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

NCT Number: NCT05192382

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Protocol Number:	CRN00808-08
Study Title:	A Randomized, Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Paltusotine in Subjects with Non-pharmacologically Treated Acromegaly
Sponsor:	Crinetics Pharmaceuticals, Inc. 6055 Lusk Blvd San Diego, CA 92121
Statistical Analysis Plan based on Protocol Version and Date:	Version 4.0, 22 November 2023
Statistical Analysis Plan Date:	02 January 2024
Statistical Analysis Plan Version:	V4.0

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SAP Approval

Authored and approved by:

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Signature & Date

[redacted]

Reviewed and approved by:

See last page for electronic signature manifestation

Signature & Date

[redacted]

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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	28 Sep 2022	Original document	[redacted]
2.0	21 Mar 2023	Major changes are: 1. Multiple imputations for primary efficacy endpoint and key secondary efficacy endpoint are removed from Sections 7.3.1.1 and 7.3.3.1. 2. Sensitivity analyses for primary efficacy endpoint in Section 7.3.2.1 are modified. 3. ANCOVA model for key secondary efficacy endpoint will be used for the analysis and worst-rank score ANCOVA is removed in Section 7.3.3.1. 4. Added time to initial response of IGF-1 in Section 7.3.4.4. 5. Exploratory analysis on paltusotine vs. injection SRLs are removed from Section 7.3.4.12. 6. Proportion of participants with GH <1 ng/mL is moved to the end of the fixed sequence testing procedure in Section 7.3.6. 7. 25% tumor reduction in volume is changed to 20% tumor reduction and is combined with change from baseline in residual tumor volume; 8. Analyses on TEAE on actual paltusotine dose and onset time category are removed from Section 7.4.1. 9. Baseline definitions on IGF-1, GH and [redacted] are modified in Section 8.3. 10. Data handling on laboratory quantitative results are added in Section 8.6. Other minor changes in wording/terminology are made throughout the document.	[redacted]
3.0	07 Aug 2023	Major Changes: 1. Add the analyses for the open-label extension phase in Section 7.3.5. 2. Add multiple imputations for the secondary efficacy endpoint of change from Baseline in IGF-1xULN as the sensitivity analysis in Section 7.3.3.1.	[redacted]

Version	Date	Summary of Changes	Author
4.0	02 Jan 2024	Major Changes are: 1. Updated FAS definition to exclude screen failures in Section 6.3. 2. Added EOR and EOT definition for clarification in Section 7.2. 3. [redacted] 4. 5. Added Analysis Windows for Efficacy and Safety Assessment for subjects directly enrolled into OLE portion of the study in Section 8.2. 6. Per protocol amendment v4.0, the major changes in section 4, section 5.1.3 and section 7.4.9 are made. Other minor changes in wording/terminology are made throughout the document.	[redacted]

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[redacted]	
AE	adverse event
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
CFR	code of federal regulations
CI	confidence interval
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EOR	end of the randomized controlled phase
EOS	end of study
EOT	end of treatment
[redacted]	
ET	early termination
FAS	full analysis set
FDA	food and drug administration
GCP	good clinical practice
GH	growth hormone
GI	gastrointestinal
HbA1c	hemoglobin A1c
ICH	international council for harmonization
IEC	independent ethics committee
IGF-1	insulin-like growth factor-1
INR	international normalized ratio
IQR	Inter-quartile range
IRB	institutional review board
IRT	interactive response technology

Abbreviation	Definition
LAR	long-acting release
MRI	magnetic resonance imaging
OLE	open-label extension
[redacted]	
PPS	per protocol set
QTcF	QT interval corrected using Fridericia's formula
QTL	quality tolerance limits
RC	randomized, controlled phase
S1, S2, S3	screening visit 1, etc
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SRL	somatostatin receptor ligand
SS	safety set
TB	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
W	week

2. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods to be implemented during the analyses of Study CRN00808-08 (PATHFNDR-2) data collected within the scope of this Crinetics-sponsored 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 9, 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 SAP must be finalized, approved by the Sponsor, and placed on file prior to the earliest of conducting an interim analysis or locking and 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] and ICH E9 (R1)[2] guidelines, ICH-E6[3] and ICH E3[4].

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 outlines analyses for the Randomized Controlled (RC) phase and Open-label Extension (OLE) phase of the study.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to evaluate the effect of paltusotine versus placebo on insulin-like growth factor-1 (IGF-1) response of ≤1.0 × upper limit of normal (ULN).

3.2. Secondary Objectives

The key secondary objective is to evaluate the effect of paltusotine versus placebo on IGF-1 level.

Other Secondary objectives are to evaluate the effects of paltusotine versus placebo on:

- IGF-1 response of <1.3 × ULN
- GH response of <1 ng/mL
- acromegaly symptoms

3.3. Exploratory Objectives

Exploratory objectives of the study are to evaluate the effect of paltusotine versus placebo on:

- GH level
- Need for rescue therapy
- Time to need for rescue treatment
- GH response of <2.5 ng/mL
- Tumor volume

3.4. Safety Objectives

The safety objective is to evaluate the safety and tolerability of paltusotine versus placebo.

3.5. Pharmacokinetics

The pharmacokinetic objective is to evaluate the pharmacokinetic parameters of paltusotine in participants with acromegaly.

4. STUDY DESIGN

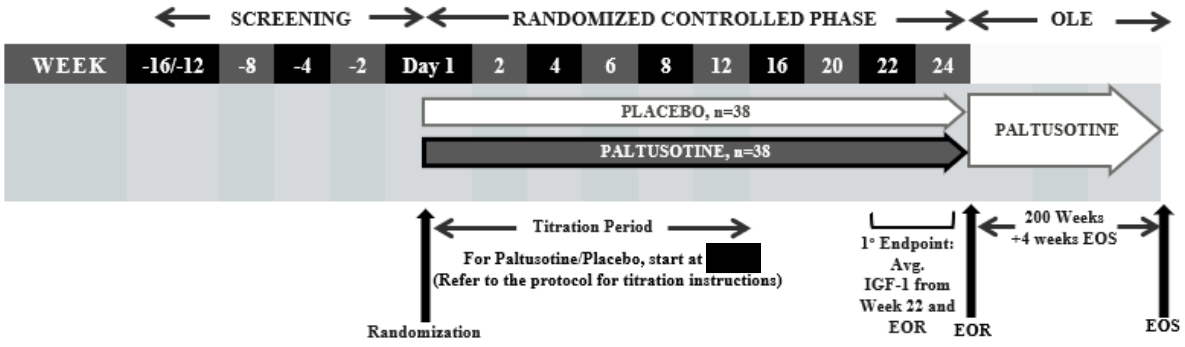
This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study where 76 participants with non-pharmacologically treated acromegaly will be randomly allocated to receive either paltusotine or placebo.

The Screening Period for this study may be approximately 2 to 4, 8, or 12 to 16 weeks, depending on prior treatment. After the Screening Period, participants will be enrolled in a 24 week Randomized Controlled (RC) phase and randomly assigned in a 1:1 ratio to receive paltusotine or matching placebo, stratified by prior treatment (medically naïve or previously treated versus washout). When approximately [redacted] participants randomize there is an option to increase the sample size due to the number of participants in stratum 2 (Section 7.3.2.3). An interim analysis may also occur when [redacted] participants complete or discontinue treatment by Week 24.

Rescue criteria are in place for those who require standard acromegaly treatment during the Randomized Control Phase. It is anticipated that the study drug dose will be stable, and titration completed prior to or at Week 12, with no dose titrations/adjustments after Week 12. Participants who require dose up-titration after Week 12 will be considered non-responders. Down-titration due to unacceptable tolerability is permitted. At the End of the Randomized Control Phase (EOR), participants who, in the opinion of the Investigator, could benefit from treatment with paltusotine, may be enrolled in a long-term open-label extension (OLE) study, during which they will receive paltusotine for up to 200 weeks.

Participants who meet rescue criteria will have treatment with paltusotine or placebo discontinued and be considered non-responders, but they should be encouraged to continue in the study on rescue therapy for assessment and observation. These participants can participate in the OLE phase if they meet all eligibility requirements, and in the opinion of the Investigator, the participant may benefit from continued participation and treatment with paltusotine and the participant is willing to participate.

Figure 1: Study Schema



The schedule of visits and assessments are listed in Sections 1.2, 1.3, 1.4, 1.5, and 1.6 (OLE) of Protocol CRN00808-08 (V4.0, 22 November 2023).

4.1. Randomization

Participants will be randomized to study treatment using an interactive, automated system 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[3].

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, a contract research organization, who is not a member of the study team; investigators and the study team will not be aware of the block size of the randomization scheme. Randomization will be stratified by prior treatment (medically naïve or previously treated versus washout).

Participants will be randomized based on prior treatment: Stratum 1 represents participants with no prior medical therapy (Group 1) and participants who last received medical therapy at least 4 months prior to Screening (Group 2), and Stratum 2 represents participants who are controlled on medical therapy for at least 3 months but agree to washout prior to beginning study treatment (Group 3). The study population will be randomized by these stratification criteria to ensure balance between active treatment versus placebo allocations in each stratum.

4.2. 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 is complete, 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 a 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.

4.3. Sample Size

The primary endpoint assumes the overall rate of response at EOR, defined as IGF-1 ≤1.0× the upper limit of normal (ULN), for paltusotine versus placebo is [redacted] and [redacted], respectively. The study population will be stratified to ensure equivalent active treatment versus placebo

allocations in each stratum. Groups 1 and 2 constitute Stratum 1 and Group 3 constitutes Stratum 2. The number of participants in each stratum is expected to be equally allocated[5]. The responder rates in Stratum 1 are expected to be [redacted] in paltusotine-treated participants and [redacted] in placebo-treated participants. The responder rates in Stratum 2 are expected to be [redacted] in paltusotine-treated participants and [redacted] in placebo-treated participants. Through simulations, power was estimated for the comparison of paltusotine versus placebo using an Exact Logistic Regression with stratum as a covariate in the model and a 2-sided alpha of 0.05. Power of [redacted] was achieved with 76 participants (38 per group), which accounts for a [redacted] dropout rate (who are treated as non-responders).

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

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

A sample size of 54 participants will provide [redacted] power to detect a difference in the key secondary endpoint of change from Baseline to EOR in IGF-1 using a Wilcoxon-rank sum test under the following assumptions: a difference of [redacted] in the mean change from Baseline to EOR in IGF-1 in units of ULN between placebo and paltusotine, a common standard deviation (SD) of 0.71, a 2-tailed alpha of 0.05, and a [redacted] drop-out rate. With 76 participants enrolled, the power increases to [redacted].

4.3.1. Hypothesis Testing and Significance Level

The primary hypothesis:

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

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

Where $\pi_{placebo}$ is the proportion of participants at EOR with IGF-1 $\leq$1×ULN while on placebo and $\pi_{paltusotine}$ is the proportion of participants at EOR with IGF-1 $\leq$1×ULN while on paltusotine. The primary hypothesis will be tested, at 2-sided alpha level of 0.05, by using an Exact Logistic Regression model with prior treatment (medically naïve or previously treated versus washout) as a fixed factor.

4.3.2. Justification for Estimates

For participants in Stratum 1, the expectation is that placebo participants will have little to no response, based on clinical practice. Assuming that paltusotine and octreotide have similar response rates, the sample size estimate was based on the rates observed in a similar patient

population in the registrational trial for pasireotide LAR in which octreotide LAR was used as an

The two stratification criteria will be included in the analysis of the primary endpoint, but estimates were not known prior to the original power calculation.

5. STUDY ENDPOINTS

5.1. Efficacy Endpoints

5.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants who achieve biochemical response in IGF-1 (≤1.0× ULN) at the EOR.

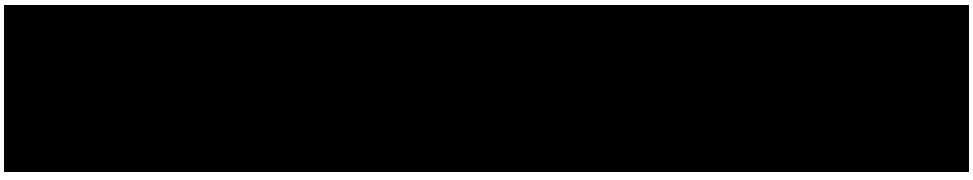
5.1.2. Secondary Efficacy Endpoints

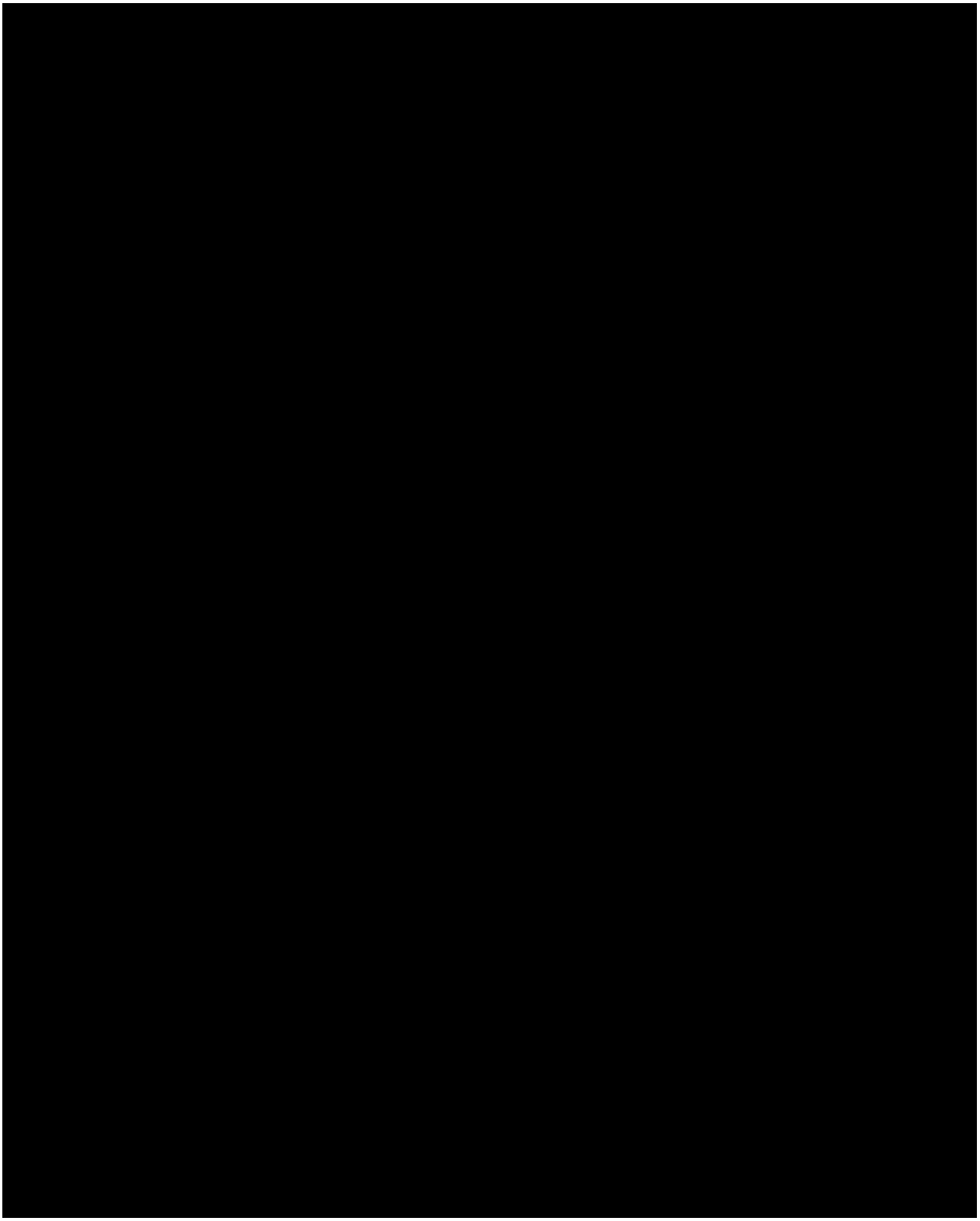
The key secondary efficacy endpoint is as follows:

- change from Baseline in IGF-1, in units of ULN, to EOR Additional secondary efficacy endpoints are:
- Proportion of participants who achieve IGF-1 <1.3×ULN at EOR
- Proportion of participants with GH <1 ng/mL at Week 22
- Change from Baseline in Total Acromegaly Symptoms Diary (ASD) score to EOR

5.1.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows. Additional endpoints were added that are not in the protocol.





5.2. Safety Endpoints

The safety endpoints are as follows:

- Incidence of treatment-emergent adverse events (TEAEs), including SAEs and TEAEs leading to discontinuation
- Change in safety parameters: clinical laboratory tests (hematology, serum chemistry, lipid panel, and hormones), weight, ring size, vital signs, and 12-lead electrocardiogram (ECG)
- Incidence of clinically significant changes in abdominal (gallbladder) ultrasound compared with Baseline
- Concomitant medications
- Ophthalmic assessments

5.3. Pharmacokinetic Endpoints

The pharmacokinetic endpoint is as follows:

- Descriptive summary of concentration data from postdose sparse PK sampling

6. ANALYSIS SETS

6.1. 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.

6.2. Safety Analysis Set (SS)

The Safety Analysis Set 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 in RC phase.

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.

6.3. Full Analysis Set (FAS)

The Full Analysis Set is defined using the intent-to-treat principle and will include all randomized participants but not screen failures. The FAS will be the primary analysis set used for efficacy analyses in RC phase. 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.

6.4. Per-Protocol Set (PPS)

The Per-Protocol Analysis Set 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 protocol deviations/violations that would affect efficacy, and 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. All major protocol deviations/violations will be defined prior to unblinding the study. 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.

6.5. Open Label Extension Safety Analysis Set (OLE SS)

The OLE SS is defined as all participants who received any amount of paltusotine in the OLE phase.

This will be the analysis set for the OLE phase. The actual treatment assigned in RC phase will be used in the OLE phase. Patients enrolled directly into OLE phase will be summarized separately.

Participants who were rescued during the RC phase will be analyzed separately from those who completed the study treatment during the RC phase for selected endpoints.

7. STATISTICAL ANALYSIS

7.1. Computer Software

All analyses and outputs will be generated from SAS® 9.4 or higher unless otherwise stated. Data will be collected in the Veeva Vault EDC system.

7.2. General Summaries

All continuous endpoints will be summarized showing the n, mean, median, interquartile range (IQR), standard deviation (SD), minimum and maximum values. Discrete endpoints will be presented showing the count and percentage. The coefficient of variation (CV) will also be presented for GH and IGF-1. Where applicable, 95% confidence intervals (CIs) will also be calculated. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

End of RC phase (EOR) is defined as the last available assessment in RC phase. For subjects who completed in the RC phase, the average available IGF-1 values from week 22 and 24 will be used for EOR and End of Treatment (EOT). For subjects who took the rescue therapy, the last available prior to rescue therapy will be considered as EOT value.

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

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 in RC phase. The OLE SS will be used in the analyses related to the OLE phase.

All IGF-1 endpoints are using IGF1 defined by the following equation (Note: to avoid confusion “IGF1” is written instead of “IGF-1”)

$$IGF1\ (in\ ULN) = \frac{IGF1\ measured\ \left(in\ \frac{ng}{mL}\right)}{ULN\ for\ the\ subject\ age\ and\ sex\ \left(in\ \frac{ng}{mL}\right)}$$

EOR for IGF-1xULN will be calculated as the average of Week 22 and Week 24 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 four or less of the five values are missing, the available values at the specified visit will be used to calculate the average.

7.2.1. Baseline Characteristics

7.2.1.1. Demographics

The following variables will be summarized by treatment group, final dose group, and overall. They also will be summarized by participants who were considered non-responders at Week 24 for IGF-1 due to missing data, prohibited medication, rescue medications, or up-titration of dose after Week 12 vs participants who did not meet these criteria by treatment group.

- US Ring size
- HbA1c (%)
- Baseline HbA1c ≥ 6.5% vs < 6.5%
- Screening IGF-1×ULN values
- Genotype
- Age at informed consent
- Age groups[10] at informed consent: <65, ≥65, 65-74, 75-84, and >84
- Sex
- Race
- Race groups: white vs all other races
- Ethnicity
- Geographic Region: North America (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
- Strata

Age groups, sex, race, race groups, ethnicity, geographic region, HbA1c groups, strata, genotype, and BMI groups will be summarized by N and percentages. Age (years), height (cm), weight (kg), U.S. ring size, HbA1c (%), screening IGF-1×ULN, and BMI (kg/m^2) 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. All summaries of tables showing baseline characteristics may be done on the FAS, PPS, and SS.

Demographic and baseline characteristics summarized by treatment group and overall will be repeated for OLE SS.

7.2.1.2. Acromegaly Disease History

The following baseline acromegaly disease characteristics may be summarized by treatment group and overall for the FAS, PPS, SS and OLE SS.

- Months since diagnosis and split into 3 groups: < 1 years, ≥ 1 to < 5 years, ≥5 years
- Elevated IGF-1 prior to pituitary surgery and associated 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
- Radiotherapy treated
- Years after radiotherapy
- Elevated IGF-1×ULN at least 3 months after surgery and associated 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 3 groups: ≤1.0×ULN, >1.0 to <1.3×ULN, and ≥1.3×ULN

7.2.1.3. Prestudy Acromegaly Symptoms

Each of the prestudy acromegaly symptoms may be summarized by treatment 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. The most bothersome of these symptoms will also be summarized by treatment group and overall.

7.2.1.4. Medical History

Reported medical history terms will be classified based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology, version 24.1. Medical history summarized by system organ class (SOC) and preferred term (PT) may be presented by treatment group and overall for the FAS, the SS, PPS, and OLE SS.

7.2.2. 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 treatment to which they were not randomized or the incorrect dose.

All PDs, important PDs and major PDs will be summarized by deviation category and treatment using the FAS. PDs specific to coronavirus disease 2019 (COVID-19) will be summarized in the same manner. A high-level summary will include 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.

7.2.3. Participant Disposition

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 and overall for the RC phase:

- The number of participants who screen failed (IGF-1<1.3×ULN for stratum 1 and IGF-1<30% increase from S1 or IGF-1<1.1×ULN for stratum 2; Inclusion/Exclusion violation; early withdrawal)
- the number of participants randomized (completed treatment period (on study drug/discontinued study drug))
- strata and group within strata: Stratum 1: Medically naïve group (Group 1), Previously Treated group (no treatment within previous 4 months) (Group 2) vs Stratum 2 Washout group (Group 3)
- discontinued RC phase with reason
- discontinued study drug with reason
- number of participants eligible for OLE (Completed RC Phase)
- If a participant is 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, number of SAEs, and who discontinued due to adverse events, and total number of SAEs, will be presented by geographic region (United States (US), European Union (EU) and 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 by site starting with the highest enrollers. 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.

7.2.4. 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 September 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, the SS and the PPS for RC phase. Similarly, concomitant medications in the OLE phase will be summarized by ATC Level 4 and Preferred Name for each treatment group and overall for the 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 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 8.5 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. Dates will not be imputed for by-participant listings.

7.3. Efficacy Analyses

All efficacy analyses in the RC phase will use the FAS. The primary endpoint will also use the PPS as 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 dose groups (20mg, 40mg, 60mg) with a total column for all paltusotine participants and a column for placebo.

7.3.1. Methods used for Discontinuations and Missing Data

The primary method will be considered missing binary efficacy endpoints as non-responders. Participants who discontinue treatment for any reason prior to Week 24, up-titrate in dose after Week 12, are missing IGF-1 values at both Week 22 and Week 24 or receives prohibited medication or rescue therapy prior to Week 24 will be considered non-responders. This will be applied to all responder analyses in the efficacy endpoints.

GH has an EOR visit at Week 22 so participants would be considered non-responders for this assessment if participants discontinued treatment, titrated up in dose after Week 12 or took rescue or prohibited medications at or prior to Week 22.

In alignment with the European Medicines Agency (EMA) guideline[11] on missing data in confirmatory clinical trials, 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 a covariate for strata 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 study 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.

7.3.2. Analysis of Primary Endpoint

Estimand:

- Population: FAS
- Variable: Primary Endpoint is the proportion of participants who achieve IGF-1 level ≤1.0×ULN based on the average of the last 2 measurements collected at Weeks 22 and 24 (EOR). The resulting average value will be rounded to 2 significant figures to determine response. If one of IGF-1 levels from weeks 22 and 24 is not available, the

single result value (rounded to 2 significant figures) will be used to determine response. Non- responders = average of last 2 measurements collected at weeks 22 and 24 are >1.0×ULN, an intercurrent event or missing IGF-1 level in both weeks 22 and 24.

- Intercurrent Event: Discontinuation of treatment, rescue therapy, prohibited medications, or up-titration in dose after week 12 are considered intercurrent events and will be treated as non-responders.
- 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 12, and discontinuations.
- Statistical Analysis: Exact Logistic Regression model with treatment group as a factor and a covariate for prior treatment strata (medically naïve or previously treated versus washout). If the exact logistic regression model fails to converge, the Firth[12] logistic regression model with the same adjustment for stratification will be applied.

In the event that the sample size is adjusted due to the unblinded interim analysis using conditional power, then the primary endpoint analysis will use the Firth[12] logistic regression, and results will be determined using the combined p-value approach as defined in Appendix 1.

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

7.3.2.1. Sensitivity Analyses for the Primary Endpoint

Changes to the estimand are described for each of the sensitivity analyses below while all other components of the estimand defined in Section 7.3.2 stay the same.

Completers Analysis- Participants in the FAS who complete the EOR on randomized treatment.

Per-protocol Set- Population is PPS.

Dose titration not non-responder- up-titrate after week 12 is no longer considered an intercurrent event so response for these participants will be based on IGF-1 values if no other intercurrent event occurred.

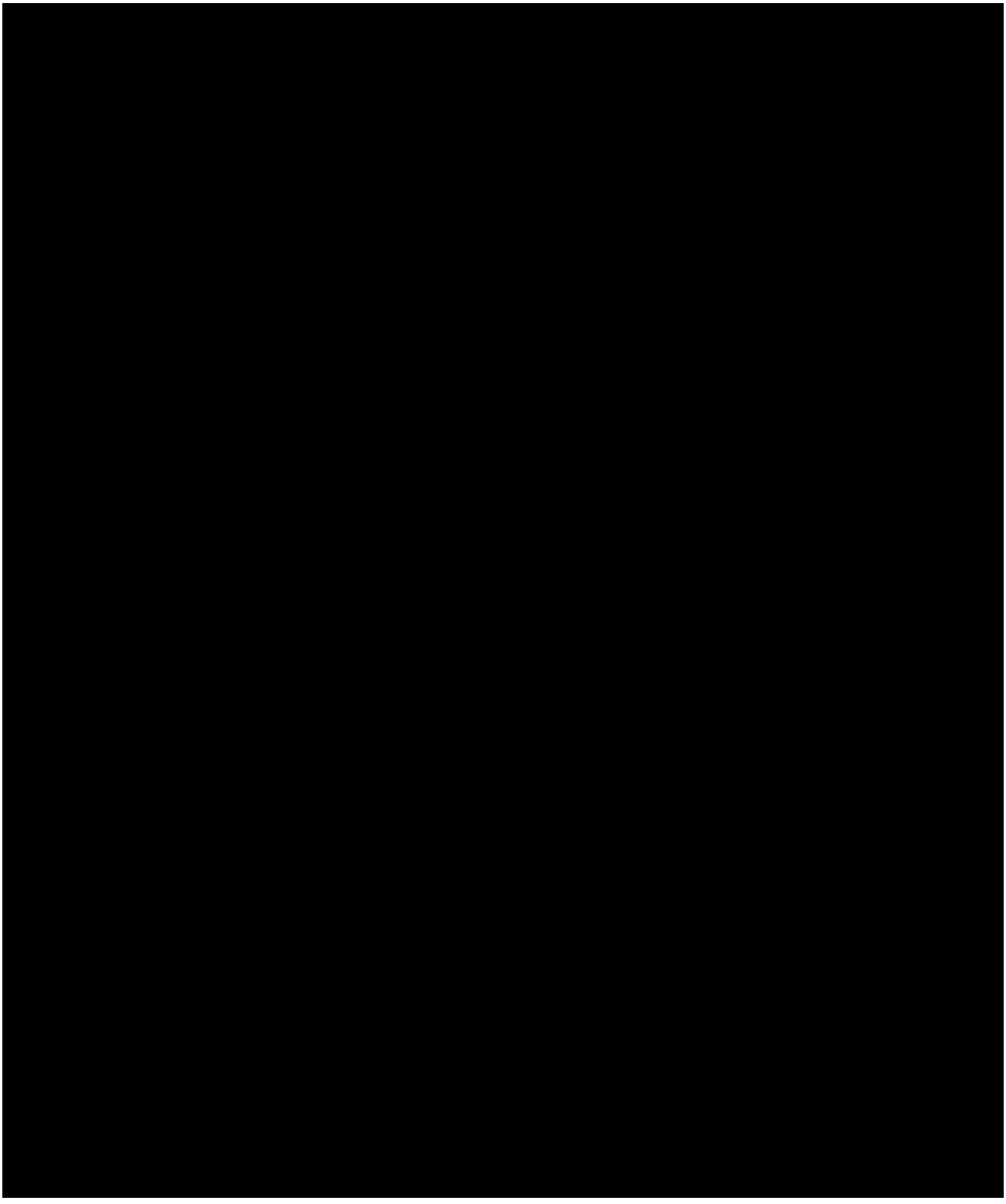
No stratum in model- the population level summary will be an odds ratio between treatment groups for each stratum separately. The statistical analysis will still be an exact logistic regression, but strata will no longer be a covariate in the model this analysis will be presented on each stratum separately.

7.3.2.2. Subgroup Analysis

Subgroup analyses will be conducted on the FAS for the subgroups sex, age, screening IGF-1 group, prior treatment (strata), body mass index (BMI) groups, weight groups, ethnicity, race, use of 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. BMI groups are <30 and ≥30 kg/m^2. Screening IGF-1, and weight groups will be split by their median values. Prior to lock, H2 blockers will be defined by a physician from the mediation taken pretreatment. Subset analyses will be conducted on the proportion of participants with the primary endpoint of IGF-1 response at EOR as defined in Section 7.3.2.

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 (prior treatment) will not be included as a covariate due to the reduced number of participants in the model.



7.3.3. Analysis of Secondary Endpoints

The methods described below will be used for each secondary endpoint. In the event that the sample size is adjusted due to the unblinded interim analysis using conditional power, then

results from these secondary endpoints will be determined using the combined p-value approach as defined in Appendix 1.

7.3.3.1. Key Secondary Efficacy Analysis

This key secondary endpoint of change from baseline in IGF-1 at EOR has the following estimand.

Population: FAS

Variable: Endpoint is change from Baseline to EOR in IGF-1 in ULN level.

Population-level Summary: treatment difference with associated 95% CI will be presented.

Statistical Analysis: an ANCOVA model including fixed effects for treatment group with prior treatment strata (medically naïve or previously treated versus washout) and baseline IGF-1 level included as covariates in the model.

Baseline IGF-1 will be defined as the average of the measurements taken on Day 1 prior to first dose of study drug and the last IGF-1 value measured just prior to this day. EOR will be defined as the average of the last 2 IGF-1 results captured at 22 and 24 weeks of treatment. If only one IGF-1 result is available at Weeks 22 and 24, then that result will be used alone. If both Week 22 and 24 results are not available, the last available IGF-1 result will be used. If there is rescue therapy administered, the last available IGF-1 result prior to rescue therapy will be used.

The treatment difference and standard error with associated 95% CI will be presented along with the p-value. LS means will be presented for each treatment group along with the standard error of adjusted means. Summary statistics will also be presented for the FAS population showing the n, mean, median, standard deviation, IQR, minimum and maximum values for IGF-1xULN by visit and change from Baseline to each post Baseline visit for IGF-1xULN. All summaries will be by treatment group. A waterfall plot will be generated for this endpoint.

Sensitivity Analyses for the Key Secondary Efficacy Endpoint

Missing insulin-like growth factor 1 (IGF-1) results and all assessments following rescue therapy will be imputed by multiple imputation using on-treatment intermediate values from the placebo group, which will take into consideration the variability from natural disease course prior to medical intervention.

7.3.3.2. Secondary Efficacy Analysis

These secondary endpoints in order of clinical importance along with their corresponding analyses are as follows.

- Variable: Endpoint is Response defined as IGF-1 <1.3×ULN at EOR based on the average of last 2 measurements collected at EOR (Weeks 22 and 24), rounded to 2 significant figures. If only one IGF-1 result is available at Weeks 22 and 24, then that result will be used alone to define this response. Other components of the estimand align with primary endpoint in Section 7.3.2.
- Variable: Endpoint is Proportion of participants with GH <1 ng/mL at Week 22. Average from the integrated GH sampling at week 22 will be used to determine

response. Other components of the estimand align with primary endpoint in Section 7.3.2.

- Variable: Endpoint is Change from Baseline in ASD at EOR. Other components of the estimand align with key secondary endpoint in Section 7.3.3.1.

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 will range from 0-70 and be computed by adding each of the individual symptom intensities for headache pain; joint pain; sweating; fatigue; weakness in legs; swelling; and numbness or tingling. [redacted]

7.3.4. Analysis of Exploratory Endpoints 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 7.3.1.

7.3.4.1. Change from Baseline to Week 22 in GH

Change from baseline to Week 22 will be analyzed using the same methods described in Section 7.3.3.1 for the FAS. Baseline is defined as the average from the fasting integrated GH samplings at screening visit.

7.3.4.2. Proportion of Participants who Receive Rescue Therapy

The number and proportion of participants who took one or more doses of rescue therapy during the RC phase will be summarized between 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 prior treatment group strata 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
- Scatterplot of IGF-1×ULN and GH at EOR
- A regression line plotted of IGF-1×ULN
- Box plots will be generated for IGF-1 by treatment group at Baseline and again at EOR 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 EOR stratified by completers and non-completers all in one graph.

7.3.4.3. Time from randomization to first dose of rescue treatment

A Kaplan- Meier plot will be generated showing number of participants at risk over time. Number of events and median time to event will be summarized by treatment group. Participants without this event will be censored at the date of discontinuation from treatment or the last date of the RC phase.

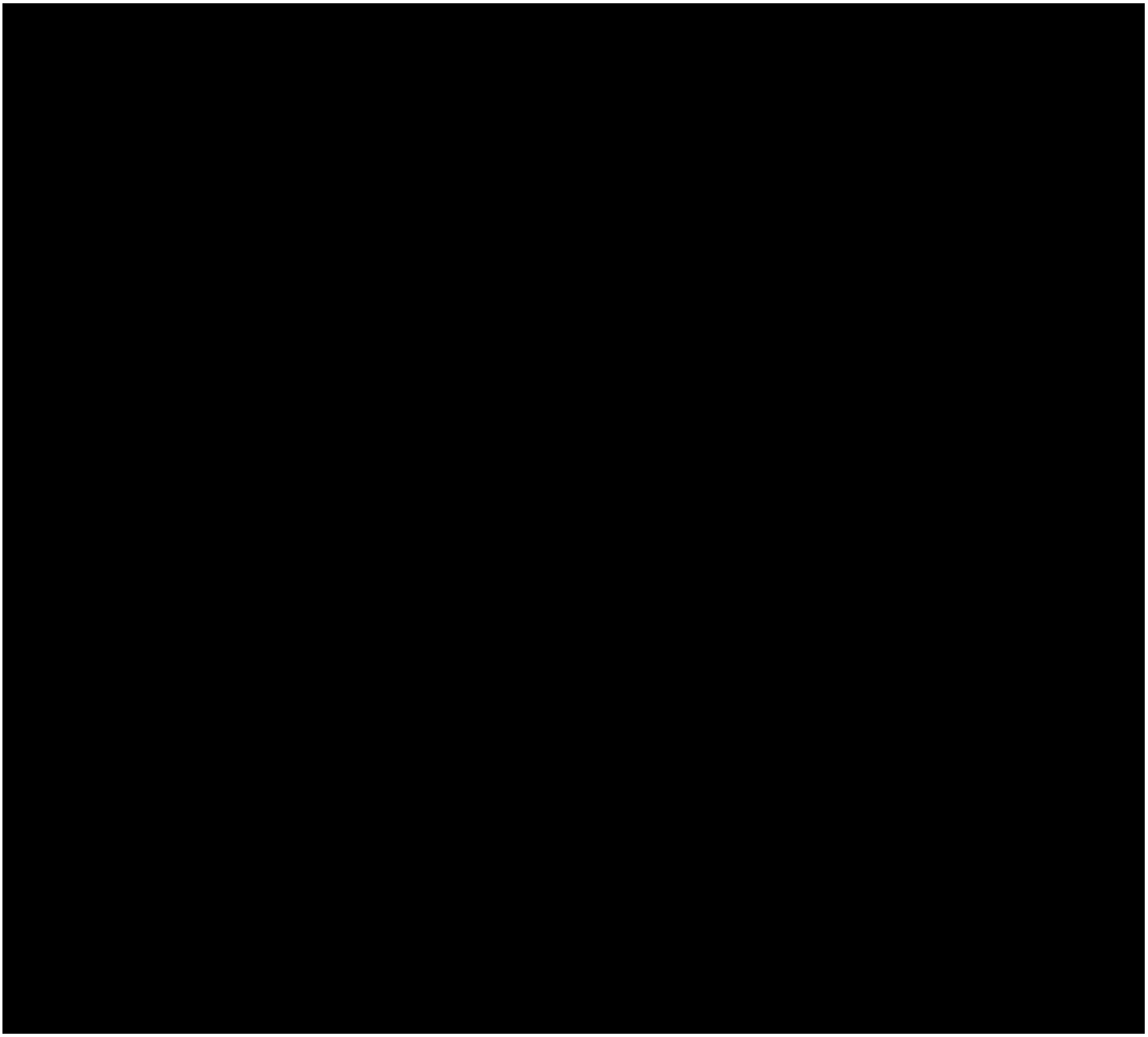
7.3.4.4. Time to Initial Response of IGF-1 ≤1.0×ULN

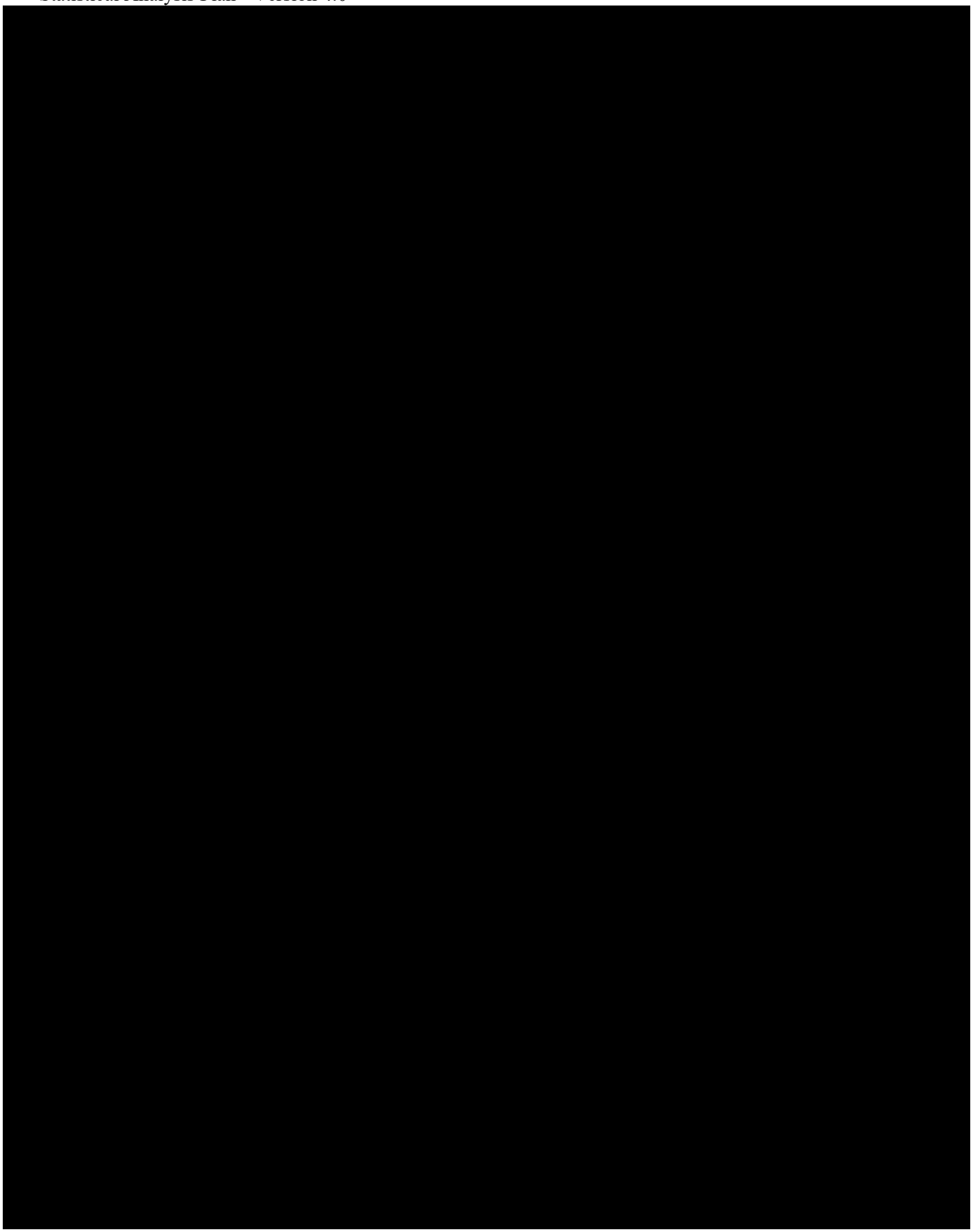
A Kaplan-Meier plot will be presented for time from randomization to first occurrence of IGF-1 ≤1.0×ULN for two consecutive visits by treatment group. All IGF-1 results (scheduled or unscheduled) will be used. Participants who do not meet IGF-1 ≤1.0×ULN for two consecutive visits prior to discontinuation of treatment will be censored at the time of last assessment prior to discontinuation of treatment during RC phase.

Number of events, censoring, median time to event and related summary statistics will be summarized by treatment group.

7.3.4.5. Proportion of Participants with GH <2.5 ng/mL at Week 22

The exploratory response variable is defined as GH<2.5 ng/mL at week 22. This endpoint will be tested using the method defined in Section 7.3.2 for the FAS.





7.3.4.10. Change from Baseline to EOR in Pituitary 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. Baseline is the value prior to first dose and EOR = Week 24. Adenoma volume is a parameter captured from the magnetic resonance imaging (MRI) central reads and will also be summarized by treatment group.

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

The percentage of participants with tumor reduction of greater than 20% from baseline to EOR will be summarized by treatment group along with Exact 95% CIs for the FAS.

7.3.4.11. 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 22 for GH and the mean of Week 22 and Week 24 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 7.3.2 for the FAS. These endpoints may also be presented over time by treatment group. The plots below will also be presented:

- Scatterplot of change from baseline to Week 22 in GH versus change from baseline to EOR in IGF-1×ULN.
- Box plot: Side by side box plots- one for IGF-1×ULN and the other for GH.

7.3.5. Analysis of OLE Efficacy Endpoints

Analysis of efficacy endpoints in OLE phase will be performed by OLE SS.

Change from OLE Baseline in IGF-1

IGF-1 and change from OLE Baseline of IGF-1 in ULN level at each visit in the OLE phase will be summarized by treatment group and overall.

Proportion of participants with IGF-1 <1.3×ULN and ≤ 1.0×ULN

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

Change from OLE Baseline in Total ASD Score

[redacted]

Change from OLE Baseline in GH

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

Change from OLE Baseline in Residual Tumor Volume

Change from baseline in residual tumor volume at each visit in the OLE phase will be summarized descriptively.

Proportion of Participants Who Received Adjunctive Therapy

The number and proportion of participants who took one or more doses of rescue therapy during the OLE phase will be summarized.

Change from OLE Baseline in [redacted]

Descriptive statistics will be used to summarize the [redacted] by visit according to the schedule of assessments.

Absolute change from OLE Baseline at all post-OLE Baseline treatment visits will also be summarized.

Change from OLE Baseline in [redacted]

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

[redacted] at each visit

[redacted] results will be summarized at each visit showing raw scores.

[redacted] at Week 120

The categorical responses will be presented at Week 120 using the counts and percentages.

Change from OLE Baseline in [redacted] Total Score

The composite scores and standardized scores for each domain and change from OLE baseline will be summarized by visit.

7.3.6. Multiple Comparisons and Multiplicity

To control the family-wise Type I Error for the primary, key secondary and secondary endpoint, all hypothesis testing will be performed using the gatekeeping test strategy based on a fixed sequential method. The key secondary and secondary endpoints will be tested in the order provided below. The hypothesis testing of key 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 subsequent comparison of key secondary and 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 Rates at EOR
2	Key Secondary: Change from Baseline in IGF-1 at EOR
3	Response of IGF-1 <1.3×ULN at EOR
4	Change from Baseline to EOR in Total ASD score
5	Proportion of participants with GH <1 ng/mL at Week 22

In the event that sample size is increased due to the unblinded interim analysis timepoint, the combined p-value approach defined in Appendix 1 will be implemented. The resulting inferential framework for the adaptive design guarantees overall Type I error rate control in the strong sense at a two-sided alpha level of 0.05 with respect to the two sources of multiplicity (data-driven decision rules at the interim analysis and analysis of the primary/secondary endpoints).

7.4. Analysis of Safety Endpoints

Safety analyses will be conducted by RC phase for the SS and OLE phase for the OLE SS separately. There will be no inferential testing done on safety endpoints.

7.4.1. Adverse Events

Reported AEs will be classified based on the MedDRA terminology, version 24.1 or later.

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 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 a calculation are handled per Section 8.5.

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 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 8.5 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 RC Phase.

TEAEs will be analyzed for RC phase using the SS and OLE phase using the OLE SS, separately. 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.

7.4.1.1. Overall AE Summaries

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

- Any TEAE

- Any Treatment-related TEAE
- TEAE by severity (mild, moderate, severe)
- Any Serious TEAE
- Any Treatment-related Serious TEAE
- Any TEAE leading to death
- Any TEAE leading to treatment interruption
- Any TEAE leading to dose reduction
- TEAE defined as serious or leading to death, treatment discontinuation, study discontinuation, or dose reduction
- TEAE leading to treatment discontinuation
- TEAE leading to study discontinuation
- TEAEs of special interest

7.4.1.2. AE Summaries by SOC and PT

TEAEs will be summarized by SOC and PT by treatment group and overall including the number and percentage of participants with each event as well as the number of events within each SOC and PT.

7.4.1.3. AE Summaries by PT

The following will be summarized by PT for each treatment group and overall including the number and percentage of participants with each event as well as the number of events within each PT.

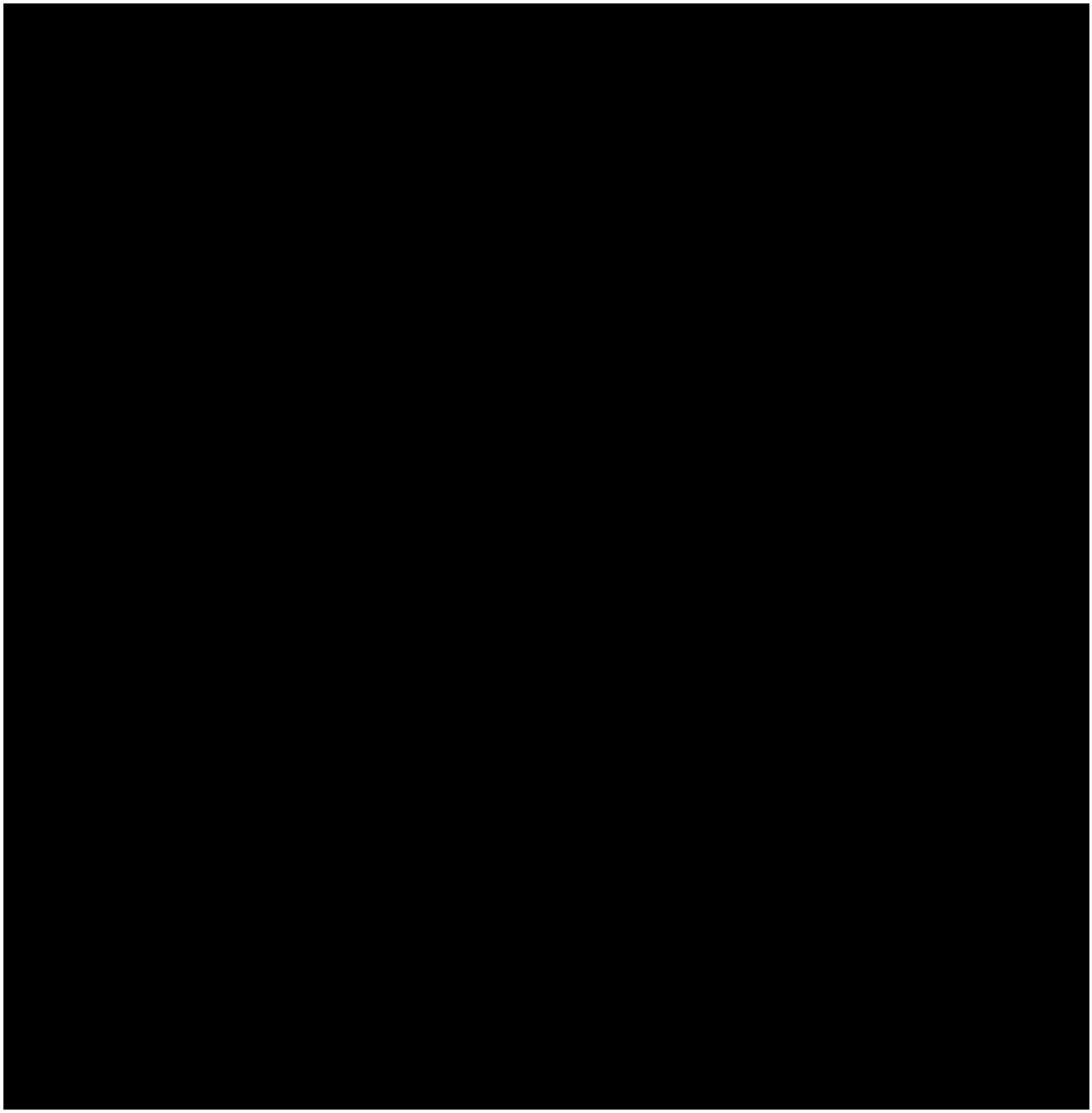
- TEAEs
- Most Frequent TEAEs with an incidence of ≥ 5% in total participants
- Most Frequent Treatment-related TEAEs with an incidence of ≥ 5% in total participants. Related is defined as relationship to paltusotine of “Possibly Related”, “Probably Related”, or “Definitely Related”. AEs with a missing relationship will be considered related for this summary
- Treatment-related TEAEs
- TEAEs by Severity
- Most Frequent TEAEs of Special Interest with an incidence of ≥ 5%
- Serious TEAEs
- Treatment-related Serious TEAEs
- TEAEs of special interest
- TEAEs excluding AEs while on Rescue Medication by treatment group and overall

- TEAEs while on Rescue Medication by treatment group and overall

7.4.1.4. AE Listings

The following listings will be also presented by participant:

- All AEs
- Related AEs (Possibly, Probably or Definitely Related)
- SAEs
- TEAEs that are serious, lead to discontinuation from study or treatment, a dose reduction or death



7.4.3. Laboratory Data

Chemistry, hematology, lipids, and quantitative urinalysis in RC phase will be summarized by treatment group and overall with descriptive statistics at every scheduled visit including Baseline and changes from Baseline to each subsequent visit for the SS. Shift tables may also be presented to show the shift in values of low-normal-high-missing at Baseline to each post-Baseline visit by treatment group. An additional shift table may be presented for the shift from Baseline to worst on- treatment value by treatment group.

Similar analyses will be conducted for chemistry, hematology, lipids, and quantitative urinalysis in the OLE phase using the OLE SS. OLE baseline will be used in the analysis instead.

Calcium Corrected for Albumin = [0.8 × (normal albumin – participant's albumin)] + serum Ca
Where normal albumin = 4 mg/dL standard units or 40 g/L SI units.

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

A by-participant listing will be generated for Liver test abnormalities. This listing will show confirmation of detected liver test abnormalities is required for any participant with 1 or more of the following:

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

Liver test abnormalities leading to treatment discontinuation will also be presented in a by-participant listing. If a participant meets any of the following 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.

7.4.4. Vital Signs

Vital sign parameters including systolic and diastolic pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), and body temperature (C) will be summarized presented by treatment group for the RC phase using the SS and by treatment group for the OLE phase using the OLE SS separately. They will also be presented by scheduled visit as observed values and changes from Baseline (or OLE Baseline) using descriptive statistics.

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

7.4.5. ECGs

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 in RC phase will be provided for the following ECG parameters for the SS: heart rate (HR), QRS duration, PR interval, QT 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 to worst (highest) post baseline result by treatment group. Change from Baseline summaries will also be presented for measurements that represent a change of >30 msec and >60 msec at each scheduled visit.

A by-participant listing of ECG results will be presented.

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 post-Baseline visit. Participants with shifts from normal to abnormal clinically significant or not clinically significant from Baseline may be listed separately including description of the abnormality and any associated comments.

ECG data in the OLE phase will be analyzed in a similar way as the RC phase using the OLE SS, except the OLE Baseline will be used instead.

7.4.6. Biliary/Gallbladder Ultrasound

The number and percentage of participants with gallstones, absent or present at Baseline and Week 24 will be presented by treatment group in the RC phase for SS. Shift tables may be created that show these values at Baseline and how they shift to Week 24 by treatment group and final dose group. Similar summaries will be presented for gallbladder 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.

Similar analyses will be conducted for biliary/gallbladder at OLE Baseline and Week 120 in the OLE phase using OLE SS.

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

7.4.7. 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 and each post-Baseline visit by treatment group for RC phase using SS. In addition, change and percent change from Baseline will be presented by treatment group.

Similarly, U.S. Ring size, weight (kg), and BMI (kg/m^2) in OLE phase will be analyzed using the OLE SS.

7.4.8. Physical Examination

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

[redacted]

7.5. Analysis of Pharmacokinetic Endpoints

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.

8. DERIVED DATA

8.1. Study Day

The definition for the study day included in each study window is defined as below: Study Day prior to Day 1 = Visit Date – Day 1 Date

Study Day on or after Day 1 = Visit Date – Day 1 Date + 1

If an assessment's mapped visit is a visit at which the participant has data from a scheduled visit present, or if no analyses are planned for the assessment at the mapped visit, the data collected at the early termination or unscheduled visit will not be included in analyses.

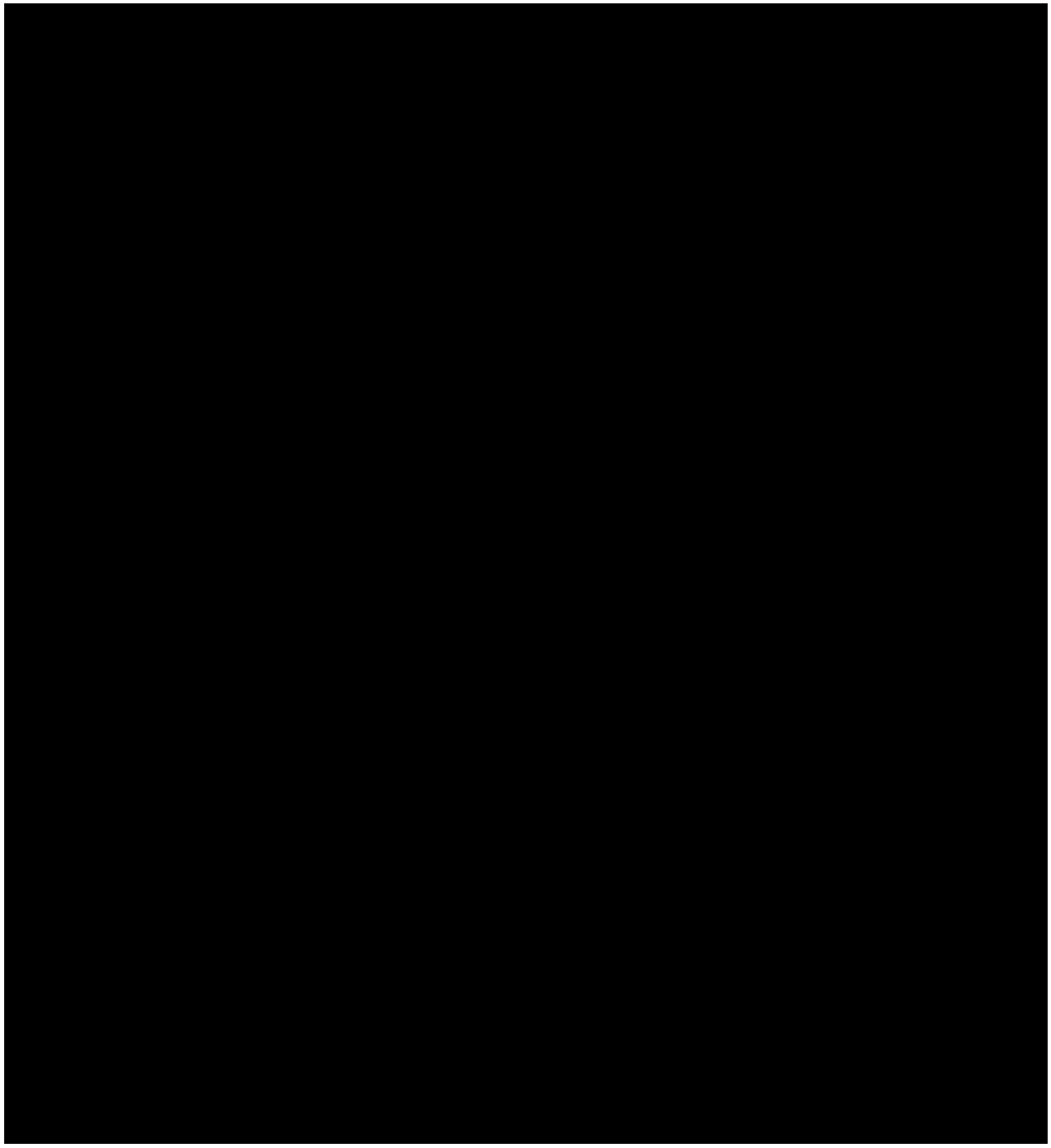
8.2. Visit Windows

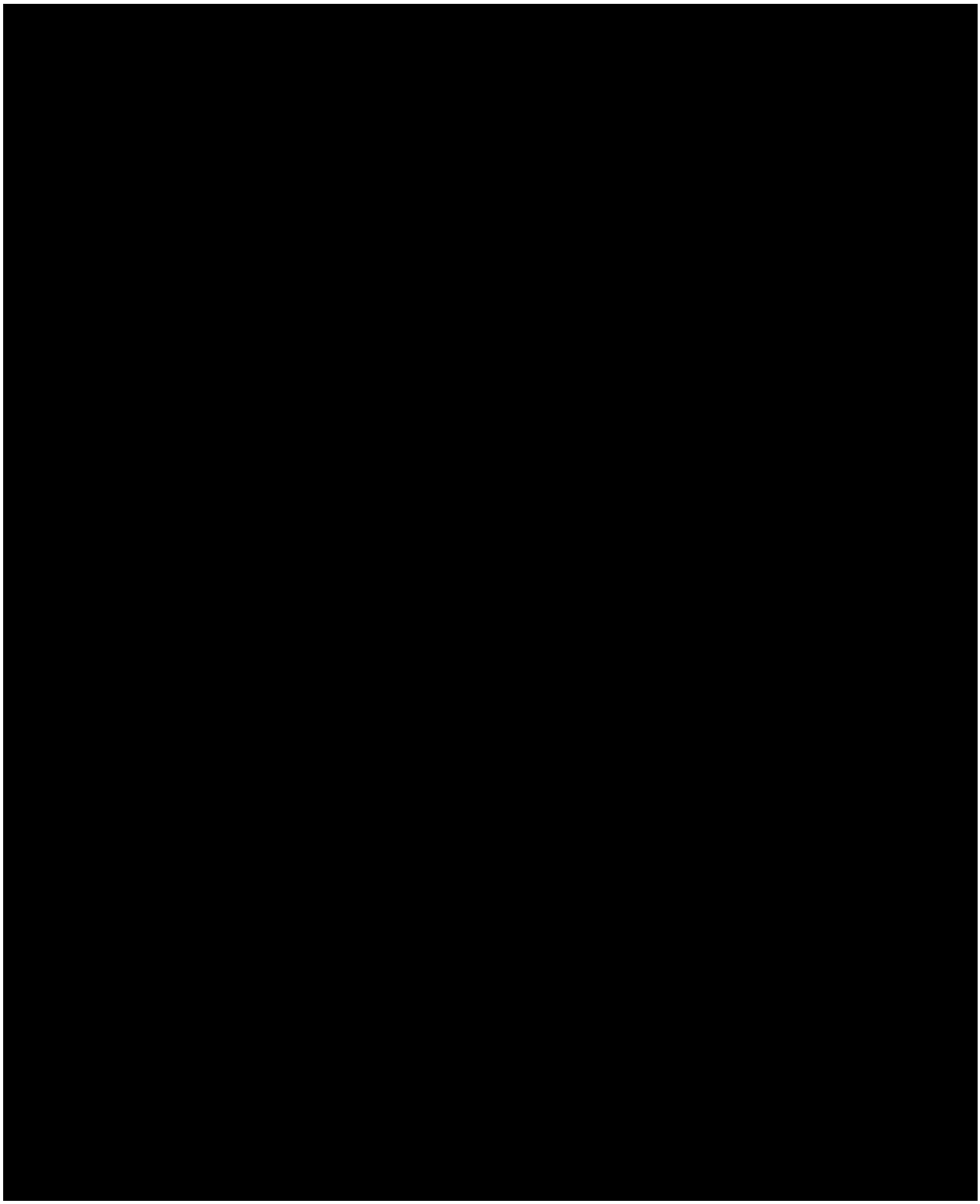
Data are summarized based on nominal visit indications with the exception of data collected at early termination and unscheduled visits. These data will be summarized based on mapped visit value based on the midpoint between visits. If an assessment's mapped visit is a visit at which the participant has data from a scheduled visit present, or if no analyses are planned for the assessment at the mapped visit, the data collected at the early termination or unscheduled visit will not be included at a mapped visit.

In the event of multiple values from unscheduled or early termination assessments within an analysis window, the value closest to the scheduled visit target study day will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected.

Data collected at all visits will be included in the data listings with visit presented as reported by the site.

Data will be summarized based on nominal visit indications except for data captured at early termination and unscheduled visits. Data from early termination and unscheduled visits will be summarized based on mapped visit values. The analysis windows for early termination and unscheduled visits are presented in the following tables.





8.3. Screening, Baseline and OLE Baseline Definitions

Screening IGF-1xULN is defined as the S1 screening visits for stratum 1 participants and the last IGF-1 value captured prior to Day 1 (S2 or S3) for stratum 2 participants. These values will be rounded to 2 decimal places by the central labs.

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. Baseline IGF-1×ULN is the mean of the value collected at day 1 prior to dose and the last screening visit prior to this. For GH, Baseline is defined as the average of all the measurements taken from fasting integrated GH 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 7.3.3.2.

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.

8.4. Change and Percent Change from Baseline/OLE Baseline

In RC phase, change from Baseline is determined by calculating (post-Baseline value – Baseline value). Percent Change from Baseline is determined by calculating ((post-Baseline value – Baseline value) / Baseline value) × 100.

For OLE phase, OLE baseline value will be used instead for the calculation of change and percentage change from OLE baseline.

8.5. 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.

8.6. 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.

9. CHANGES TO PLANNED ANALYSIS IN PROTOCOL

Due to health authority feedback, last observation carried forward was removed from the sensitivity analysis for responder analyses. Residual tumor volume was moved from a safety endpoint to an efficacy endpoint and added as an exploratory objective.

A maximum sample size of 240 was added to the interim analysis for sample size re-estimation.

Sensitivity analyses for primary endpoint using multiple imputation methods were removed.

The secondary endpoints of change from Baseline in IGF-1 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.

The secondary endpoint of proportion of participants with GH <1 ng/mL was moved to the end of the fixed sequence testing procedure.

The following exploratory endpoints are not listed as endpoints in the protocol and were added to the SAP as they are collected in the study:

- Time to initial response of IGF-1 ≤1.0×ULN
- Change from Baseline to EOR in residual tumor volume
- Change from Baseline to EOR in [redacted]
- Change from Baseline to EOR in [redacted]
- [redacted] at EOR
- [redacted] at EOR

- Change from Baseline to EOR in [redacted]
- Proportion of participants with IGF-1≤1.0×ULN from weeks 12 through EOR
- 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

10. REFERENCES

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3. International Council on Harmonisation ICH E6 guideline entitled, “Guidance for Industry: E6 Good Clinical Practice: consolidated Guidance”
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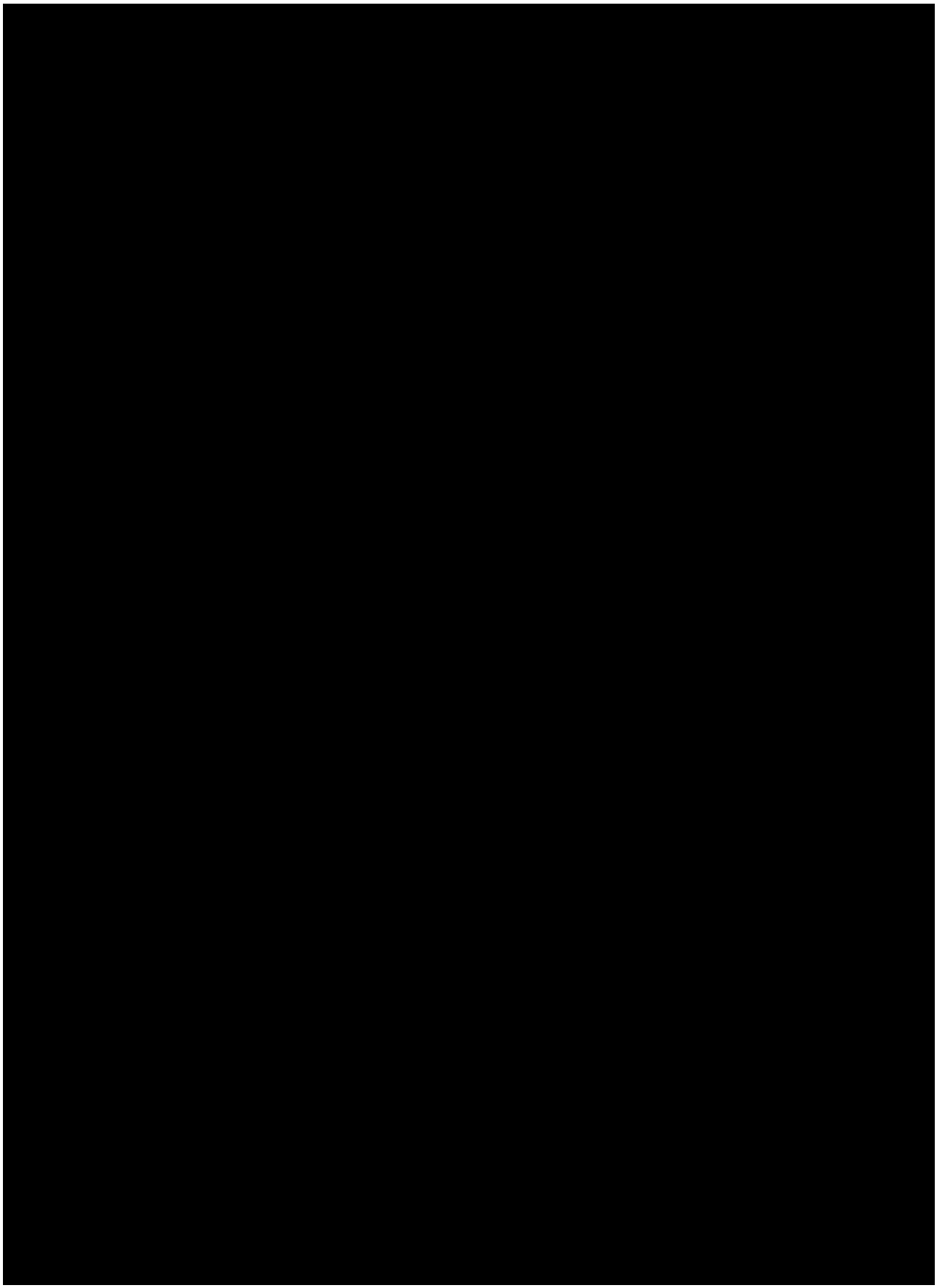

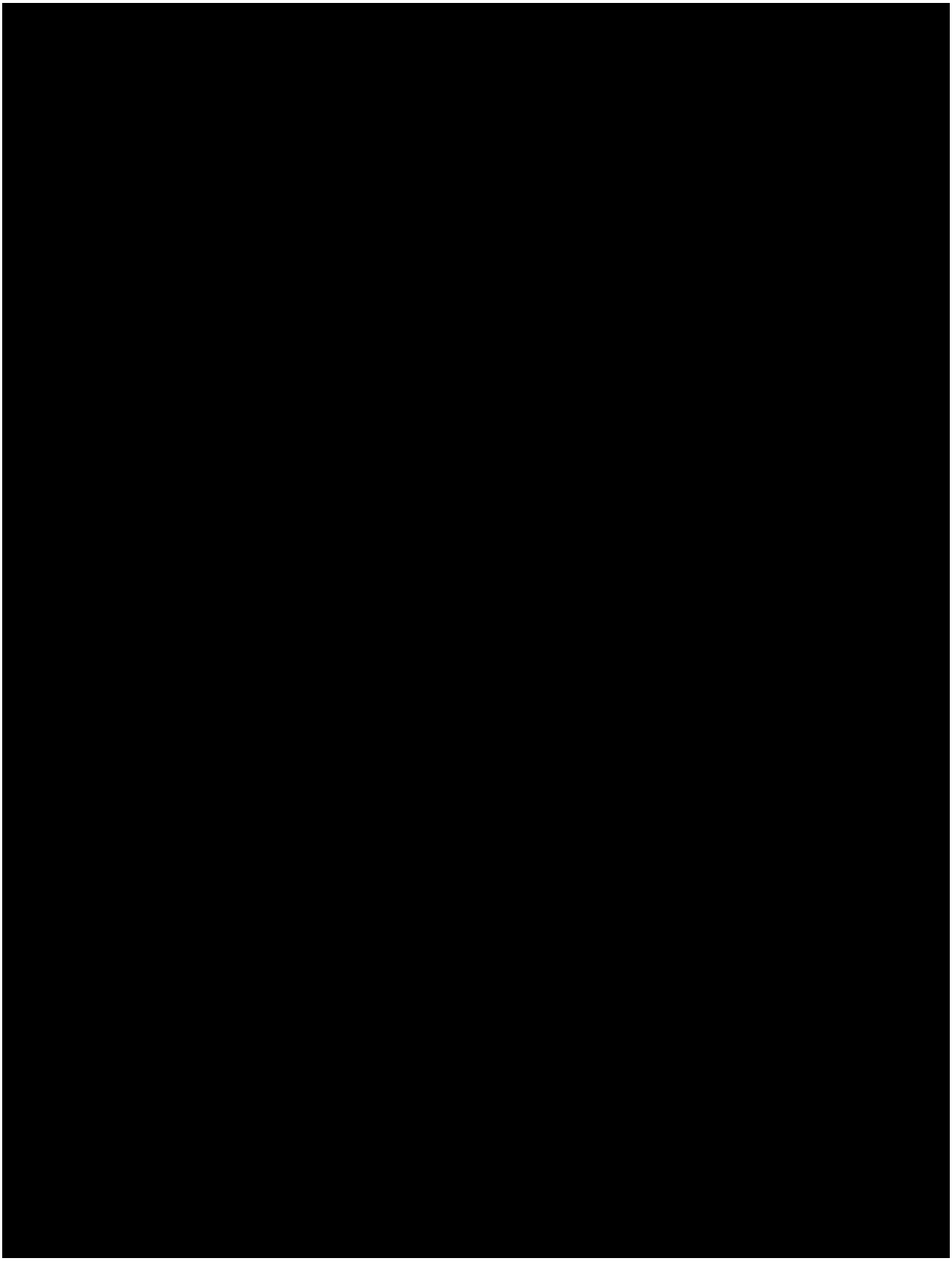

Signature Page for VV-CLIN-001098 v1.0
CRN00808-08 Statistical Analysis Plan v4.0

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