Official Title:	A Randomized, Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Acromegaly Treated with Long-acting Somatostatin Receptor Ligands
NCT Number:	NCT04837040
Document Date:	Statistical Analysis Plan Version: 3.0 07 AUG 2023

STATISTICAL ANALYSIS PLAN

Protocol Number:	CRN00808-09
Study Title:	A Randomized, Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Acromegaly Treated with Long-acting Somatostatin Receptor Ligands
Study Period:	Randomized Control Phase and Open-label Extension Phase
Development Phase of Study:	3
Statistical Analysis Plan based on Protocol Version:	Version 3.0, 14 SEP 2021
Russian Specific Protocol:	Version 4.0, 22 NOV 2021
Statistical Analysis Plan Date:	07 AUG 2023
Statistical Analysis Plan Version:	V3.0

SAP Approval

Authored and Approved by:

See last page for electronic signature manifestation

SIGNATURE & DATE:

[redacted]

Reviewed and Approved by:

See last page for electronic signature manifestation

SIGNATURE & DATE:

[redacted]

See last page for electronic signature manifestation

SIGNATURE & DATE:

[redacted]

Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment except for minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

SAP Change History

Version	Date	Summary of Changes	Author
1.0	08JUL2022	Original document	[redacted]
2.0	21MAR2023	Major changes: 1. Baseline definitions for IGF-1, GH, and ASD are modified in Section 6.2.2; 2. Multiple imputations for efficacy endpoints are removed from Sections 6.2.5 and 6.10.3.1; 3. Proportion of participants with GH <1 ng/mL is moved to the end of the fixed sequence testing procedure in Section 6.2.7; 4. Worst rank ANCOVA model on change from baseline IGF-1 is replaced by ANCOVA model in Section 6.10.3.1; 5. 25% Tumor reduction in volume (Section 6.10.4.13) is combined with change from baseline in residual tumor volume; 6. Analyses on TEAE for paltusotine dose and weekly interval groups are removed from Section 6.11.2 7. Add TEAEs summary under study treatment and rescue medications separately in Section 6.11.2; 8. Shift in normal range is removed in Section 6.11.3. 9. Rounding criteria of IGF-1 endpoints for all but primary efficacy removed. Other minor changes including consistency on wording/terminology are also made throughout the document.	[redacted] providing updates for [redacted]
3.0	07AUG2023	Major changes: 1. Add the analyses for the open-label extension phase in Section 6.10.5. 2. Add multiple imputations for the secondary efficacy endpoint of change from Baseline in IGF-1xULN as the sensitivity analysis in Section 6.10.3.1.	[redacted] and [redacted]

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

[redacted]	[redacted]
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASD	acromegaly symptoms diary
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
C	Celsius
CI(s)	confidence interval(s)
COVID-19	coronavirus disease 2019
CS	clinically significant
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DC	discontinuation
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
EOR	End of Randomized Controlled
EOT	End of Randomized Treatment
[redacted]	[redacted]
FAS	full analysis set
GH	growth hormone
HR	heart rate
ICH	International Council on Harmonization
IGF-1	insulin-like growth factor-1
IQR	interquartile range
IRT	interactive response technology
LOCF	last observation carried forward
LOESS	locally-estimated scatterplot smoothing
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities

mmHg	millimeter of mercury
MNAR	missing not at random
MRI	magnetic resonance imaging
ms	millisecond
OLE	open-label extension
PATHFNDR-1	CRN00808-09
PD	protocol deviation
[redacted]	[redacted]
pH	potential of hydrogen
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PPS	per-protocol analysis set
PT	preferred term
QoL	quality of life
QTcF	absolute QT interval corrected for heart rate by Fridericia's formula
RC	randomized controlled
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SD	standard deviation
SI	International system of units
SOC	system organ class
SRL	somatostatin receptor ligand
SS	safety analysis set
TB	total bilirubin
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
[redacted]	[redacted]
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WHODrug Global	World Health Organization Drug Global Dictionary

2. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods to be implemented during the analyses of Study CRN00808-09 (PATHFNDR-1) data collected within the scope of the protocol. The purpose of this plan is to provide details on analysis populations, how variables will be derived, how missing data will be handled, as well as details on statistical methods to analyze safety and efficacy data. If there are any deviations from protocol planned analyses, these are documented in Section 8, and the SAP takes precedence.

This 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 the earliest of conducting an interim analysis or unblinding the database. 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[1], ICH E9 (R1)[2] guidelines, and ICH E3[3].

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.

This SAP is for both the Randomized Controlled (RC) Phase and the Open-label Extension (OLE) Phase of the study.

3. STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety and efficacy of paltusotine versus placebo on Insulin-like growth factor-1 (IGF-1) response in acromegaly participants treated with long-acting somatostatin receptor ligands (SRL).

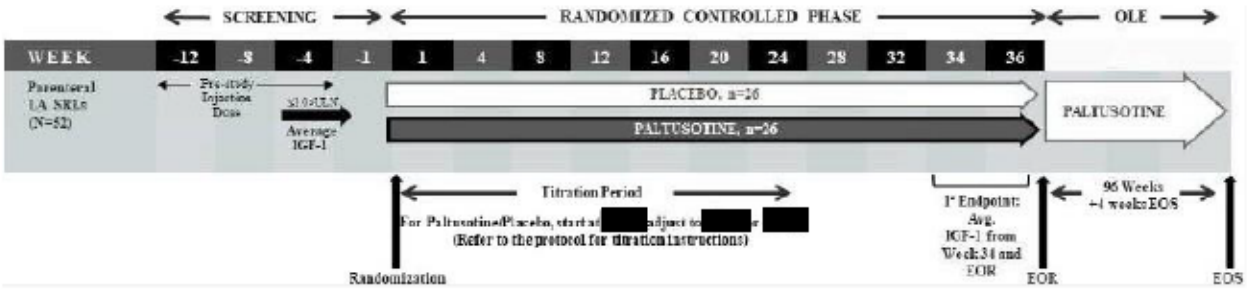
Secondary objectives are to evaluate the effects of paltusotine versus placebo on IGF-1 level, growth hormone (GH) response, and acromegaly symptoms.

4. STUDY DESIGN

4.1 Overall Study Design

This is a randomized, placebo-controlled, multi-center study. The study includes a Screening Period of up to 12 weeks for most participants. Participants will receive two to three IGF-1 measurements during screening. If the mean of these measurements is ≤1.04×upper limit of normal (ULN) after rounding to two decimal places, then the participant meets IGF-1 eligibility criteria. After the Screening Period, participants will be randomly assigned in a 1:1 ratio to receive either paltusotine or placebo for 36 weeks of treatment. At the end of the RC Phase (EOR), participants, who in the opinion of the Investigator, may benefit from treatment with

paltusotine, may be enrolled in a long-term, OLE for up to 96 weeks. During the OLE, all participants will receive paltusotine.



4.1.1 Schedule of Visits and Assessments

The schedule of assessments can be found in Sections 1.2 and 1.3 of the protocol and Sections 1.2, 1.3, and 1.4 of the Russia specific protocol.

4.1.2 Method of Assigning Participants to Treatment Groups

Participants will be randomized to study treatment, using an interactive, automated system which has been validated for the intended use under the International Society of Pharmaceutical Engineers Good Automated Manufacturing Practice guidelines, 21 CFR 11 (FDA regulation for Electronic Records and Electronic Signatures) and the ICH Guidance E6[4].

Randomization will be performed using a fixed-block randomization scheme. The randomization scheme will be generated prior to the initiation of the study by an independent statistician/programmer at Abond CRO, who is not a member of the study team; all Investigators and the study team will not be aware of the block size of [redacted] and prior treatment (lanreotide or octreotide).

4.1.3 Blinding

The Sponsor, the CRO, the investigator, study site personnel and participants will be blinded to the treatment assignment during the RC Phase. The randomization schedule will be kept strictly confidential and accessible only to authorized persons. Only when the RC Phase has been completed, the protocol deviations (PDs) determined, and the study database locked will the randomization schedule be made available for unblinding and analysis.

The Interactive Response Technology (IRT) System will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a participant's intervention assignment unless this could delay

emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

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

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is:

- Proportion of participants who maintain biochemical response in IGF-1 (≤1.0×ULN) at EOR

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Change from Baseline to EOR in IGF-1×ULN
- Proportion of participants with GH <1.0 ng/mL at Week 34, out of those who had GH <1.0 ng/mL at Baseline
- Change from Baseline to EOR in Total Acromegaly Symptoms Diary (ASD) score

5.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows.

RC Phase

- Change from Baseline to Week 34 in GH
- Proportion of participants who receive rescue therapy during the RC Phase
- Proportion of participants with IGF-1 <1.3×ULN at EOR
- Proportion of participants with GH <2.5 ng/mL at Week 34, out of those who had GH <2.5 ng/mL at Baseline
- Change from Baseline in residual tumor volume at EOR
- Time from randomization to first IGF-1>1×ULN for 2 consecutive visits

- Time from randomization to first IGF-1≥1.3×ULN for 2 consecutive visits
- Change from Baseline to EOR in [redacted][5] [redacted]
- [redacted] at EOR
- Change from Baseline to EOR in [redacted]
- Change from Baseline to EOR in [redacted]
- [redacted] at EOR
- Pharmacokinetic (PK) concentration parameters
- Proportion of participants who achieve IGF-1≤1.0×ULN and GH<1.0 ng/mL at EOR
- Proportion of participants who achieve IGF-1≤1.0×ULN and GH<2.5 ng/mL at EOR
- Proportion of participants who achieve IGF-1<1.3×ULN and GH<1.0 ng/mL at EOR
- Proportion of participants who achieve IGF-1<1.3×ULN and GH<2.5 ng/mL at EOR
- Percentage of participants with >25% reduction in tumor volume from Baseline to EOR

OLE Phase

- Proportion of participants with IGF-1 ≤1.0×ULN and < 1.3×ULN at each visit in the OLE phase
- Change from OLE Baseline in IGF-1×ULN to the visits in the OLE phase
- Proportion of participants with GH <1.0 ng/mL at each visit in the OLE phase, out of those who had GH <1.0 ng/mL at OLE Baseline
- Change from OLE Baseline in Total ASD score to the visits in the OLE phase
- Change from OLE Baseline in GH to the visits in the OLE phase
- Proportion of participants who received permitted adjunctive standard acromegaly treatment during the OLE phase
- Proportion of participants with GH <2.5 ng/mL at each visit in the OLE phase, out of those who had GH <2.5 ng/mL at OLE Baseline
- Change from OLE Baseline in residual tumor volume to the visits in the OLE phase
- Change from OLE Baseline in [redacted]
- Change from OLE Baseline in [redacted] to

the visits in the OLE phase

- Change from OLE Baseline in [redacted] to the visits in the OLE phase
- [redacted] at EOT in the OLE phase

5.2 Safety Endpoints

The safety endpoints are as follows:

- Incidence of treatment-emergent adverse events (TEAEs), including SAEs and TEAEs that lead to discontinuation
- Change in safety parameters: clinical laboratory tests (hematology, serum chemistry, lipid panel, and hormones), vital signs, and 12-lead electrocardiogram (ECG) parameters
- Incidence of clinically significant changes from Baseline in abdominal (gallbladder) ultrasound results.

6. STATISTICAL AND ANALYTICAL PLANS

6.1 Data Sets Analyzed

Participants will be presented/summarized based on the participant population set.

6.1.1 Screen Failure Set

The screen failure set (SFS) will include all participants who signed informed consent and either discontinued or failed any screening or entry criteria needed to randomize. Since this analysis set should not receive treatment, it will only be used to show the details around why each participant did not meet eligibility.

6.1.2 Full Analysis Set

The Full Analysis Set (FAS) is defined from the intention-to-treat principle and will include all randomized participants. The FAS will be the primary analysis set used for efficacy analyses. Treatment assignment will be based on the randomized treatment.

The randomization number that is integrated into electronic data capture (EDC) from IRT will link to the randomization number in the randomization file generated by the independent statistician prior to study start. This file is generated to prospectively link each randomization number to a treatment group for the randomization. Once the database is locked, the independent biostatistician will send the randomization file to be merged with the EDC data to define the randomized treatment per participant.

6.1.3 Safety Analysis Set

The Safety Analysis Set (SS) will include all participants who received study drug with treatment assignment based on the treatment received. If a participant receives any amount of paltusotine then the participant will be assigned to the paltusotine group. The SS will be the primary analysis set used for safety analyses.

Drug dispensing unit IDs are assigned by IRT only and will be exported in the Drug accountability report. To determine what study drug was received per participant, subset to the dispensing unit ID where visit name is set to randomization (Day 1) and reconciled status is set to used. The drug dispensing unit number file that was generated by the independent statistician contains the drug unit number linked to treatment. Once the database is locked, the independent biostatistician will send the drug dispensing unit file to be merged with this IRT data. The treatment that is linked to the dispensing unit ID number will be used to define treatment received.

6.1.4 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPS) is defined as all randomized participants who completed the RC Phase of the study and received the dose that aligns with the randomized treatment, with no major PDs, and with at least 75% treatment compliance based on tablet counts. If a participant is treated with a drug that does not align with the randomized treatment, then the participant is excluded. This PPS will be used as a sensitivity analysis for the primary endpoint. Major PDs will be determined and signed off prior to database lock. They will be documented within the PD tracker.

Drug dispensing tablet counts are entered into IRT and will be exported in the Drug accountability report. If the treatment associated with this dispensing unit ID does not match the treatment linked to the randomization number, then the participant was not treated per the randomization. The treatment linked to the dispensing unit ID that was used will define treatment group for this analysis set. Tablet counts will be used to define compliance per Section 6.11.1.

6.1.5 OLE Safety Analysis Set (OLE SS)

The OLE SS will include all participants who received any amount of paltusotine in the OLE. The actual treatment assigned in RC phase will be used in the OLE phase. Participants who are rescued during the RC phase will be analyzed separately from those who completed the study treatment during the RC phase for selected endpoints.

6.2 General Methodology

All statistical processing will be performed using SAS® unless otherwise stated. An interim

analysis may be conducted depending on the pace of enrollment. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of participants in each category will be presented. For continuous parameters, descriptive statistics will include n (number of participants), mean, standard deviation (SD), interquartile range (IQR), median, minimum, and maximum. The coefficient of variation (CV) will also be presented for GH and IGF-1. Where applicable 95% confidence intervals (CIs) will also be calculated.

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 participants discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0.

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

The FAS will be the primary analysis set used for efficacy analyses and the PPS will be used as a sensitivity analysis for the primary endpoint. The SS will be the primary analysis set used for safety analyses. The OLE SS will be the analysis set for the OLE phase analyses.

All IGF-1 endpoints are defined from IGF-1×ULN

- IGF-1×ULN = IGF-1 result in ng/mL divided by IGF-1 ULN ng/mL for the subject age and sex

EOR for IGF-1×ULN will be calculated as the average of Week 34 and Week 36 rounded to two significant figures. If either value is missing, the available value at the specified visit will be rounded to two significant figures and used as EOR.

Integrated GH summaries will use the average of the five values obtained at the specified visit. If one or more of the five values are missing, the available values at the specified visit will be used to calculate the average.

6.2.1 Statistical Analysis

All analyses, tables, listings, and figures will be performed using SAS® Version 9.4 or later.

The standard operating procedures (SOPs) of the sponsor will be followed in the creation and quality control of all data displays and analyses.

6.2.2 Screening and Baseline Definitions

Screening IGF-1×ULN is defined as the mean of the measurements prior to Day 1.
Baseline is defined as the last non-missing assessment prior to first dose of study drug for all

assessments except IGF-1, GH, and ASD. For IGF-1, baseline is defined as the average of IGF-1×ULN values at Day 1 and all screening values collected prior to Day 1. For GH, baseline is defined as the average of all the measurements taken from fasting integrated GH samples at screening visit. Baseline ASD score (9 items) is derived from a weekly average of daily values where the weekly average is defined as the sum of each item seven days on or prior to Day 1 divided by the number of days on which the item is completed. Baseline Total ASD score is defined as the sum of the 7 items as defined in Section 6.10.3.3.

OLE baseline is defined as the last non-missing assessment prior to the first dose of study drug in OLE phase. For IGF-1, GH and ASD, OLE baseline will be defined consistent with this definition relative to the first dose of study drug in OLE phase.

6.2.4 Adjustments for Covariates

The stratification factors Screening IGF-1 groups [redacted] and prior treatment groups (lanreotide, octreotide) will be included in analysis models, as specified in Section 6.10. Other covariates, such as Baseline values of the correspondent parameters, will also be considered.

The screening IGF-1 groups and prior treatment groups used for the randomizations are captured in IRT. These IGF-1 groups should align with results captured in the central labs, and prior treatment groups should align with what is captured in prior acromegaly treatment in EDC. If these values do not align, then the results from the central labs and EDC should be used for the analysis.

6.2.5 Handling of Discontinuations or Missing Data

In general, missing data will not be imputed unless otherwise specified.

6.2.5.1 Primary Method for Efficacy Responder Data

The primary method for handling missing efficacy data will be to consider missing binary efficacy endpoints as non-responders. Participants who discontinue treatment for any reason prior to Week 36, up-titrate in dose after Week 24, are missing IGF-1 values at both Week 34 and Week 36 or receive prohibited medication or rescue therapy prior to Week 36 will be considered non-responders. This will be applied to all responder analyses for the efficacy endpoints.

GH has an EOR visit at Week 34 so participants would be considered non-responders for this assessment if the participant discontinued treatment, titrated up in dose after Week 24 or took rescue or prohibited medications at or prior to Week 34.

In alignment with the European Medicines Agency (EMA) guideline[7] on missing data in confirmatory clinical studies, a Kaplan- Meier plot will be generated for each of the following showing the number of events and median time to event within each treatment group. A Cox proportional hazards model with covariates of Screening IGF-1 groups [redacted] and Baseline prior treatment groups (lanreotide, octreotide) will be used to generate a hazard ratio showing the differences between treatment groups for the FAS. For each predictor variable in this model, an interaction term will be created of the predictor variable*log(time). If any of these interaction terms are statistically significant at alpha = 0.05 then it is assumed that the proportional hazard assumption is not met for that predictor and this interaction term will stay in the final model. All predictors that do not show statistical significance in their interaction term will be removed from the final model:

- time from randomization to treatment discontinuation date by treatment group. Participants who do not discontinue the treatment will be censored at the last date of the RC Phase.
- time from randomization to first dose of prohibited medication or rescue therapy by treatment group. Participants without one of these events will be censored at the date of discontinuation from treatment or the last date of the RC Phase.

6.2.5.2 Missing Data Handling for Primary Efficacy Endpoint

IGF-1 level ≤1.0×ULN is based on the average of last two measurements prior to the EOR (Weeks 34 and 36). This endpoint will be based on a single result value when results are not available for both visits. If values for both visits are missing, participants will be considered as non-responders (not meeting IGF-1 level ≤1.0×ULN).

6.2.5.3 Laboratory Results

Quantitative laboratory tests containing less than (<) and greater than (>) symbols are test results that are below or above quantifiable limits, respectively. To retain these values for analysis purposes, 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.

Lab values that are retests will overwrite the previous result. Retests are typically performed when the sample is lost or there is clotting.

6.2.5.4 Partial Dates

If only partial dates are available for adverse events (AEs) or medications and are required for calculation, the following standards will be applied:

- Start Dates (eg, AE onset date or start date of medication)
    - For missing start day only – Day will be imputed as the first day of the month (ie, 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 calculation.
    - For missing start day and month – Day and month will be imputed as the first day of the year (ie, 1 January) with the following exception: if the partial date falls in the same year as the first study drug administration date, then partial date will be imputed to equal the first study drug administration date being used for the calculation.
    - Imputed start dates must be on or prior to the stop date.
- Stop Dates (eg, AE resolution date or stop date of medication)
    - For missing stop day only – Day will be imputed as the last day of the month (ie, 28, 29, 30, or 31).
    - For missing stop day and month – Day and month will be imputed as the last day of the year (ie, 31 December).

Dates will be presented on the listing as recorded, without imputation. All data will be included in data listings that will accompany the CSR.

[redacted]

6.2.7 Multiple Comparisons/Multiplicity

To control the family-wise Type I Error for the primary and secondary endpoints, all hypothesis testing will be performed using the sequential test strategy based on a fixed sequential method. The secondary endpoints will be tested in the order provided below. The hypothesis testing of secondary endpoints will be conducted only if the primary analysis of the primary efficacy endpoint comparison is statistically significant at the predefined alpha level of 0.05. If this comparison is not statistically significant, then the comparison of secondary efficacy endpoints will be considered nominal, descriptive, and exploratory. Proportion of participants with GH < 1.0 ng/mL is moved to the end of the fixed sequence testing procedure to remain consistent with the order of clinical relevance.

Step Number	Endpoint
1	Primary endpoint for IGF-1 Response ≤ 1.0×ULN at EOR
2	Change from Baseline in IGF-1 at EOR
3	Change from Baseline in Total ASD score at EOR

4	GH maintenance of response defined as GH<1.0 ng/mL at Baseline and Week 34

6.2.8 Examination of Subgroups

Subgroup analyses will be conducted on the FAS for the subgroups sex, age, screening IGF-1 group (strata), prior treatment (strata), body mass index (BMI) groups, weight groups, race, ethnicity, use of proton pump inhibitor (PPI) and H2 blockers, and geographic region. Age will be dichotomized to less than 65 years old and greater than or equal to 65 years old. Race will be broken down to white and non-white. Geographic region will be presented by United States (US) sites, and non-US sites. Additional groupings for geographic region may be explored. BMI groups are < 30 and ≥ 30 kg/m^2. Weight groups will be split by their median values. Prior to database lock, PPI and H2 blockers will be defined by a physician from medications taken pretreatment. Subgroup analyses will be conducted on the proportion of participants who maintain biochemical response in IGF-1×ULN at EOR as defined in Section 6.10.1.

The number and percent who show a response in each subgroup by treatment group will be presented in a table. A forest plot of the odds ratios and corresponding 95% exact CIs will be presented for each subgroup. This forest plot will be generated for subgroups from an exact logistic regression model. The stratification factors (screening IGF-1 group and prior treatment) will not be included as covariates due to the reduced number of participants in the model.

6.3 Disposition of Participants

The number of participants included in the FAS, PPS and SS will be summarized for all screened participants by treatment group, final dose group, and overall for the RC phase. Participants who are excluded from an analysis population will be presented in a listing along with the reasons for exclusion.

The following data will be summarized by treatment group, final dose group, and overall for the RC phase:

- the number of participants who screen failed with most recent reason
- the number of participants randomized (completed treatment period (on study drug/discontinued study drug))
- [redacted]
- discontinued treatment period with reason
- discontinued study drug with reason

- number of participants eligible for OLE (Completed RC Phase)
- If participant eligible for OLE and does not enroll in OLE, state reason
- number of participants who entered OLE
- If the number of participants in the FAS differs from the number of participants in the PPS, then the following categories of reasons are presented: randomization/treatment error, <75% compliance, or major PD.

The number of participants screened, screen failures, randomized, discontinued RC Phase, completed the RC Phase, on Paltusotine, on placebo, who discontinued due to adverse events, and total number of SAEs, will be presented by geographic region (US, European Union [EU], rest of world [ROW]), and country within geographic region. Additionally, the proportion of participants on study over time in days may be presented in a time to discontinuation line graph.

The following data will be summarized by treatment group and overall for the OLE phase using OLE SS:

- number of participants who entered OLE and took at least one dose in OLE phase
- discontinued OLE phase with reason
- discontinued study drug in OLE phase with reason

By-participant data listings for all the above study disposition data including study completion and any reasons for premature study withdrawal will be presented. Also, by-participant listings of informed consent, re-consent, and eligibility criteria details will be presented. For participants who discontinued treatment, the details of why will be presented in a listing. Reasons for rescue medication use will be listed which will include acromegaly symptom data that will be classified as a reason for rescue medication use prior to database lock.

6.4 Protocol Deviations

Important and major PDs will be identified and signed off prior to database lock and unblinding of individual participant treatment or dose information. Major PDs include, but are not limited to

- Participants who entered the study even though they did not satisfy the entry criteria.
- Participants who received the wrong treatment or incorrect dose.

All PDs and important PDs will each be summarized by deviation category and treatment group using the FAS. PDs specific to coronavirus disease 2019 (COVID-19) will also be summarized in the same manner. A high-level summary will exist showing any PD, any important PD, any COVID-19 PD, and any major PDs by treatment group and overall.

All PDs including important, major, and COVID-19 PDs will be presented in a by-participant

data listing.

6.5 Demographic and Other Baseline Characteristics

All Baseline summaries may be done on the FAS, PPS, SS, and OLE SS. The following demographic variables will be summarized by treatment group, final dose group, and overall. Baseline characteristics will also be summarized by participants who were considered as non-responders at Week 36 for IGF-1 due to missing data, prohibited medication, rescue medications or up titration of dose after Week 24 vs participants who did not meet these criteria by treatment group.

- Age at informed consent
- Age groups[9] at informed consent: <65, ≥65, 65-74, 75-84, and >84
- Sex
- Race
- Race groups: white vs all other races
- Ethnicity
- Geographic Region: US vs European Union vs rest of the world (ROW). In addition, US vs Non-US.
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI groups: <30, ≥30 kg/m^2
- US Ring size
- HbA1c (%)
- Baseline HbA1c ≥ 6.5% vs < 6.5%
- Average screening IGF-1×ULN values
- Screening IGF-1 groups: [redacted]
- Baseline SRL: octreotide, lanreotide
- Genotype
- Dose group of each injected SRL
    - Low: 60mg/month or 120mg/8 weeks lanreotide or 10mg/month octreotide
    - Mid: 90mg/month or 120mg/6 weeks lanreotide or 20mg/month octreotide
    - High: 120 mg/month lanreotide or ≥30 mg/month octreotide

Age groups, sex, race, race groups, ethnicity, geographic region, BMI groups, glycemic index, SRL, and dose of SRL will be summarized by counts and percentages. Age, height (cm), weight (kg), BMI, screening IGF-1, and ring size will be summarized with descriptive statistics.

No inferential statistical comparisons will be performed. All demographic and baseline characteristics data will be presented in by-participant data listings. If errors occurred in the stratification factors or randomization, then the listing will present the details of how the participant was randomized per IRT and stratified and treated per EDC.

6.6 History of Acromegaly

The following may be summarized by treatment group, final dose group, and overall for the FAS, PPS, SS, and OLE SS.

- Months since diagnosis and split into groups: <10 years, ≥10 to <20 years, ≥20 years
- Elevated IGF-1 prior to pituitary surgery
    - IGF-1×ULN Result
    - Assay platform
- Confirmed pituitary tumor
    - Pituitary tumor size (mm) prior to first pituitary surgery
    - Tumor confirmation method (MRI, CT Scan, Surgical Pathology, Other)
- Pituitary surgery performed
- Months since pituitary surgery
- Elevated IGF-1×ULN at least 3 months after surgery
    - Assay platform
- GH level after oral glucose load
- Most recent IGF-1×ULN prior to screening
- Days since most recent IGF-1×ULN measurement prior to screening
- Baseline IGF-1×ULN
- Baseline IGF-1×ULN in the following groups: ≤1.0×ULN, > 1.0 to < 1.3×ULN, and ≥ 1.3×ULN

6.7 Prestudy Acromegaly Symptoms

Each of the prestudy acromegaly symptoms may be summarized by treatment group, final dose group, and overall for the FAS, PPS, SS, and OLE SS. The symptoms are headache, joint pain, sweating, fatigue, weakness in legs, swelling, numbness or tingling, difficulty sleeping, and difficulty with short term memory. [redacted]

6.8 Medical History

Reported medical history terms will be classified based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology, version 24.0. Medical history summarized by system organ class (SOC) and preferred term (PT) may be presented by treatment group and overall for the FAS, PPS, SS, and OLE SS.

6.9 Prior and Concomitant Medications

Concomitant medications will be coded to preferred name and Anatomical Therapeutic Chemical (ATC) classification of ingredients using the WHODrug Global terminology, Format GLOBALB3, Version March 2021.

Pretreatment medications are those medications with start dates prior to the first administration of study drug and stop dates on/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, prior, new, prior and new concomitant medications may each be summarized by ATC Level 4 and Preferred Name for each treatment group and overall for the FAS, PPS, SS, and OLE SS.

New concomitant medications occurring on or after the first administration of study drug and prior to the first administration of study drug in the OLE phase will be considered as new concomitant medications in RC phase. Medications occurring on or after the first administration of study drug in the OLE phase will be considered as concomitant medications in the OLE phase. If time of medication administration is available, time will be included for the determination. Partial dates will be imputed according to Section 6.2.5.4 before the determination. If it cannot be determined whether the medications occurred in RC or OLE phase, then such medications will be counted as medications in RC phase.

Non-pharmacological treatments will be listed separately. Pretreatment, prior, and new concomitant medications will also be presented in a by-participant listing.

Incomplete medication start and end dates will be imputed as described in Section 6.2.5.4. Dates will not be imputed for by-participant listings.

6.10 Analysis of Efficacy

All efficacy analyses in the RC phase will use the FAS. The primary endpoint will also use the PPS as a sensitivity analysis. Efficacy data in OLE phase will be summarized using OLE SS.

All efficacy endpoints will be presented in by-participant data listings. Tables will include descriptive statistics by treatment group. Some endpoints, where specified, will be presented by final dose groups [redacted] with a total column for all paltusotine participants and a column for placebo.

For responder endpoints, missing data or data after rescue medication use will be considered non-responders.

6.10.1 Primary Efficacy Analysis

The estimand for the primary analysis is defined by the following components.

Population:

The target study population comprises of acromegaly participants who meet the inclusion and exclusion criteria as specified in Protocol Section 5. The analysis set is the FAS as defined in Section 6.1.2.

Variable:

The variable is the primary endpoint, defined as the proportion of participants who maintain biochemical response in IGF-1 (≤1.0×ULN) at EOR.

Inter current events and their handling rules are as follows:

IGF-1 level ≤1.0×ULN is based on the average of last two measurements prior to the EOR (Weeks 34 and 36). The resulting average value will be rounded to 2 significant figures to determine response. This endpoint will be based on a single result value when results are not available for both visits. If values for both visits are missing, participants will be considered as non-responder. Participants who discontinue treatment for any reason prior to Week 36, up-titrate in dose after Week 24, or receive prohibited medication or rescue medication prior to Week 36, will be considered non-responders.

Analysis:

The primary efficacy analyses will test the following hypothesis for the primary efficacy endpoint, at a 2-sided alpha level of 0.05, using an Exact Logistic Regression with covariates of Screening IGF-1 groups [redacted]) and Baseline prior treatment groups (lanreotide, octreotide).

The primary hypothesis:

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

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

Where $\pi_{placebo}$ is the proportion of participants at EOR with IGF-1 $\leq 1 \times$ULN while on placebo and

$\pi_{Paltusotine}$ is the proportion of participants at EOR with IGF-1 $\leq 1 \times$ULN while on paltusotine.

The odds ratio along with a corresponding 95% CI and p-value will also be presented. If the exact logistic regression model fails to converge, the Firth[8] logistic regression model will be performed with the same parameter adjustment for stratification applied.

Population-level summary:

The number and proportion of responders will be presented by treatment groups as well as by final dose groups. Summaries will also be presented for reasons for non-responder classification based on IGF-1 results, prohibited medication use in the absence of meeting protocol defined rescue criteria, rescue medication with criteria met, dose up-titration after Week 24, and discontinuations.

Bar charts and box plots will be presented for the primary endpoint.

6.10.2 Sensitivity Efficacy Analysis of Primary Endpoint

Each of the sensitivity analyses will be performed on the FAS unless stated otherwise.

6.10.2.1 Completers Analysis

A completers analysis will be performed to include only FAS participants who complete at least 34 weeks of treatment. The same analysis will be performed as described above in Section 6.10.1.

6.10.2.2 PPS Analysis

Primary endpoint analysis described in Section 6.10.1 will be performed on the PPS.

6.10.2.3 Non-responder Excluding Dose Titration

The same analysis as defines in Section 6.10.1 will be performed, but participants who dose titrate up after Week 24 will no longer be considered non-responders.

6.10.3 Secondary Efficacy Analysis

A stepwise process will be conducted for testing the secondary efficacy endpoints to control for multiplicity, refer to Section 6.2.7.

6.10.3.1 Change from Baseline in IGF-1×ULN

ANCOVA model will be used to analyze change from Baseline in IGF-1×ULN at EOR, including treatment group, screening IGF-1×ULN group [redacted] and Baseline prior treatment group (lanreotide, octreotide) as fixed effects, and Baseline IGF-1×ULN as a covariate. Participants who are rescued or drop out prior to Week 36 will be imputed with their last available value prior to rescue medication or discontinuation date. Participants with prohibited medication use or who up-titrated after Week 24 will be imputed with their last available value prior to prohibited medication or up-titration. The treatment difference and standard error with associated 95% CI will be presented along with the p-value. LSmeans will be presented for each treatment group along with the standard error of adjusted means.

A sensitivity analysis will be performed. In this sensitivity analysis, IGF-1 results for all assessments following the first the occurrence of intercurrent events such as dropout, taking rescue therapy or prohibited medications, or up-titration in dose after Week 24 will be evaluated as missing data. The missing measurement will be imputed by multiple imputation procedure using on-treatment intermediate values from the placebo group, which will take into consideration the variability from natural disease course prior to medical intervention.

6.10.3.2 GH Maintenance of Response <1.0 ng/mL

GH maintenance of response will be analyzed for the FAS in participants with GH<1.0 ng/mL at Week 34, out of those who had GH<1.0 ng/mL at Baseline, using the same methodology as the primary endpoint Section 6.10.1. Nonresponse is defined as GH ≥1.0 ng/mL at Week 34.

Participants who discontinue treatment for any reason prior to Week 34, take prohibited medication or rescue medication, or dose titrate up after Week 24 will be considered non-responders. The following graphs may be created for this endpoint:

- Median GH levels ± IQR over time by treatment group
- Box plots of GH for screening through Week 34 by treatment group
- By participant plot of GH over time
- Box plot of GH at Baseline and EOR by treatment group

6.10.3.3 Change from Baseline in ASD

Change from Baseline to Week 36 in Total ASD score will be analyzed for the FAS using the same methodology specified in Section 6.10.3.1, where EOR = Week 36. Total ASD scores and change from Baseline scores will be summarized by visit, treatment group, and overall for the FAS.

ASD consists of nine items (headache pain; joint pain; sweating; fatigue; weakness in legs; swelling; numbness or tingling; difficulty sleeping; short term memory), where the participant ranks the intensity of each item from 0 – 10.

The Total ASD score is the sum score of the average of headache pain, joint pain, sweating, fatigue, weakness in legs, swelling, and numbness or tingling, with a range from 0 to 70.

6.10.4 Exploratory Efficacy Analysis in RC Phase

All exploratory efficacy analysis will be performed for the FAS unless stated otherwise. Exploratory endpoints will include nominal p-values with descriptive statistics. For response data, the values captured after rescue medication use, prohibited medication use, or dose up-titration after Week 24 will be set to missing and considered non-responders as defined in Section 6.2.5.1.

6.10.4.1 Time to Loss of Response Defined as IGF-1>1.0×ULN

Shift tables may be generated for FAS and PPS populations to show the shift in IGF-1 response defined as IGF-1≤1.0×ULN vs IGF-1>1.0×ULN from Baseline to each posttreatment visit.

Baseline and EOR are defined in Section 6.10.1.

A Kaplan-Meier plot will be presented for time from randomization to first occurrence of IGF-1>1.0×ULN, for two consecutive visits where the participant is on 3 tablets per day for a minimum of 2 weeks by treatment group. Participants who complete the study treatment and do not meet IGF-1>1.0×ULN criteria during the RC Phase will be censored at EOR. All IGF-1 results (scheduled or unscheduled) will be used. Analysis will be performed using two different methods as follows:

- Participants who discontinue treatment prior to IGF-1>1.0×ULN will be counted as having had an event (IGF-1>1.0×ULN) at the time of treatment discontinuation.
- If the participant discontinued treatment prior to reaching IGF-1>1.0×ULN, the participant will be considered censored at the time of last assessment prior to discontinuation of treatment. If no postbaseline values are available, then the time to IGF-1>1.0×ULN will be censored at Day 1.

Loss of response is defined as IGF-1>1.0×ULN, for 2 consecutive visits after receiving a minimum of 2 weeks of treatment on 3 tablets a day. A summary table will be generated that shows the N, mean, median, standard deviation, IQR, minimum and maximum values, counts and percentage of participants with a loss of response and counts and percentages for participants censored for time from randomization to loss of response by each treatment group. Elapsed times (days) will be computed from randomization date. A Cox proportional hazards model with factors of Screening IGF-1 groups [redacted] and Baseline prior treatment groups (lanreotide, octreotide) will be used to generate a hazard ratio showing the differences between treatment groups in time to first IGF-1>1.0×ULN for two consecutive visits after receiving a minimum of 2 weeks of treatment on 3 tablets a day for the FAS. For each predictor variable in this model, an interaction term will be created of the predictor variable*log(time). If any of these interaction terms are statistically significant at alpha = 0.05 then it is assumed that the proportional hazard assumption is not met for that predictor, and that specific interaction will stay in the final model. All other interaction terms can be removed.

6.10.4.2 Time to Loss of Response Defined as IGF-1≥1.3×ULN

The same analysis as described in Section 6.10.4.1 will be performed but for time to loss of response defined as IGF-1≥1.3×ULN, for two consecutive visits where participants are on 3 tablets per day for at least 2 weeks of treatment.

6.10.4.3 Proportion on Rescue Therapy

The N and proportion of participants who took one or more doses of rescue therapy during the RC Phase will be summarized by dose groups, defined as dose the participant was on at time rescue therapy was administered, paltusotine, placebo, and Total. An Exact Logistic Regression with covariates of baseline IGF-1 groups [redacted] and baseline prior

treatment groups (lanreotide, octreotide) will be performed to compare the proportion of participants that received rescue therapy in paltusotine vs placebo groups for the FAS.

Since IGF-1 elevations are expected for placebo participants, many of the missing values may be due to rescue medication needed. IGF-1 and GH response will therefore be presented in a variety of ways for rescue medication. The following graphics may be displayed to show these results:

- Participant level graph of IGF-1×ULN values over time for each dose and placebo separately
- Scatterplot of IGF-1xULN by GH values at EOR for each treatment group and rescue medication use
- A regression line plotted of IGF-1×ULN
- Box plots will be generated for IGF-1 by treatment group at Baseline and again at end of randomized treatment (EOT) stratified by completers and non-completers all in one graph
- Box plots will be generated for GH by treatment group at Baseline and again at EOT stratified by completers and non-completers all in one graph

6.10.4.4 Change from Baseline to Week 34 in GH

Change from Baseline to Week 34 will be analyzed using the same methods described in Section 6.10.3.1 for the FAS. EOR = mean of value collected from integrated samples at Week 34. An participant-level line plot may also be generated.

6.10.4.5 Maintenance of GH < 2.5 ng/mL Response

The exploratory response variable is defined as GH<2.5 ng/mL. Maintenance is defined as response at baseline and Week 34.

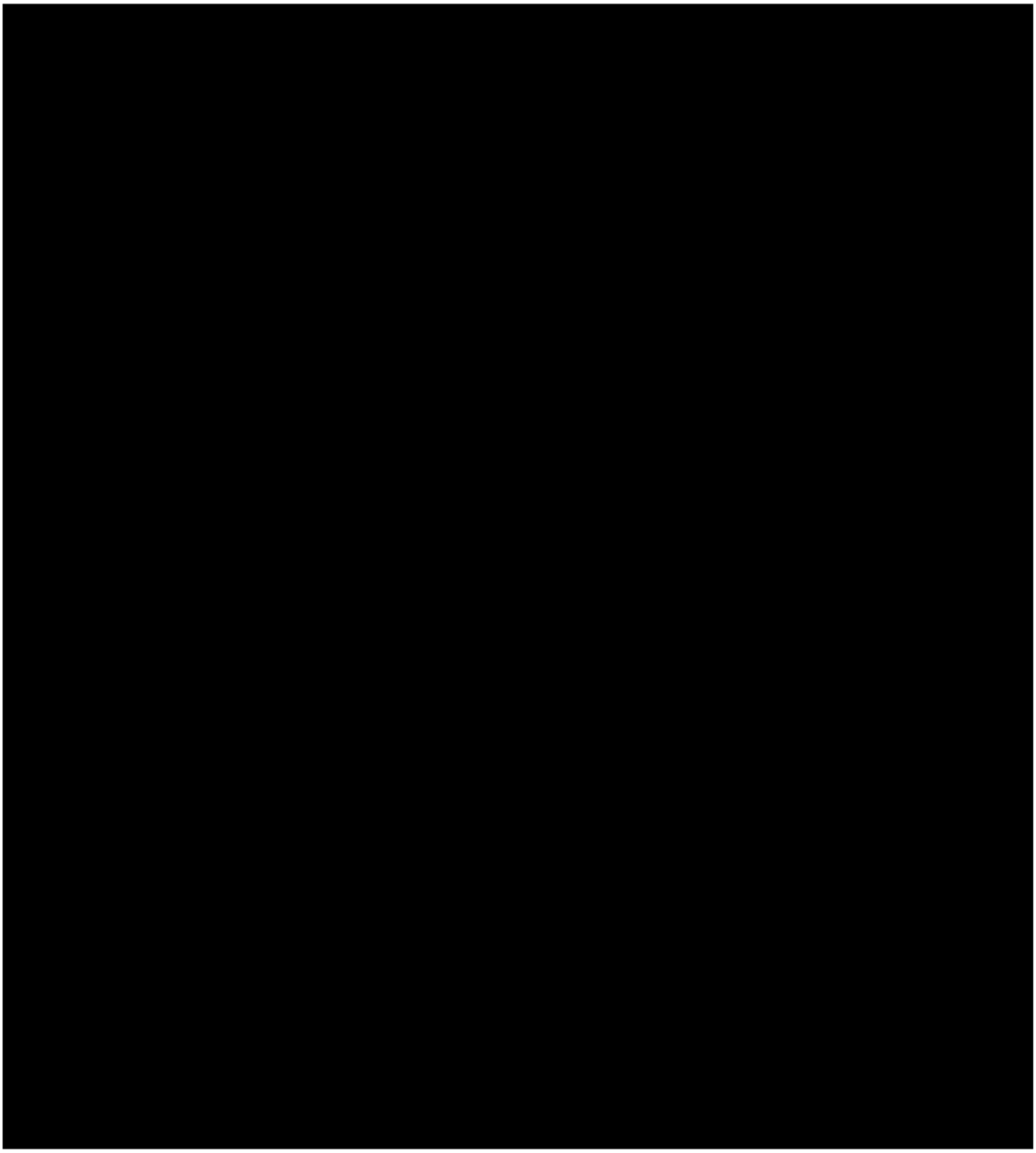
This endpoint will be tested using the method defined in Section 6.10.1 for the FAS. EOR is defined as Week 34 and baseline is the mean of the GH values prior to first dose.

6.10.4.6 Change from Baseline in Residual Tumor Volume

Not all participants are expected to have measurable pituitary tumor remnants in this population. Summary statistics and exact 95% CIs of the mean at each visit as well as change from baseline in residual tumor volume will be presented for the FAS. Adenoma volume is a parameter captured from the magnetic resonance imaging (MRI) central reads and will also be summarized by treatment group.

The percentage of participants with tumor reduction of greater than 25% from Baseline to EOR without rescue medication will be summarized by treatment group. Only observed values will be presented.

MRI data will be presented in a by-participant listing.



[redacted]

[redacted]

6.10.4.11 Pharmacokinetic Analyses

Plasma paltusotine concentrations and elapsed time frame from the last paltusotine dose taken will be listed. A summary of concentrations by paltusotine dose for each timepoint will be presented. Summaries of concentration data from postdose sparse PK sampling may include stratification into bins of time since last dose, with bin selection based on quartiles of the sampling times. Plasma concentrations reported as less than the limit of quantitation (LLOQ) or 2.0 ng/mL will be presented as "BLQ" in the listings and will be imputed to LLOQ/2 for summaries of concentrations.

PK concentrations will be reported to three significant figures.

6.10.4.12 IGF-1 < 1.3xULN

An additional IGF-1 response variable will be derived for exploratory purposes. IGF-1<1.3×ULN at EOR will be analyzed using the same methods as Section 6.10.1 for the FAS.

6.10.4.13 Combining IGF-1 and GH Response

The following exploratory endpoints will be created from IGF-1 and GH responses together. IGF-1 and GH responses will be:

- IGF-1≤1.0×ULN and GH<1.0 ng/mL at EOR
- IGF-1≤1.0×ULN and GH<2.5 ng/mL at EOR
- IGF-1<1.3×ULN and GH<1.0 ng/mL at EOR
- IGF-1<1.3×ULN and GH<2.5 ng/mL at EOR

EOR is defined as Week 34 for GH and the mean of Week 34 and Week 36 for IGF-1×ULN. If only one IGF-1×ULN value exists for these two visits, then that value alone will define EOR. Analysis of each of these endpoints will be performed using the same methods described in Section 6.10.1 for the FAS. These endpoints will also be presented over time by treatment group. The below plots may also be presented:

- Scatterplot of change from baseline to Week 34 in GH versus change from baseline to EOT in IGF-1×ULN
- Box plot: Side by side box plots- one for IGF-1×ULN and the other for GH

6.10.5 Exploratory Efficacy Analysis in OLE Phase

All exploratory efficacy analyses in the OLE phase will use OLE SS.

6.10.5.1 IGF-1 ≤1.0×ULN and < 1.3×ULN

The number and proportion of participants with IGF-1 ≤1.0×ULN and < 1.3×ULN at each visit in the OLE phase will be summarized.

6.10.5.2 Change from Baseline in IGF-1×ULN

IGF-1xULN and change from OLE Baseline at each visit in the OLE phase will be summarized descriptively.

6.10.5.3 GH Maintenance of Response < 1.0 ng/mL

The number and proportion of participants with GH < 1.0 ng/mL at each visit in the OLE phase, out of those who had GH < 1.0 ng/mL at OLE Baseline will be summarized.

6.10.5.4 Change from Baseline in ASD

ASD and change from OLE Baseline at each visit in the OLE phase will be summarized descriptively.

6.10.5.5 Change from Baseline in GH

GH and change from OLE Baseline at each visit in the OLE phase will be summarized descriptively.

6.10.5.6 Proportion on Adjunctive Treatment

The number and proportion of participants who received any adjunctive standard acromegaly treatment during the OLE phase will be summarized.

6.10.5.7 GH Maintenance of Response < 2.5 ng/mL

The number and proportion of participants with GH < 2.5 ng/mL at each visit in the OLE phase, out of those who had GH < 2.5 ng/mL at OLE Baseline will be summarized.

6.10.5.8 Change from Baseline in Residual Tumor Volume

Residual tumor volume and change from OLE Baseline at each visit in the OLE phase will be summarized descriptively.

6.10.5.9 Change from Baseline in [redacted]

[redacted] and change from OLE Baseline at each visit in the OLE phase will be summarized descriptively.

6.10.5.10 Change from Baseline in [redacted]

[redacted] scores and change from OLE Baseline at each visit in the OLE phase will be summarized descriptively.

6.10.5.11 Change from Baseline in [redacted]

[redacted] and change from OLE Baseline at each visit in the OLE phase will be summarized descriptively.

[redacted] results will be summarized at EOT in the OLE phase showing raw scores.

6.11 Safety Evaluation

All safety analyses will use the SS for the RC phase and OLE SS for the OLE phase, separately. There will be no inferential testing done on safety endpoints.

6.11.1 Extent of Exposure

The number and percentage of participants exposed to each dose of paltusotine will be presented. The duration of study exposure (in days) and duration of final dose will be summarized by treatment group and dose group. The duration will represent the time in days

those participants are on each dose. Duration of study drug exposure will be calculated as date of last dose – date of first dose + 1.

In addition, the number and proportion of participants at each dose level per visit will also be presented. Duration groups will be generated in 3-month intervals (eg, 0 to <3 months, 3 to < 6 months, etc) to determine who was on each dose by each of these groups.

Each bottle dispensed includes [redacted] tablets, each at [redacted] mg. Sometimes multiple bottles are dispensed at a visit depending on dose and visit. When, in the investigator's judgment, the study medication is not tolerated, the study medication may be held for up to a total of 14 days per year, but no more than seven consecutive days per year during the study, followed by resumption of the study medication at the same or reduced dose as appropriate. These missed doses are not considered non-compliant as they are allowed per the protocol. Expected dose taken and missed doses are calculated from the EDC data including scheduled and unscheduled visits as follows:

6.11.2 Adverse Events

Reported AEs will be classified based on the MedDRA terminology, version 24.0.

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 emerges during study treatment, having been absent pretreatment, or worsens in severity post treatment relative to the pretreatment state. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such. Partial dates used in calculation are handled per Section 6.2.5.4.

Adverse events (AEs) occurring on or after the first administration of study drug and prior to the first administration of study drug in the OLE Phase will be considered as TEAEs in the RC

phase. AEs occurring on or after the first administration of study drug in the OLE Phase will be considered AEs in the OLE Phase. If time of an AE is available, time will be included for the determination. Partial dates will be imputed according to Section 6.2.5.4 before the determination. If it cannot be determined whether an AE occurred in the RC or OLE Phase, then such events will be counted as an event in the RC Phase.

Each AE summary may display the number of participants who have the AE as well as the number of times the AE occurs by treatment group.

A summary of TEAEs will be displayed by SOC and PT presented in descending order of total incidence of SOC and PT within each SOC. This summary will be presented by treatment group and overall.

An overall summary table of AEs including the number and percent of participants with at least one of the following and the number of AEs for each of the following will be presented by treatment group and overall:

- Any TEAE
- TEAEs by Severity (mild, moderate, severe)
- Serious TEAE
- Treatment-related Serious TEAE
- TEAE leading to death
- Treatment-related TEAE
- Serious TEAE, TEAE leading to death, permanent study drug discontinuation, dose reduction or withdrawal from study
- TEAE leading to permanent study drug discontinuation
- TEAE leading to withdrawal from study
- TEAE leading to dose reduction
- TEAE leading to drug interruption
- TEAEs of special interest defined as symptoms related to acromegaly.

Separate tables will be generated for each of the following. Summaries will include the number and percentage of participants with events as well as the number of events, presented by treatment group and overall:

- TEAEs with an incidence of ≥ 5% in total participants by PT
- Treatment-related TEAEs with an incidence of ≥ 5% in total participants by PT. Related is defined as relationship to paltusotine of "Possibly Related", "Probably Related", or

"Definitely Related". At each level of participant summarization, a participant is classified according to the closest relationship to study drug if the participant reported one or more events. AEs with a missing relationship will be considered related for this summary.

- TEAEs by severity and PT. At each level of participant summarization, a participant is classified according to the highest severity if the participant reported one or more events. AEs with missing severity will be considered severe for this summary.
- Treatment-related TEAEs by PT.
- Serious TEAEs by SOC and PT.
- TEAEs of special interest, defined as a symptom of acromegaly, by PT.
- TEAEs by PT for AEs that occur while on randomized treatment only.
- TEAEs by PT for AEs that occur while on rescue medication only.
- A listing of deaths, SAEs or other significant TEAEs (defined as TEAEs leading to study treatment discontinuation, withdrawal from study, or dose reduction).

The following listings will be presented by participant:

- All AEs
- Treatment-related TEAEs (this is a subset of the TEAEs where relationship marked as Possibly, Probably or Definitely Related)
- SAEs

No statistical inference between treatments will be performed on AEs.

6.11.3 Clinical Laboratory Evaluation

Quantitative laboratory tests will be summarized with descriptive statistics at every scheduled visit including Baseline (OLE Baseline for the OLE phase) and changes from Baseline (OLE Baseline for the OLE phase) by treatment group for the following groups and tests:

- Hematology: basophils; basophils/leukocytes; eosinophils; eosinophils/leukocytes; ery. mean corpuscular hemoglobin; ery. mean corpuscular volume; erythrocytes; hematocrit; hemoglobin; leukocytes; lymphocytes; lymphocytes/leukocytes; monocytes; monocytes/leukocytes; neutrophils; neutrophils/leukocytes; platelets
- Chemistry: alanine aminotransferase; albumin; alkaline phosphatase; amylase; aspartate aminotransferase; bilirubin; calcium; calcium corrected for albumin; chloride; creatinine; direct bilirubin; glomerular filtration rate; glucose; indirect bilirubin; lipase; magnesium; phosphate; potassium; protein; sodium; urate; urea
- Hemoglobin A1c

- Hormones: thyrotropin; free thyroxine
- Lipids: cholesterol; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; triglycerides
- Quantitative urinalysis: specific gravity; pH

Individual laboratory test results will be presented in a by-participant listing.

Liver test abnormalities will be presented in a by-participant listing. If a participant meets any of the following liver test abnormality criteria, present the baseline result, the first occurrence of the post baseline abnormality, and all subsequent results for that parameter.

- ALT or AST <ULN at Baseline (OLE Baseline for the OLE phase) and >3×ULN post treatment
- ALT or AST >ULN at Baseline (OLE Baseline for the OLE phase) and >3×ULN post treatment and 2x the Baseline (OLE Baseline for the OLE phase) result
- TB <ULN at Baseline (OLE Baseline for the OLE phase) and >2×ULN post treatment
- TB >ULN at Baseline (OLE Baseline for the OLE phase) and >2×ULN post treatment and 2x the Baseline (OLE Baseline for the OLE phase) result
- Alkaline Phosphatase (ALP) <ULN at Baseline (OLE Baseline for the OLE phase) and > 3×ULN post treatment
- ALP >ULN at Baseline (OLE Baseline for the OLE phase) and >3×ULN post treatment and 2x the Baseline (OLE Baseline for the OLE phase) result

Liver test abnormalities leading to treatment discontinuation will be presented in a by-participant listing. If a participant meets any of the following liver test abnormality criteria, present the first occurrence and all subsequent results for that parameter.

- Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) > 8×ULN at any visit
- ALT or AST >5×ULN for more than 2 weeks (there should be at least two values)
- ALT or AST >3×ULN and Bilirubin (TB) >2×ULN or international normalized ratio > 1.5 for more than 2 weeks. A participant is required to meeting all of these criteria at least twice.
- ALT or AST >3×ULN and AE = fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophils/leukocytes > 5%). The AE start date should occur ± 7 days from the date of this lab result.

Pregnancy testing and urine drug screen results will also be presented in a by-participant listing.

6.11.4 ECG Measurements

ECG measurements will be made in triplicate and assessed by a central reader. For summary purposes the average of the triplicate measurements will be used. If any of the three measurements are not available or more than three measurements are available, all available measurements will be used in the average.

Descriptive statistics by treatment group and visit will be provided for the following ECG parameters: heart rate (HR), QRS duration, PR interval, QT interval, RR interval, and QTcF interval at each scheduled visit. In addition, change from Baseline will also be presented.

A categorical summary of the following abnormal QTcF values will be presented: >450 msec, >480 msec, and >500 msec. Shift tables may be generated from Baseline (OLE Baseline for the OLE phase) to worst (highest) post baseline result by treatment group. Change from Baseline (OLE Baseline for the OLE phase) summaries will also be presented for measurements that represent a change of >30 msec and >60 msec at each scheduled visit.

A listing of ECG results will be presented and participants with any QTcF >450 msec or a QTcF change from Baseline (OLE Baseline for the OLE phase) >30 msec, based on the average of the triplicates, will be flagged.

The investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant. Shift tables may be generated for these outcomes to show how they change from baseline to each postbaseline visit. Participants with shifts from normal to abnormal clinically significant or not clinically significant from Baseline (OLE Baseline for the OLE phase) may be listed separately including description of the abnormality and any associated comments.

6.11.5 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 by treatment group. They will also be presented by scheduled visit as observed values and changes from Baseline (OLE Baseline for the OLE phase) using descriptive statistics.

All vital signs will be presented in a by-participant data listing.

6.11.6 U.S. Ring Size, Weight, and Body Mass Index

U.S. Ring size, weight (kg), and BMI (kg/m^2) will be summarized at Baseline (OLE Baseline for the OLE phase) and each postbaseline visit by treatment group. In addition, change and percent change from Baseline will be presented by treatment group.

6.11.7 Physical Examination

Physical examination data will be presented in a by-participant listing.

6.11.8 Gall Bladder Ultrasound

The number and percentage of participants with gallstones, absent or present at Baseline (OLE Baseline for the OLE phase) and Week 36 for the RC phase (EOT for the OLE phase) will be presented by treatment group. Similar summaries will be presented for gall bladder sludge, wall thickening, and dilation of biliary tract. Common Bile Duct will also be summarized by descriptive statistics at each visit and change from baseline.

All gall bladder ultrasound data will be presented in a by-participant listing.

8. CHANGES IN THE PLANNED ANALYSES

- Screen failure set was added as a new population to be analyzed.
- The details that went into the calculation for compliance are more detailed than what is in the protocol.
- Definition for Baseline IGF-1 calculations was updated to include all screening measurements taken prior to Day 1, instead of the last value measured prior to Day 1, and removed significant figures from definition.
- Multiple imputation for the primary endpoint was removed.
- The secondary endpoint of proportion of participants with GH <1.0 ng/mL at Week 34 was moved to the end of the fixed sequence testing procedure.
- The secondary endpoints of change from Baseline in IGF-1×ULN and change from Baseline in ASD will be analyzed using an ANCOVA. The worst rank ANCOVA analysis was removed and method of imputation was updated to use last observation carried forward.
- Multiple imputation for the secondary endpoints of change from Baseline in IGF-1×ULN was added as a sensitivity analysis.
- The following exploratory endpoints were added that are not in the protocol:
  - Change from baseline to EOR in [redacted]
  - [redacted] at EOR
  - Change from baseline to EOR in [redacted]
  - Change from baseline to EOR in [redacted]
  - [redacted] at EOR
  - PK parameters
  - Proportion of participants who achieve IGF-1≤1.0×ULN and GH<1.0 ng/mL at EOR
  - Proportion of participants who achieve IGF-1≤1.0×ULN and GH<2.5 ng/mL at EOR
  - Proportion of participants who achieve IGF-1<1.3×ULN and GH<1.0 ng/mL at EOR
  - Proportion of participants who achieve IGF-1<1.3×ULN and GH<2.5 ng/mL at EOR
  - Percentage with >25% reduction in tumor volume from baseline to EOR

9. REFERENCES

1. International Council on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: E9 Statistical Principles for Clinical Trials"
2. International Council on Harmonisation ICH E9 (R1) guidelines entitled, "E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials"
3. ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports"
4. International Council for Harmonization (ICH) Guidance E6 for Industry on Good Clinical Practice

[redacted]

7. European Medicines Agency. Guideline on Missing Data in Confirmatory Trials. 2Jul2010
8. Karabon, P. Rare Events or Non-Convergence with a Binary Outcome? The Power of Firth Regression in Proc Logistic SAS Global Forum 2020.
9. Geriatric Information in Human Prescription Drug and Biologic Product Labeling
10. Samson, SL. Treatment with oral octreotide capsules may not adversely affect glycemic control in patients with acromegaly: Results from the Phase 3 chiasma OPTIMAL study. American Association of Clinical Endocrinologists (2020).

Signature Page for VV-CLIN-000724 v3.0
CRN00808-09 Statistical Analysis Plan v3.0

Approval	[redacted] 07-Aug-2023 20:23:25 GMT+0000
Approval	[redacted] 08-Aug-2023 16:25:05 GMT+0000
Approval	[redacted] 08-Aug-2023 16:25:29 GMT+0000