheduled visit starting at TP Baseline through FP Week 17 (Visit 16) for the ITT Analysis Set. Response is defined as IGF-1 ≤ULN and non-response is defined as >ULN. Subjects missing IGF-1 measurement are counted as a non-responder.

8.8. Key Secondary Efficacy Analyses

Key secondary efficacy endpoints are described in Section 2.3.2 and missing data conventions in Section 8.2.

8.8.1. Change in IGF-1 Levels Between Week 10 to Week 13

The key secondary efficacy analysis will test the following hypotheses:

- H_0: The median IGF-1 change from RWP Baseline/Week 10 to Week 13 is equal between placebo and CRN00808.
- H_1: The median IGF-1 change from RWP Baseline/Week 10 to Week 13 is different between placebo and CRN00808.

CRN00808 and placebo will be compared for the mITT Analysis Set on change from RWP Baseline/Week 10 to Week 13 using a rank ANCOVA model including fixed effects for randomization strata and treatment, and with the ranked RWP Baseline/Week 10 value included as a covariate. The Hodges-Lehman estimate of the median treatment difference with associated 95% CI will be presented. Descriptive statistics of ranks will not be presented.

Descriptive statistics for IGF-1 values, change from RWP Baseline/Week 10, and percent change from RWP Baseline/Week 10 will be presented for the RWP and FP visits by treatment.

Sensitivity analyses using observed cases will be presented.

8.8.2. Change in GH Levels Between Week 8 and Week 13

The key secondary efficacy analysis will test the following hypotheses:

- H_0: The median GH change from RWP Baseline/Week 8 to Week 13 is equal between placebo and CRN00808.
- H_1: The median GH change from RWP Baseline/Week 8 to Week 13 is different between placebo and CRN00808.

CRN00808 and placebo will be compared for the mITT Analysis Set on change from RWP Baseline/Week 8 to Week 13 using a rank ANCOVA model including fixed effects for randomization strata and treatment, and with the ranked RWP Baseline/Week 8 value included as a covariate. The Hodges-Lehman estimate of the median treatment difference with associated 95% CI will be presented. Descriptive statistics of ranks will not be presented.

Descriptive statistics for GH values, change from RWP Baseline/Week 8, and percent change from RWP Baseline/Week 8 will be presented for the RWP and FP visits by treatment.

Sensitivity analyses using observed cases will be presented.

8.8.3. Change in Total ASD Score Between Week 10 and Week 13

The key secondary efficacy analysis will test the following hypotheses:

- H_0: The median total ASD score change from RWP Baseline/Week 10 to Week 13 is equal between placebo and CRN00808.
- H_1: The median total ASD score change from RWP Baseline/Week 10 to Week 13 is different between placebo and CRN00808.

CRN00808 and placebo will be compared for the mITT Analysis Set on change from RWP Baseline/Week 10 to Week 13 using a rank ANCOVA model including fixed effects for randomization strata and treatment, and with the ranked RWP Baseline/Week 10 value included as a covariate. The Hodges-Lehman estimate of the median treatment difference with associated 95% CI will be presented. Descriptive statistics of ranks will not be presented.

Descriptive statistics for total ASD scores and change from RWP Baseline/Week 10 will be presented for each RWP visit by treatment.

8.9. Exploratory Efficacy Analyses

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

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 using observed cases, in the same manner as specified for the first secondary endpoint (Section 8.8.1) for the mITT Analysis Set, and separately without hypothesis testing for the ITT Analysis Set.

8.9.1.2. GH

Changes in serum GH as specified in Section 2.3.3.1.2 will presented using observed cases, in the same manner as specified for the first key secondary endpoint (Section 8.8.1) for the mITT Analysis Set, and separately without hypothesis testing for the ITT Analysis Set.

8.9.1.3. [redacted]

[redacted] and changes in [redacted] will presented in a by-subject listing only.

8.9.2. Patient and Investigator Assessed Reported Outcomes Endpoint Analyses

8.9.2.1. Patient Assessed Symptoms of Acromegaly: [redacted]

The change in the [redacted] will be presented using the same methods specified in Section 8.8.3 for the mITT Analysis Set, and separately without hypothesis testing for the ITT Analysis Set.

8.9.2.2. Investigator Assessed Symptoms of Acromegaly

Investigator assessed symptoms of acromegaly will be presented in a by-subject listing only.

8.9.2.3. [redacted]

[redacted] index score, VAS, and each of the 5 dimension scores and their respective changes will be presented in a by-subject listing only.

8.9.2.4. [redacted]

[redacted] each of the 22 individual items, and their respective changes will be presented will be presented in a by-subject listing only.

8.9.2.5. [redacted]

[redacted] will be presented in a by-subject listing only.

8.9.3. Pharmacokinetic (PK) Analyses

Plasma CRN00808 concentrations and elapsed time from the last CRN00808 dose taken will be listed. The results at each visit and the percent change in CRN00808 concentration from end of CRN00808 treatment to each visit 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. The number and percentage of subjects on each CRN00808 dose when entering the RWP will be presented for the mITT 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) / 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 AE summary will be displayed

1) For All CRN00808 dosed subjects and by CRN00808 dose using the Safety Analysis Set for any AE occurring after first dose of CRN00808
2) By treatment for the Safety Analysis Set for any AE occurring on or after the date of first dose of double-blind study drug in the RWP

Each summary will be presented by treatment 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 CRN00808 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 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 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 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".

The following listings will be presented by treatment 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. Quantitative clinical chemistry, hematology, coagulation, and urinalysis laboratory tests will be assigned grades based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, where applicable. The by-subject data listings will include flags for out of range (L for Low and H for High) and NCI CTCAE grade (G1, G2, G3, G4).

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

Additional listings for each laboratory category will be presented for any subject with a post- TP Baseline CTCAE grade 3 or 4 laboratory value.

Normal ranges provided by the central laboratory will be presented in a 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.

9.3.1. Serum Chemistry, Hematology, and HbA1c

Quantitative serum chemistry, hematology, and HbA1c results for each scheduled visit, TP baseline through FP Week 17 (Visit 16), and changes from TP Baseline will be listed using the Safety Analysis Set. Similarly, changes from RWP Baseline/Week 10 through FP Week 17 (Visit 16), will be listed separately using the Safety Analysis Set.

9.3.2. Hormones

Hormone levels of free triiodothyronine hormone (fT3), free thyroxine hormone (fT4), anti-thyroid antibody, thyroid stimulating hormone (TSH), cortisol, adrenocorticotropic hormone

(ACTH), lutenizing hormone (LH), follicle stimulating hormone (FSH) and prolactin will be assessed at Screening (Visit 1b), Week 10 (Visit 11), and Week 13 (Visit 14).

Hormone levels will be listed using the Safety Analysis Set. In addition, change and percent change from TP Baseline will also be presented. Similar listings will be presented including changes from RWP Baseline/Week 10 to Week 13.

9.3.3. 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 body temperature (C), systolic and diastolic pressure (mmHg), pulse rate (beats/min) and respiratory rate (breaths/min) will be presented in a data listing using the Safety Analysis Set.

Listings will include change from TP Baseline through FP Week 17 (Visit 16). Similar listings will be presented for changes from RWP Baseline/Week 10 to each post- RWP Baseline/Week 10 visit through FP Week 17 (Visit 16). 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 presented in a data listing. In addition, change and percent change from TP Baseline will be also be included. Similar listings will be presented for changes from RWP Baseline/Week 10 to each post- RWP Baseline/Week 10 visit through FP Week 17 (Visit 16).

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. 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 listed for each triplicate measurement and the average of the triplicates using the Safety Analysis Set. In addition, change from baseline will be presented. Similar listings will be presented from RWP Baseline/Week 10 to each post- RWP Baseline/Week 10 visit through FP Week 17.

A separate listing for those subjects with any QTcF >450 msec or a QTcF change from TP 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.

The investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant. Subjects whose interpretation shifts from normal at TP Baseline to abnormal clinically significant or not clinically significant post TP Baseline 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

Gall bladder ultrasound data for absence or presence of gallstones or gall bladder sludge will be listed including any changes as Newly Appeared and No Longer Present.

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

Given the reduced, small sample size, the Per Protocol Analysis Set was removed.

The protocol includes change from W10 to W13 in GH, however, since GH is not measured at W10, this endpoint will not be evaluated.

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.

To assess the protocol specified endpoint of the amount of increase in IGF-1 or GH levels after withdrawal of CRN00808, the change from end of CRN00808 treatment will be used.

The following exploratory endpoints will be listed only, instead of being summarized, due to the small sample size:

- Changes from baseline in serum GH, IGF-1, and [redacted] levels measured at W10 and W13
- compared to baseline (D1; [V2 for GH])
- Change from baseline in [redacted] score at W10 and between W10 and W13
- Change from baseline in [redacted] at W10 and between W10 and W13
- Change in investigator assessed symptoms of acromegaly between W10 and W13
- Change from baseline in investigator assessed symptoms of acromegaly at W10
- Change in [redacted] scores between W10 and W13
- Change from baseline in [redacted] scores at W10
- [redacted] scores at W10 and W13.

The following exploratory endpoints will not be summarized, due to the small sample size:

- Proportion of subjects who achieve serum GH <5.0 ng/mL at W13
- Proportion of subjects who achieve serum GH <2.5 ng/mL at W13
- Time to loss of response (IGF-1 >ULN) after withdrawal of CRN00808
- Increase in serum [redacted] levels 3+ weeks after withdrawal of CRN00808.