STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	A phase 3, randomized, open-label, active controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes in acromegaly patients treated with octreotide capsules, and in patients treated with standard of care parenteral somatostatin receptor ligands, who previously tolerated and demonstrated a biochemical control on both treatments
PROTOCOL (Short Name, Version, and Date):	MPOWERED, OOC-ACM-302 Version 4.0, [redacted]
STUDY DRUG:	Octreotide capsules
STUDY PHASE:	3
SPONSOR:	Chiasma, Inc. [redacted]
SAP DATE:	15May 2019

Signature Page

Approvals:

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LIST OF ABBREVIATIONS

%	Percent
ACRO-TSQ	Acromegaly Treatment Satisfaction Questionnaire
AE	Adverse Event
AIS	Acromegaly Index of Severity
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BL	Baseline
CAS	Combination Analysis Set (sub-study in selected sites)
CI	Confidence Interval
CPK	Creatine Phosphokinase
CR	Complete Responder
d	Day
dL	Deciliter
EAS	Enrolled Analysis Set
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End-of-Treatment
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Levels Quality of Life questionnaire
EXT-AS	Extension Analysis Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-up
g	Gram
GGT	Gamma-Glutamyl Transferase
GH	Growth Hormone
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GOT (AST)	Glutamic Oxaloacetic Transaminase (aspartate aminotransferase)
GPT (ALT)	Glutamic Pyruvic Transaminase (alanine transaminase)
Hb	Hemoglobin

HbA1c	Glycosylated Hemoglobin
Htc	Hematocrit
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IGF-1	Insulin-like Growth Factor 1
IMP	Investigational Medicinal Product
kg	Kilogram
L	Liter
LAR	Long-acting Release
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
lsmeans	Least square means
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MID	Minimal Important Difference
mL	Milliliter
ng	Nanogram
NI	Non-inferiority
NR	Non-Responder
OAS	Octreotide Analysis Set
PR	Partial Responder
PRO	Patient Reported Outcome
PT	Preferred Term
RCT	Randomized Controlled Treatment Phase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Steering Committee
SD	Standard Deviation
SOC (treatment)	Standard of Care
SOC (safety)	System Organ Class
SOP	Standard Operation Procedures
SRL	Somatostatin Receptor Ligands
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent AE
TSH	Thyroid Stimulating Hormone
TWA	Time Weighted Average

ULN	Upper Limit of Normal
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire Specific Health Problem V2.0
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

2 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis and reporting to be implemented for the Run-in Phase, Randomized Control Phase (RCT) and Combination Phase of Chiasma, Inc. Trial ID MPOWERED, protocol OOC-ACM-302 (*A phase 3, randomized, open-label, active controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes in acromegaly patients treated with octreotide capsules, and in patients treated with standard of care parenteral somatostatin receptor ligands who previously tolerated and demonstrated a biochemical control on both treatments).* The SAP should be used in conjunction with the protocol; however, the SAP will be used as the authoritative document concerning the statistical analyses for this study. When differences exist in descriptions and explanations in the protocol and this SAP, the SAP will prevail. Any deviations from this SAP that are implemented in the analyses will be documented with sound clinical and statistical rationale in the Clinical Study Report (CSR).In the event of any changes to the primary endpoint or analysis the change(s) will be documented through a protocol amendment which is consistent with ICH E9.

The study includes several study phases which are described in the protocol. These phases are Screening, Run-In, RCT, Combination, Study Extension and Follow-Up. The core focus of this SAP is to describe the analyses for the Run-In, RCT and combination phases. The analyses for the Study Extension phase will be detailed in a separate SAP. At the conclusion of the Run-in Phase, and following evaluation of the measurement properties of the new items added to the acromegaly treatment satisfaction questionnaire (Acro-TSQ), and the minimum important difference (MID) for each scale is estimated, the SAP will be amended.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) and International Conference (ICH) on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: E9 Guidance on Statistical Principles in Clinical Trials.

This SAP is based on the protocol Version 4, Amendment 3 dated 04 March 2018. In the event of future amendments to the protocol, this SAP will be modified as necessary to account for changes relevant to the statistical analysis.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

Core Study

- To assess maintenance of biochemical control of octreotide capsules compared to parenteral SRLs in patients with acromegaly, who previously demonstrated biochemical control on both treatments.
- To assess maintenance of biochemical control of octreotide capsules in patients with acromegaly, who previously tolerated and demonstrated biochemical control on SRL injections [redacted].
- To assess symptomatic response to octreotide capsules compared to parenteral SRLs.
- To assess patient reported outcome (PRO) in patients treated with octreotide capsules compared to parenteral SRLs.
- To evaluate the safety profile of octreotide capsules compared to parenteral SRLs.

[redacted]

Extension phase objective

- To assess the long-term safety, efficacy and patient reported outcomes of octreotide capsules in acromegaly patients.

Combination phase sub-study (in selected sites)

- To assess the efficacy of octreotide capsules co-administered with cabergoline in the treatment of acromegaly patients with modestly elevated IGF-1 levels (defined as $1.3 \leq$ IGF-1 $< 2 \times$ ULN, or IGF-1$<1.3 \times$ ULN and GH ≥ 2.5 ng/mL).

3.2 Trial Design

This will be a phase 3, randomized, open-label, active controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes (PROs) in acromegaly patients treated with octreotide capsules and in patients treated with SOC parenteral SRLs, who previously tolerated and demonstrated biochemical control on both treatments.

The Core study will consist of three phases: A Screening phase, Run-in phase and an RCT phase.

A Steering Committee (SC) will act in an advisory capacity to the Sponsor to provide oversight to the trial conduct and to support its successful completion.

An Independent Data Monitoring Committee (IDMC) will act in an advisory capacity to the Sponsor to monitor patient safety during the study.

Following up to 4 weeks Screening phase, eligible patients who are biochemically controlled (defined as IGF-1 < 1.3 × ULN and mean integrated GH <2.5 ng/mL), on parenteral SRLs will be switched to octreotide capsules for a 26-week Run-in phase. During this phase the effective dose for each patient will be determined through dose titration (see Run-in phase below).

Patients whose acromegaly is being controlled biochemically on octreotide capsules at the end of the Run-in Phase will enter a 36-week open-label RCT phase where they will be randomized to continue on octreotide capsules or switch back to their injectable SRL treatment (as received prior to Screening) or other treatment as determined by their physician.

Following the completion of the Core study (Screening, Run-in and RCT phases), eligible patients will be offered to enter the Study Extension phase and receive octreotide capsules for 2 years or until product marketing or study termination (the earliest of which). Beyond 2 years Extension phase, the Sponsor will either extend the Extension phase (via protocol amendment for an additional year or until product marketing or study termination) or consider compassionate (if requested by the principal investigator under compassionate use protocol).

[redacted]

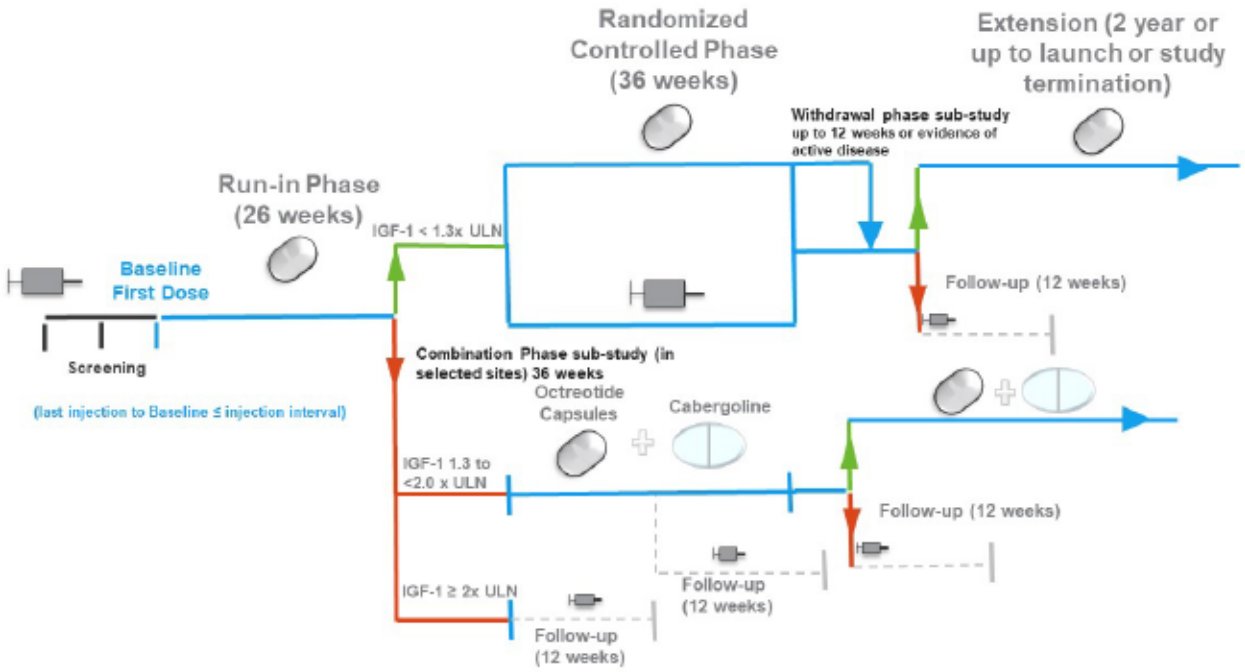
In selected sites where the Combination phase sub-study is conducted, patients who fail to respond to octreotide capsules 80 mg for at least 2 weeks therapy during the course of the Run-in phase, or patients ineligible to enter the RCT phase on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 ≥ 1.3 x ULN to IGF-1 <2 x ULN, or IGF-1<1.3 × ULN and GH ≥2.5 ng/mL), will be eligible to enter the Combination phase sub-study. These patients will receive co- administration of octreotide capsules (80 mg/day) with cabergoline [redacted] for a total of 36 weeks. At the end of the Combination phase sub-study, eligible patients will be offered to enter the Study Extension phase and continue the same combined treatment regimen. Patients discontinuing early from the Combination phase sub-study or all other patients not meeting the

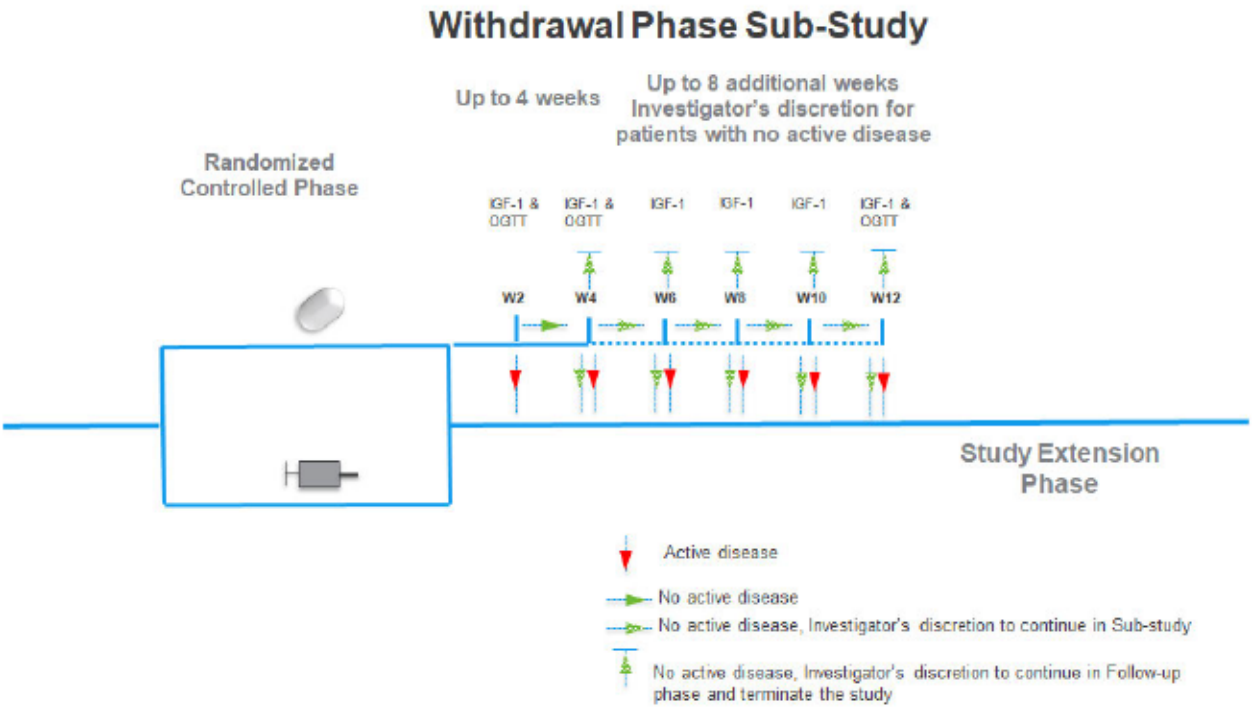
criteria for randomization into the RCT phase or Combination phase sub-study will revert to their prior injectable SRL treatment (prior to Screening) or other treatment as determined by their physician, and be followed for 12 weeks after last dose.

Patients who early terminate the Run-in phase for any reason in sites who do not participate in the Combination phase sub-study will revert back to their injectable SRL treatment (prior to Screening) or other treatment as determined by their physician and will be followed up for 12 weeks after last dose of study medication.

Database lock for the Core study and the Combination phase sub-study will occur at the completion of both the RCT phase/End of Treatment (EOT) (last patient completes week 62) and the Combination phase sub-study (last patient completes week 36), and will not include the Follow-up phase, [redacted] or Study Extension treatment phase. Interim analyses of the Extension Phase will be conducted periodically, after completion of the RCT phase. Data collected post RCT, phase or Combination phase sub-study will be included in the Study Extension database. Details of these analyses will be outlined in a separate SAP.

Figure 2.2-1 Study Overview





For Study Decision Tree, please refer to Appendix A in the Study protocol.

Core study duration will be 66 weeks, comprised of:

Phase	Duration	Visit window
Screening phase:	up to four weeks	
Run-in phase (octreotide capsules):	26 weeks	±3 days*
Randomized Controlled Treatment (RCT) phase (octreotide capsules vs. Parenteral SRLs):	36 weeks	±3 days

* At week 26, the visit window will be – 3 days to 10 days

Duration of other study phases will be as follows:

Combination phase sub-study (in selected sites): Administration of octreotide capsules 80 mg (each capsule strength is 20 mg) with [redacted]. However, if the patient is biochemically controlled (defined as IGF-1 < 1.3 × ULN) at the week 4 assessment of the Combination phase sub-study, based on clinical judgement, the cabergoline dose can be maintained (i.e. no further dose escalation is required). The study phase is 36 weeks (in parallel to the core study durations). Visit window ±3 days.

[redacted]

Study Extension phase: Two years or until study medication is commercially available or Sponsor terminates the study (the earliest of which). The Study Extension phase may be extended (protocol amendment) or treatment may be provided under a separate Compassionate Use protocol following specific request by the Principal Investigator. Visit window ±3 days.

Follow-up Phase:

Any patient early discontinuing treatment during the study (Run-in phase, RCT phase, Combination sub-study or Extension phase), or patient ineligible to enter the RCT phase or Combination phase sub-study, patients ineligible or not opting to continue into the [redacted] Extension phase, will undergo three follow-up visits over 12 weeks (+4, +8 and +12 weeks) after their last study medication dose for safety and efficacy assessments.

3.3 Primary Hypothesis:

The following primary hypothesis is being tested for the EMA:

H_o: The proportion of patients who are biochemically controlled $P_{\text{octreotide capsules}}$ - P_{SRL} throughout the RCT phase $\leq$ -20%

H_a: The proportion of patients who are biochemically controlled $P_{\text{octreotide capsules}}$ - P_{SRL} throughout the RCT phase > -20%

An assessment of non-inferiority (NI) will be made by comparing the lower bound of the two-sided 95% confidence interval (CI) for the difference in proportions of patients who are biochemically controlled (octreotide capsules - SRL) to a NI margin of -20%. If the lower bound of the CI is greater than the NI margin of -20%, octreotide capsules will be declared non-inferior to injectable SRLs.

A patient will be considered biochemically controlled if their IGF-1 Time Weighted Average (TWA), during the RCT phase is < 1.3 x ULN.

[redacted]

3.4 Study Sample Size

Approximately 150 patients will be enrolled into the Run-in phase of the study. The total number of patients will be adjusted to ensure a minimum of 80 patients will enter the RCT phase, with approximately 48 patients assigned to octreotide capsule arm and 32 patients assigned to SRL injection arm.

[redacted]

[redacted]

4 STUDY ENDPOINTS

4.1 Efficacy Endpoints

4.1.1 Primary Endpoint [redacted]

The proportion of patients who are biochemically controlled throughout the RCT phase. A patient will be considered biochemically controlled if their IGF-1 Time Weighted Average (TWA) during the RCT phase is < 1.3 x ULN.

4.1.2 Additional [redacted] Endpoints [redacted]

- [redacted]
- RCT phase - Proportion of patients on octreotide capsules who are biochemically controlled at the end of the RCT phase, defined as IGF-1 <1.3 × ULN (based on the average of week 62 and week 58).

4.1.3 Secondary Endpoints

- The proportion of patients who are biochemically controlled throughout the RCT phase. A patient will be considered biochemically controlled if their IGF-1 TWA during the RCT phase is < 1.3 × ULN [redacted]
- [redacted]
- Proportion of patients who maintain or reduce the overall number of active acromegaly symptoms, at the end of the RCT phase (week 62/EOT), compared to week 26 (start of RCT phase).

- Proportion of patients who maintain or improve their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score), compared to week 26 (start of RCT phase)
- Change from baseline (week 26) in Acromegaly treatment satisfaction questionnaire (ACRO-TSQ) scale scores to the end of the RCT phase.
- Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country), who enter the Study Extension phase, overall and by treatment group.
- Change from the start of the randomized phase of the study (week 26) through the end of the RCT (week 62) for IGF-1.
- Change from the start of the randomized phase of the study (week 26) to end of the RCT (week 62) in mean integrated GH.

[redacted]

4.1.4 Exploratory Endpoints

[redacted]

- Proportion of patients with TWA IGF-1 ≤1 x ULN during the RCT Phase in patients who started the RCT with IGF-1≤1 x ULN.

[redacted]

- [redacted] Proportion of patients with a reduction in the overall number of active acromegaly symptoms, at the end of the Run-in phase compared to Baseline.
- Proportion of patients with improved AIS score at the end of the Run-in phase compared to Baseline.
- Change from Baseline in Acromegaly treatment satisfaction questionnaire (ACRO-TSQ) scale scores at to the end of the Run-in phase.
- Health economic outcomes (EQ-5D, WPAI).

4.2 Safety Endpoints

- Frequency and severity of AEs and serious adverse events (SAEs) across each phase of the study
- Clinically significant laboratory abnormalities

4.3 Combination Phase Sub-Study Endpoints

The following exploratory endpoints will be defined for the Combination phase sub-study (in selected sites) of the study:

- Proportion of patients with the following IGF-1 and mean integrated GH values at the end of the Combination phase sub-study compared to Combination phase Baseline
  - IGF-1 <1.3 x ULN and mean integrated GH <2.5 ng/mL
  - IGF-1 < 1.0 x ULN and mean integrated GH < 1.0 ng/mL
  - IGF-1 < 1.3 x ULN
  - IGF-1 ≤ 1.0 x ULN
  - Mean integrated GH < 2.5 ng/mL
  - Mean integrated GH < 1.0 ng/mL
- Rate of change in IGF-1 (i.e., slope)
- Descriptive changes in IGF-1 or GH from combination study baseline to end of the combination (mean (SD), median (interquartile range), change from baseline, median% change from baseline, min, max, individual waterfall plots)
- Proportion of patients who reduced the overall number of active acromegaly symptoms, at the end of the Combination phase sub-study, compared to baseline
- Proportion of patients who improved their AIS score at the end of the Combination phase sub-study compared to baseline (improvement defined as reduction of at least 1 point in the AIS score)

[redacted]

4.5 Derivations of the Endpoints

4.5.1 IGF-1 and GH

IGF-1 and GH levels will be assessed by a central laboratory.

IGF-1 concentration in the blood will be assessed at all study visits (single sample).

GH concentration in the blood will be assessed at selected study visits. Blood samples for GH will be collected prior to the administration of IMP and every 30±5 minutes over 0-2 hours or over 2-

4 hours according to the Schedule of Assessments Appendix B through Appendix D given in the protocol. The mean integrated concentration will be calculated. A minimum of three GH samples are needed to calculate the mean integrated concentration or the data point will be considered missing.

At each visit that both IGF-1 and GH are collected, patients will be classified into 1 of 3 groups based on their IGF-1 and mean GH values as follows:

- Complete Responder (CR): IGF-1 $\leq$ 1 x ULN and GH < 2.5 ng/mL
- Partial Responder (PR): 1 x ULN < IGF-1 < 1.3 x ULN and GH < 2.5 ng/mL
- Non-Responder (NR): IGF-1 $\geq$ 1.3 x ULN or GH $\geq$ 2.5 ng/mL

4.5.2 IGF-1 Time Weighted Average (TWA)

The TWA response, over the treatment phase represents an integrated measure of efficacy across time. It is derived as the area under the curve (AUC) divided by the total amount of time under observation between the first and last IGF-1 value. All measurements will be used, including data collected at "Discontinuation" visits and "Unscheduled" visits. TWA will be derived as follows:

1) At each post baseline time point calculate $[(Y_t + Y_{t-1}) * \Delta \text{ time (in days)}]/2$
2) Sum up the values to obtain overall AUC
3) Divide by the total time under observation (in Days) between the first and last IGF-1 values,

where Y_t and Y_{t-1} are the IGF-1 values at the time point and the previous time point, and Δ time is the time between the two time points in days. The first time point should be the week 26 (baseline for the RCT phase) value. The last time point should be the week 62/EOT value. Any values collected > 1 day after the date of last dose will not be used in the derivation.

4.5.3 AIS

The acromegaly index of severity (AIS) will be assessed throughout the study as specified in Schedule of Assessments (Appendix B through Appendix D in protocol). At each visit the following symptoms will be assessed: Headache, Swelling of extremities, Joint pain, Sweating and Fatigue. Each symptom will be graded by its highest severity during the last four weeks, from no symptoms (score 0), to mild symptoms (1), moderate (2) or severe symptoms (3).
The overall AIS score is the sum of severity scores for each of the 5 acromegaly symptoms. The range will be 0 to 15, with 0 representing no symptoms and 15 representing severe symptoms.

A patient will be considered to be clinically controlled if their overall AIS score at week 62/EOT, as compared to week 26 (start of RCT), is the same or better (i.e., reduced).

Symptoms are considered to be active if the score is greater than 0.

4.5.4 Acro-TSQ

The new version of the Acro-TSQ includes six scales: Symptom Interference contains four items related to interference with symptoms; Treatment Convenience contains six items related to the convenience/inconvenience and ease of administration; Injection Site Interference contains two items related to injection site reactions; GI Interference contains three items related to GI side effects; Treatment Satisfaction contains three items related to treatment satisfaction; and Emotional Reaction includes three items related to emotional reactions to treatment.

Each scale score can range from 0 to 100, with 0 representing the lowest and 100 representing the best possible score for each of the six scales. Acro-TSQ scale scores are calculated if responses from at least 50% of the items within that scale are provided.

4.5.5 EQ-5D-5L

EQ-5D-5L (five severity levels EQ-5D), developed by the EuroQoL, is a standardized instrument to be completed by the patient for use as a measure of health outcome applicable to a wide range of health conditions (Herdman et al., 2011).

It comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression.

Based on qualitative and quantitative studies conducted by the EuroQol Group, there are five options (levels) under each dimension: 'no problems' (assigned a value of 1), 'slight problems' (assigned a value of 2), 'moderate problems' (assigned a value of 3), 'severe problems' (assigned a value of 4) and 'unable to/extreme problems' (assigned a value of 5) (reference Appendix G in protocol). The 1-digit level values for the 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score; however, the responses to all five dimensions, can be converted from a 5-digit number to a single summary index using the EQ-5D-5L Crosswalk Value Sets available online at http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html. The index values range from 0 to 1 where higher index values represent better health states. Only sites located in the following countries will have an index score given: France, Germany, Netherlands, Spain, UK and US. If there are any missing level values for any of the 5 dimensions, then the index score will be missing.

The EQ-VAS records the patient's self-rated health on a 20-cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' (value of 100) and 'the worst health you can imagine' (value 0).

4.5.6 WPAI:SHP

Work Productivity and Activity Impairment Questionnaire Specific Health Problem V2.0 (WPAI:SHP) is a standardized and validated tool to measure health outcomes in clinical trial settings (Reilly et al., 1993).

Specifically, this self-administered tool measures time missed from work, impairment of work and regular activities due to overall health and symptoms, relative to measures of general health perceptions, role (physical), role (emotional), pain, symptom severity and global measures of work and interference with regular activity (Appendix H).

The WPAI yields four types of scores:
1. Absenteeism (work time missed)
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment

Each of the 4 WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

The WPAI-SHP consists of the following 6 Questions:
- Q1 = currently employed
- Q2 = hours missed due to specified problem
- Q3 = hours missed other reasons
- Q4 = hours actually worked
- Q5 = degree problem affected productivity while working
- Q6 = degree problem affected regular activities

Each of the 4 WPAI scores are derived as follows:
- Percent work time missed due to problem: Q2/(Q2+Q4)*100
- Percent impairment while working due to problem: Q5/10*100
- Percent overall work impairment due to problem:
- Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)] *100
- Percent activity impairment due to problem: Q6/10 *100

5 GENERAL ANALYSIS DEFINITION

5.1 General Considerations

For categorical parameters, the number and percentage of patients in each category will be presented. The population count of each table will generally be the denominator used for percentage calculations or will be based on the number of patients appropriate for the purpose of analysis. The counts of missing values will be presented in summary tables along with percentages, if required. For continuous parameters, descriptive statistics will generally include number of patients (n), mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum, and maximum.

Unless otherwise specified, Baseline for the Run-in phase will be defined as the last value recorded prior to or equal to the date of the first dose of octreotide capsules (i.e., the date of assessment will be $\leq$ date of first dose), anytime during screening or Baseline visit. The week 26 value will be used as the baseline value for the RCT phase. In case of missing values at week 26, the last available

value on study drug, prior to week 26 and not earlier than week 20 will be used as the Baseline value for the RCT phase. Baseline for the combination phase will be the last value recorded during the run-in phase, and before the initiation of treatment with cabergoline.

All data will be pooled across all sites for reporting purposes, given the large number of sites in relation to the total sample size.

The general rule of presenting the decimal places are minimum and maximum values will be presented with the same number of decimals as collected for the data, means and medians will display 1 additional decimal, SD and standard errors will be displayed with 2 additional decimals. If the data has higher precision with 3 or more decimal places (for example Laboratory data) then the data will be determined on a by-parameter basis. Percentages will be displayed with 1 decimal places, if the percentage is zero or 100 then they will be displayed as "0%" and 100% respectively. All p-values will be presented to 3 decimals, if p-values are less than 0.001 they will be displayed as "<0.001".

The design of the study allows for patients to have varying numbers of visits during the Run-in and RCT Phase of the study. The duration of exposure to each dose will also vary. For analysis purposes data will be presented separately for each phase of the study as follows:

1. Summaries in the Run-in Phase will be presented overall and when applicable also by final target dose level (40, 60 or 80).
2. Summaries in the RCT Phase will be presented by Octreotide capsules, SRL injections (Octreotide LAR or Lanreotide) and for all patients regardless of treatment assignment. Octreotide capsules in these summaries will imply the final target dose level achieved during the Run-in phase. When applicable Octreotide capsules will be presented by target dose level (40, 60 or 80) and SRL injections will be presented by dose level as follows:

SRL Injection Dose	**Dose Level Category**
Any octreotide dose < 20mg total/month or lanreotide < 90mg total/month	Low
Any octreotide dose < 30mg total/month or lanreotide<120mg total/month	Middle
Any octreotide dose ≥ 30mg total/month or lanreotide ≥ 120mg total/month	High

3. Summaries in the Combination Phase will be presented for all applicable patients, and when applicable by Carbergoline dose.

5.2 Subgroups

The following subgroups will be summarized for specific tables, analyses and phases:

- Gender: Male, Female
- Region: (Eastern Europe, Western Europe, N. America)

- Age: <65 years old, ≥65 years old
- Target Dose of Oral Octreotide: 40 mg, 60 mg, 80 mg
- Prior Dose of SRL Injectables: Low, Middle, High (See Section 4.1)
- Run-in Baseline IGF-1: ≤1 ULN, [>1, <1.3 ULN], ≥1.3 ULN
- Run-in Baseline Response: Complete Response (CR), Partial Response (PR), No Response (NR)
- RCT Baseline (week 26)- IGF-1: ≤1 ULN, [>1, <1.3 ULN], ≥1.3 ULN
- RCT Baseline (week 26) Response: Complete Response (CR), Partial Response (PR), No Response (NR)

5.3 Data Handling Conventions

5.3.1 Missing Data

Primary Endpoint Based on EMA Advice

Should a patient dropout, all data collected up to that point and including the time of discontinuation will be included in the primary analysis. Given this approach for calculating the TWA response for an endpoint, no missing value will be imputed. However, if a patient discontinues during the RCT phase for lack of efficacy, he/she will be considered to be NOT biochemically controlled, regardless of their TWA.

Additionally, a sensitivity analysis will be conducted to examine the impact of missing data by imputing missing IGF-1 values using the Markov Chain Monte Carlo (MCMC) method for multiple imputation. It is the expectation that the missingness pattern will be intermittent or nonmonotone.

Multiple imputation and the subsequent analysis will involve the tasks described below:

1. Create a data set, one for each treatment group, of subjects with observed values and those needing estimation by multiple imputation. The missing IGF-1 values in each data set will be filled in using the MCMC method with a total of 50 sets of imputations being performed. The procedure will sequentially estimate an imputation model for IGF-1 values at each post-Baseline visit (up to Week 62), with baseline dose and baseline IGF-1 as predictors. Note that IGF-1 values at earlier visits will also be used as predictors for the model of IGF-1 at later visits. The resulting data sets for each treatment arm will be combined into one complete data set based on each of the 50 imputations.
2. Note: The imputation model based on the MCMC method will only allow continuous variables as predictors. Therefore, baseline dose (for each treatment group) will be re-coded with indicator variables. The number of indicator variables will be one less than the total number of baseline dose categories (i.e., 2).
3. For each complete imputed data set, the dichotomous TWA responder rate based on the IGF-1 values will be computed. Each complete imputed data set will then be analyzed based on the details in Section 8.1.

4. The results from the analysis of each of the 50 imputed data sets will be combined into a single inference using SAS PROC MIANALYZE.

Primary Endpoint [redacted]

For the 2 co-primary descriptive [redacted] endpoints, a patient will be classified as a responder based on the average of two values, week 24 & 26 for the end of the run-in phase and week 58 & 62, for the end of the RCT phase. If a patient only has a single value, but an unscheduled assessment was conducted in the same time frame (i.e., between week 24 & 26, +/- 3 days, or between week 58 & 63, +/- 3 days), then the unscheduled assessment will be used. If there is only a single value and no unscheduled assessment, the single value will be used. If a patient completes the respective phase of the study, but is missing both values, the worst observation (highest value) observed during the respective phase will be used to determine their response. If a patient discontinues the phase early, they will be classified as a non-responder.

Other Endpoints

Details for imputation rules for secondary and exploratory endpoints are provided in sections 8.2 and 8.3, respectively.

Missing Dates

For start dates of medications/adverse events, if only the year is specified, January 1 will be imputed for analysis purposes. If the month and year only are provided, the 1st of the specified month will be imputed.

For stop dates of medications/adverse events, if only the year is specified, December 31 will be imputed for analysis purposes. If the month and year only are provided, the end of the specified month will be imputed.

If further imputations are deemed necessary to facilitate reporting, then the conventions used will be either added into the SAP and/or documented specifically in the study report.

6 STUDY PATIENTS

6.1 Analysis Populations

6.1.1 Full Analysis Set (FAS)

FAS is defined as all randomized patients to the RCT phase who receive at least one dose of study medication and have one post randomization measurement of IGF-1. This population will serve as the primary efficacy analysis population for the RCT phase of the core study. Patients will be included in the group to which they were randomized.

6.1.2 Per-Protocol Analysis Set (PP)

Per-Protocol Analysis Set (PP) is defined as all patients in the FAS without a major protocol violation.

6.1.3 Safety Analysis Set (SAS)

SAS is defined as all randomized patients who receive at least one dose of study medication during the RCT phase. This population will serve as the primary safety analysis population for the RCT

phase of the core study. Patients will be included in the group according to which medication they actually received. If a patient received both medications, they will be counted in both groups.

6.1.4 Enrolled Analysis Set (EAS)

EAS is defined as all patients who are enrolled into the Run-in phase of the core study and receive at least one dose of study medication. This population will be used for the analysis of safety and efficacy data during the Run-in phase of the core study.

6.1.5 Octreotide Analysis Set (OAS)

OAS is defined as all patients who receive at least one dose of octreotide capsules during the run-in and at least one dose of octreotide capsules during the RCT phase. This population will be used to summarize efficacy and safety data across the run-in and RCT phases of the study.

6.1.6 Combination Analysis Set (CAS)

CAS is defined as all patients who are enrolled into Combination phase sub-study. This population will be used for the analysis of safety and efficacy data collected in the combination arm.

6.1.7 All Randomized Patients

All Randomized Patients are all patients that were randomized to study medication for the RCT phase. This population will be used for the analysis of disposition.

6.1.8 All Screened Patients

All Screened Patients are all patients with an informed consent date.

6.1.9 Run-in Phase Completers

Run-in Phase Completers are all patients that did not discontinue the Run-in Phase early. These patients completed the Run-in Phase as reported on the Phase Completion eCRF.

6.1.10 RCT Phase Completers

RCT Phase Completers are all patients that did not discontinue the RCT Phase early. These patients completed the RCT Phase as reported on the Phase Completion eCRF.

6.1.11 Combination Phase Completers

Combination Phase Completers are all patients that did not discontinue the Combination Phase early. These patients completed the Combination Phase as reported on the Phase Completion eCRF.

6.2 Protocol Deviations

All protocol deviations will be reviewed and classified as major or minor before database lock. Major protocol deviations are compliance issues that impact patient safety or the scientific integrity of the study data. They include, but are not limited to:

- Violations of inclusion and exclusion criteria (Run-In, RCT and/or Combination Phases).

- Receiving the wrong study medication, or receiving study medication at incorrect dosing or frequency
- Non-compliance with study medication. A patient is defined as non-compliant if the patient took < 75% of the study medication assigned to each specific phase.
- Taking a prohibited prior medication or receiving a prohibited prior therapy as listed in Protocol Section 6.10.2
- Taking a prohibited concomitant medication as listed in Protocol Section 6.10.4 Failure to adhere to study termination rules in the run-in period
- Failure to adhere to study termination rules in the run-in period

The final major protocol deviations definitions will be determined prior to database lock. Major protocol deviations will be summarized for All Randomized Subjects, EAS and CAS populations.

6.3 Disposition of Patients

Disposition will be summarized for the run-in phase, RCT phase and combination phase separately using the EAS, All Randomized Patients and the CAS, respectively.

Disposition for the Run-in Phase

For the run-in phase a separate summary presenting the overall number of patients screened as well as the number of patients classified as screen failures, and associated reasons will be provided.

The following patient data will be summarized for the EAS:

- Overall number of patients enrolled as well as the number of patients that discontinued during the Run-in Phase and associated reasons. The number of patients that were treatment failures in the Run-in Phase and enrolled in the Combination Phase will also be summarized.
- Overall number of patients that completed Run-in Phase. Out of which the number of patients that continued into the RCT, continued into the combination phase or completed the run-in but not continued treatment (not eligible for RCT or not eligible for combination or eligible for RCT yet decided to discontinue)
- Overall number of patients that completed follow up per protocol (in populations that require follow up)

The summary table will present data for all patients and by target oral dose.

Disposition for the RCT Phase

For the RCT phase a summary will be provided tabulating the number and percentage of patients; randomized, discontinued, including reason for discontinuation, completed, out of which continued into the Extension phase, or completed the RCT but not continued treatment (not eligible for Extension or eligible for Extension yet declined to enter) and completed follow-up (in populations that require follow up per protocol), using the All Randomized Set. Data will be summarized overall, and by treatment group.

The treatment group columns for the summary table will include oral octreotide total; oral octreotide target doses of 40, 60, or 80 mg; injection SRLs (total); and injection SRLs (low, middle or high doses).

Disposition for the Combination Sub study

For the combination sub study a summary will be provided tabulating the number and percentage of patients; enrolled, discontinued, including reason for discontinuation, completed, out of which competed and continued into the Extension or completed the RCT but not continued into the extension (not eligible for Extension or eligible for Extension yet declined to enter), and number of patients that completed follow-up (in populations that require follow up per protocol) using the CAS.

Data will be presented overall (i.e., cabergoline total).

7 DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

7.1 Demographics and baseline disease characteristics

Demographic and baseline disease characteristics data will be summarized for the run-in phase, RCT phase, and combination phase using the EAS, FAS and CAS populations, respectively. For the RCT phase, if the FAS and SAS populations are different, then the SAS will also be used to summarize data for the RCT phase. For the EAS the summary table will present data for all patients and by target dose (40, 60, 80). For the FAS and SAS populations, the summary table will present data overall and by treatment group (oral vs. SRLs). If the FAS and SAS populations are the same, only the FAS will be provided. For the CAS population the summary table will present data for all patients

The following continuous demographics data will be summarized:

- Age at screening in years. Age will be derived from the year of birth (year of Study Day 0 – year of birth).
- Weight at screening in kg
- Height at screening in cm
- BMI at screening in kg/m^2. BMI is calculated as weight / height in meters squared.

The following categorical demographics data will be summarized:

- Age: <65 years old, ≥65 years old; <75 years old, ≥75 years old
- Gender: Male, Female
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
- Race: Asian, American Indian or Alaskan Native, Black African or African/American, Native Hawaiian or Pacific Islander, White/Caucasian, Other. If more than one race can is selected the patient will be presented in each racial category in the summary table(s).

The following continuous baseline disease characteristics data will be summarized:

- Time from Last Surgery (if applicable)
- Time from Last Radiation (if applicable)
- AIS Score at Baseline

- IGF-1 levels in ULN values (Baseline, Week 26 and Combination Phase Baseline)
- GH levels in ng/mL (Baseline, Week 26 and Combination Phase Baseline)

The following categorical baseline disease characteristics data will be summarized:

- Duration of Acromegaly: <10 years, 10-<20 years, ≥20 years, unknown. Duration will be calculated as the difference in years from the date of diagnosis to date of informed consent.
- Pituitary Tumor Characteristics: Microadenoma, Macroadenoma, Other
- Previous Treatments for Acromegaly any Time in the Past:
  - Surgery only (Yes/No)
  - Radiotherapy only (Yes/No)
  - Surgery and radiotherapy (Yes/No)
  - Neither Surgery nor radiotherapy (Yes/No)
- Residual Tumor Size: No remnants, < 5mm, 5-10 mm, >10 mm
- Acromegaly Symptoms Anytime in the Past (Based on Screening) and at Baseline, separately: Joint Pain, Perspiration (Sweating), Swelling of Extremities, Fatigue, Headache, Snoring, Sleep apnea, Carpal Tunnel Syndrome, Other
- At Least One or more Active Symptoms at Baseline: At least 1, At Least 2, at Least 3, …
- IGF-1 at Baseline: ≤1 ULN, >1-1.3 ULN, ≥1.3 ULN for the EAS only
- IGF-1 at Baseline and Week 26: ≤1 ULN, >1-1.3 ULN, ≥1.3 ULN for the FAS only
- IGF-1 at Baseline and Combination Phase Baseline: ≤1 ULN, >1-1.3 ULN, ≥1.3 ULN, ≥ 2 ULN for the CAS only
- Response at Baseline and week 26: (CR, PR, NR) for the FAS only
- Response at Baseline: (CR, PR, NR) for the EAS and CAS only
- GH at Baseline: <1 ng/mL, 1-2.5 ng/mL, ≥2.5 ng/mL for the EAS and CAS
- GH at Baseline and Week 26: <1 ng/mL, 1-2.5 ng/mL, ≥2.5 ng/mL for the FAS
- Medical Treatment on randomization: Octreotide capsules vs. SRLs (Octreotide LAR (low, middle and high doses) and Lanreotide (low, middle and high doses)
- Target Dose on Oral Octreotide for the FAS only
- Prior Injectable Treatment Octreotide LAR (low, middle and high doses) and Lanreotide (low, middle and high doses)

Baseline disease characteristics will be summarized for select subgroups listed in Section 5.3.

7.2 Medical history

Medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or later and summarized by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages. A patient will only be counted once in an SOC and an SOC/PT combination.

Medical history will be summarized for the run-in phase, RCT phase and extension phase using the EAS, FAS and CAS, respectively. For the RCT phase, if the FAS and SAS populations are different, then the SAS will also be used to summarize data for the RCT phase. For the EAS the summary table will present data for all patients and by target dose (40, 60, 80). For the FAS and SAS populations, the summary table will present data overall and by treatment group (oral vs. SRLs). For the CAS population the summary table will present data for all patients

7.3 Prior Medications, Concomitant Medications and Concomitant Procedures

All medications taken within 12 weeks of the initial Screening visit (within 1 year for acromegaly treatments), through the end of the study will be recorded on the prior and concomitant medications eCRF. All concomitant procedures will be recorded on the concomitant procedures eCRF.

The World Health Organization (WHO) Drug Dictionary (September 2015) will be used to map each reported medication to a specific anatomic therapeutic class (ATC) Level 4 and preferred term (PT). MedDRA 18.1 or later will be used to map each reported therapy/procedure to a specific ATC Level 4 and PT.

Concomitant medications and procedures will be summarized for the run-in phase, RCT phase and extension phase using the EAS, FAS and CAS, respectively. For the RCT phase, if the FAS and SAS populations are different, then the SAS will also be used to summarize data for the RCT phase. For the EAS the summary table will present data for all patients and by target dose (40, 60, 80). For the FAS and SAS populations, the summary table will present data overall and by treatment group (oral vs. SRLs). For the CAS population the summary table will present data for all patients

For the Run-in Phase

For the purpose of analyses, concomitant medications are defined as all medications (excluding study drug) taken on or after the day of the first dose of octreotide capsules during the Run-in until the end of the Run-in Phase or continuing during the run-in phase. Concomitant procedures are defined as all procedures performed on or after the day of the first dose of octreotide capsules during the Run-in until the end of the Run-in Phase. Prior concomitant medications are defined as all medications taken prior to the first dose of octreotide capsules and that are not continuing (i.e., the stop date is prior to the start date of octreotide capsules). Prior concomitant procedures are defined as all procedures performed prior to the first dose of octreotide capsules.

For the RCT Phase

For the purpose of analyses, concomitant medications are defined as all medications (excluding study drug) taken on or after the day of the first randomized dose of study drug during the RCT Phase until the end of the RCT Phase or medications which are continuing at the start of the RCT Phase. Concomitant procedures are defined as all procedures performed on or after the day of the first randomized dose of study drug during the RCT Phase until the end of the RCT Phase. Prior concomitant medications are defined as all medications taken prior to the first randomized dose of study drug and that are not continuing. Prior concomitant procedures are defined as all procedures performed prior to the first randomized dose of study drug.

For the Combination Sub study

For the purpose of analyses, concomitant medications are defined as all medications (excluding study drug) taken on or after the day of the first dose of study drug during the combination phase until the end of the combination Phase or continuing during the combination phase. Concomitant procedures are defined as all procedures performed on or after the first dose of study drug during the combination phase until the end of the combination Phase. Prior concomitant medications are defined as all medications taken prior to the first dose of study drug in the combination phase and

that are not continuing. Prior concomitant procedures are defined as all procedures performed prior to the first dose of study drug in the combination phase.

8 TREATMENT EXPOSURE AND COMPLIANCE

8.1 Extent of Exposure and Compliance: Octreotide Capsules

Octreotide capsules (each capsule is 20 mg strength) will be administered twice daily (AM and PM). Octreotide capsule exposure and compliance will be summarized for patients in the Run-in phase using the EAS, for patients in the RCT phase using both the SAS and FAS, and for patients in the Combination phase using the CAS. If the FAS and SAS populations are the same, only the SAS will be provided for the RCT phase. Additionally, a summary of exposure will be presented across the Run-In and RCT phases combined using the OAS.

Octreotide Capsules Taken during Run-in phase

Octreotide capsules can be up-titrated during the initial Run-in phase from 40 mg/day to 60 mg/day and 60 mg/day to 80 mg/day, based on clinical and biochemical response.

In the Run-in phase, the duration of study drug exposure (in weeks) will be summarized by the dose level and overall, using standard descriptive statistics.

Descriptive statistics for the time to the first dose escalation from 40 mg to 60 mg and time to the second dose escalation from 60 mg to 80 mg will be presented. A figure depicting the time to each dose escalation for each patient will be presented.

The number and proportion of patients at each dose level (40, 60 and 80 mg/day) by visit, will also be presented.

Compliance to each dose level of octreotide capsules from first dose in the Run-in phase through the last visit of Run-in phase will be calculated and summarized for the EAS patients for each target dose level and overall.

For the purpose of analysis, compliance to each dose level of octreotide capsules during the Run-in phase will be calculated as 100× (total number of capsules actually taken / total number of capsules expected to be taken). This calculation will be used for each dose level the patient received during the Run-in phase and overall. The numbers and percentages of patients <75% compliant, 75-100% compliant, 100-120 compliant and >120% compliant will be tabulated.
The number of actual capsules taken for each dose level will be the total number of capsules dispensed – total number of capsules returned during the time the patient was on that particular dose.

The number of expected capsules taken for the target dose level will be derived as follows:

Dose Level	Expected Number of Capsules Taken
40 mg	2 capsules × (first day of the phase – last day of the phase)

60 mg	3 capsules × (first day of the phase – last day of the phase)
80 mg	4 capsules × (first day of the phase – last day of the phase)
Overall	Sum of expected number of capsules taken over all of the dose levels assigned

For the run-in phase, the summary table will present columns for octreotide capsules overall and by final target octreotide capsule doses of 40, 60, or 80 mg.

Octreotide Capsules Taken during RCT phase

Patients who are biochemically controlled at the end of the Run-in phase will be randomized to either continue octreotide capsules treatment (target dose level 40, 60 or 80 mg) or revert to their SOC injectable SRL during the RCT phase. The SRL injections compliance and extent of exposure is detailed in Section 7.2 below.

The following parameters will be calculated for the RCT Phase similarly to the algorithms and logic used for the Run-in Phase:

- Duration of exposure in weeks
- Compliance

Summaries will include columns for octreotide capsules overall and octreotide capsule target doses of 40, 60, or 80 mg.

Octreotide Capsules Taken During Combination Phase

Patients entering the Combination phase sub-study will receive co-administration of octreotide capsules at 80 mg with cabergoline [redacted]. Cabergoline compliance and extent of exposure is detailed in Section 7.3 below.

The following parameters will be calculated for the Combination Phase similarly to the algorithms and logic used for the Run-in Phase:

- Duration of exposure in weeks
- Compliance

Summaries will be presented for all patients, as all patients will be on 80 mg.

8.2 Extent of Exposure and Compliance: SRL Injections (Octreotide and Lanreotide)

In the RCT phase, for patients randomized to the active control arm, SRLs will be injected subcutaneously at site visits at the same dose and administration frequency as received prior to study entry. For this study, the dose ranges allowed for Octreotide or Lanreotide are any dose used on the market (Octreotide 10, 20 and 30 mg and Lanreotide 60, 90 and 120 mg) as long as the dosing interval does not exceed once every 8 weeks (e.g. dosing intervals of every 4, 5, 6, 7 or 8 weeks are allowed). Dosing every 2 weeks is not allowed unless the patient was stabilized for 4 months on a monthly dosing regimen.

For the FAS and SAS populations the summary table will present all patients randomized to SRLs injections, and by prior dose of SRL Injectables: Low, Middle, High. If the FAS and SAS populations are the same, only the SAS will be provided.

The duration of exposure (in weeks) will be summarized by standard descriptive statistics.

Compliance is calculated as 100× (total number of SRL injections received / total number of injections expected to be taken) and will be summarized using standard descriptive statistics. The numbers and percentages of patients <75% compliant, 75-100% compliant, 100-120 compliant and >120% compliant will also be tabulated.

8.3 Extent of Exposure and Compliance: Cabergoline

As mentioned in Section 7.1 cabergoline will be co-administered with 80 mg octreotide capsules in the Combination Phase. [redacted]

The duration of exposure (in weeks) will be summarized using standard descriptive statistics.

The amount of time from date of first initial dose level to the date of first dose of final stable dose level during the Combination phase (in days) will be described using descriptive statistics.

Compliance to cabergoline from first dose of the highest dose level in the Combination phase through the last visit/ end of Combination phase will be calculated and summarized for the CAS patients.

[redacted]

9 EFFICACY ANALYSES

9.1 Primary Efficacy Analysis [redacted]

The primary efficacy analysis will estimate the proportion of patients biochemically controlled throughout the RCT phase within each treatment arm. A patient will be considered biochemically controlled if his/her TWA, during the RCT phase, for IGF-1 is < 1.3 x ULN. The use of TWA response over time is a simple longitudinal data analysis approach intended to minimize the number of missing patients from a primary effectiveness analysis and to account for natural variation among the measure of interest that may be observed over the time phase of monitoring. The TWA response, over the treatment phase represents an integrated measure of efficacy across time. See section 3.5.2 for the derivation of TWA. See section 4.2 for the handling of missing TWA responses.

[redacted]

d_j [redacted]

[redacted]

[redacted]

9.3 Secondary Efficacy Analyses

[redacted]

Endpoints that are Proportions

The following endpoints will be analyzed using the same approach as the primary endpoint:

[redacted]

- Proportion of patients who maintain or reduce the overall number of active acromegaly symptoms, at the end of the RCT phase (week 62/EOT), compared to week 26 (start of RCT phase). If a patient discontinues the trial early, they will be considered to have worsened. If a patient has not discontinued but is missing their week 62/EOT acromegaly symptom assessment, then the LOCF approach will be used to impute their acromegaly symptoms, prior to determination of response status. Additionally, another analysis will be performed that will impute all missing acromegaly symptoms using the LOCF approach.
- Proportion of patients who maintain or improve their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score), compared to week 26 (start of RCT phase). If a patient discontinues the trial early, they will be considered

to have worsened. If a patient has not discontinued, but is missing their week 62/EOT AIS assessment, then the LOCF approach will be used to impute their AIS score, prior to determination of response status. Additionally, another analysis will be performed that will impute all missing AIS scores using the LOCF approach.

For the endpoint of "Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country), who enter the Study Extension phase", a summary of the number and proportion of patients will be provided, including the 95% confidence intervals based on the Clopper-Pearson Approach, overall and by each treatment group (octreotide and SRL). No inferential testing and or estimation between groups will be conducted. The denominator will be determined at the time of the completion of the RCT phase based on commercial availability of octreotide. If octreotide is not commercially available in any of the countries included in this study, the denominator will be that of the FAS completers.

Endpoints that are Changes from Baseline

Analyses of the change from the start of RCT phase (week 26) through the end of the RCT phase (week 62/EOT) for IGF-1 and the change from the start (week 26) to the end of the RCT phase (week 62/EOT) in mean integrated GH will be conducted using an analysis of covariance (ANCOVA) to adjust for baseline (IGF-1 and GH, respectively). The adjusted mean ratio (i.e., relative change), and associated 95% CIs will be reported. Data will be analyzed on the log scale and back transformed for reporting. The change through the end of the RCT phase for IGF-1 will be derived as a time weighted average change (See Section 3.6.2), starting with the first observed value following randomization (i.e., week 26), and using the week 26 value as the baseline value to calculate the change at each visit. All measurements will be used, including data collected at "Discontinuation" visits and "Unscheduled" visits. Given this approach for calculating the TWA response for an endpoint, no missing value will be imputed for IGF-1. For GH, if a patient is missing the week 62/EOT value, it will be imputed using the LOCF approach. In addition, an analysis of the change from baseline from week 26 to end of the RCT phase (week 62/EOT) will also be conducted for IGF-1. If a patient is missing their week 62/EOT IGF-1 value, it will be imputed using the LOCF approach.

Shifts from week 26 (RCT Baseline) to week 62/EOT, in IGF-1 and GH, for the RCT phase will also be presented by treatment group. Shift tables will be produced for IGF-1 using the following categories (IGF-1 $\leq$1 x ULNL, IGF-1 between >1 x ULN and <1.3 x ULN, IGF-1 $\geq$ 1.3 x ULN, early terminated, missing). A shift table summarizing GH (<1.0 ng/ml, 1.0 – 2.5 ng/ml, >2.5 ng/ml, early terminated, missing) from RCT baseline (week 26) to the to week 62/EOT of the RCT phase will also be presented.

ACRO-TSQ

The SAP will be amended with further details on the analyses of ACRO-TSQ as stated in Section 1. The questionnaire was developed according to best practices for PRO development. It was validated in a stand-alone study using data from 79 acromegaly patients enrolled from 14 Clinical practices in the US and Europe and the Acromegaly Community. Its measurement Properties, including internal consistency reliability, test-retest reliability, construct validity and known groups validity were evaluated and found to be acceptable. Items related to

Emotional Impact and injection site reactions were revised based on these results, and, together with responsiveness to change and minimal important difference (MID) for all scales, will be evaluated using data from the run-in phase of the current study.

Analysis of the Acro-TSQ during the RCT Phase will be conducted using the Full Analysis Set (FAS). Analyses will be based upon all available data, and missing scale data will not be imputed. Only data from the new versions of the Acro-TSQ will be analyzed, and we will only include data from subjects that have completed the Week 26 and at least one additional time point during the RCT Phase. Descriptive statistics will be reported for all Acro-TSQ scale scores at Weeks 26, 38, 50 and 62, including sample size, mean, median, standard deviation, minimum, maximum, and 95% confidence interval. Descriptive statistics will be reported separately by treatment arm and also by treatment arm and biochemical control status during the RCT, defined as an IGF-1 Time Weighted Average (TWA) during the RCT Phase of $< 1.3 \times$ ULN (see definition of Primary Endpoint above) and the end of treatment (EOT) IGF-1 value based on the average from Weeks 58 and 62.

Descriptive statistics will also be reported for change from Week 26 in Acro-TSQ scale scores at Weeks 38, 50 and 62, including sample size, mean, median, standard deviation, minimum, maximum, and 95% confidence interval. Descriptive statistics for change scores will be reported by treatment arm and also by treatment arm and biochemical control status during the RCT, defined as an IGF-1 Time Weighted Average (TWA) during the RCT Phase of $< 1.3 \times$ ULN (see definition of Primary Endpoint above) and the end of treatment (EOT) IGF-1 value based on the average from Weeks 58 and 62. A comparison of the treatment groups will be made for each scale separately using a repeated measures mixed model, with the change from Baseline (i.e., Week 26 of the Run-In Phase) as the dependent variable, baseline (i.e., Week 26 of the Run-In Phase) as a covariate and fixed effects for treatment group, time point and the treatment group by time point interaction. Subject will be treated as a random effect, using an unstructured covariance.

If the model fails to converge, alternative covariance structures will be considered (e.g., CS, AR(1), etc..), and the one which provides the lowest AIC will be chosen. The least square means (lsmeans) treatment difference for each timepoint and the 95% CI will be reported. For the three Acro-TSQ scales with established MID estimates (Symptom Interference: MID = 11; Treatment Convenience: MID=10; GI Interference: MID=9), subjects will be classified as Improved (scale scores increase by MID value or greater from Week 26 to Week 62), Unchanged (scale scores do not increase or decrease by MID value from Week 26 to Week 62) or Worsened (scale scores decrease by MID value or greater from Week 26 to Week 62). In addition, for all six Acro-TSQ scales, subjects will be classified as Improved (scale scores increase by > 0.5 SD or greater from Week 26 to Week 62), Unchanged (scale scores do not increase or decrease by 0.5 SD from Week 26 to Week 62) or Worsened (scale scores decrease by < 0.5 SD or greater from Week 26 to Week 62).

9.4 Exploratory Efficacy Analyses

RCT Phase

Analysis of the exploratory endpoints based on the RCT phase will be summarized using the FAS and FAS completers and additionally will be summarized for select subgroups listed in Section 5.3.

The following exploratory endpoints will be analyzed using the same approach as the primary endpoint:

[redacted]

[redacted]

- Proportion of patients with TWA IGF-1 ≤1 × ULN during the RCT Phase in patients who started the RCT with IGF-1≤1 × ULN. If a patient discontinues during the RCT phase for lack of efficacy, he/she will be considered to be NOT biochemically controlled, regardless of their TWA.

[redacted]

Shifts from run-in baseline to week 62/EOT, in IGF-1 and GH, for the RCT phase, will also be presented by treatment group. Shift tables will be produced for IGF-1 using the following categories (IGF-1 ≤1, IGF-1 between >1 and <1.3, IGF-1 ≥ 1.3, early terminated, missing). Shift tables summarizing GH will use the following categories (<1.0, 1.0 – 2.5, >2.5, early terminated, missing).

Additionally, the rate of change for IGF-1 within each treatment group will be estimated using a repeated measures mixed effects model (without imputation of missing data). Data will be analysed on the log scale. The model will contain fixed effects for baseline IGF-1, treatment group, visit and the interaction between baseline IGF-1 and visit and treatment and visit. Subject will be treated as random, nested within treatment group, with and unstructured covariance matrix. If the model will not converge, alternative covariance structures will be evaluated with the best fit

determined by the AIC and SBC criteria. Results will be back transformed and displayed in both graphical and tabular form.

The EQ-5D-5L will be summarized by treatment group and visit during the RCT phase as follows:

- A summary of the frequency and proportion of reported problems for each level and dimension,
- A descriptive summary of the VAS,
- A descriptive summary of the index value.

No inferential statistics will be reported.

Each of the 4 WPAI scores will be summarized by treatment group and visit during the RCT phase using descriptive statistics. No inferential statistics will be reported.

Run In Phase

Analysis of the exploratory efficacy endpoints based on the run-in phase will be summarized using the EAS and reported overall and by target dose. Additionally, they will be summarized for select subgroups listed in Section 5.3.

The following exploratory endpoints will be summarized using counts, percentages, and two-sided 95% confidence intervals (based on the Wald Approach):

[redacted]

- Proportion of patients with a reduction in the overall number of active acromegaly symptoms, at the end of the Run-in phase compared to Baseline. If a patient discontinues during the run-in phase, he/she will be considered to NOT have had a reduction. The last assessment in the Run-in for patients who do not discontinue will be used to determine their response. In addition, a separate analysis that use the last assessment in the Run-in for all patients will be used to determine their response.
- Proportion of patients with improved AIS score at the end of the Run-in phase compared to Baseline. If a patient discontinues during the run-in phase, he/she will be considered to NOT have had an improvement. The last assessment in the Run-in for patients who do not discontinue will be used to determine their response. In addition, a separate analysis that use the last assessment in the Run-in for all patients will be used to determine their response.

Additionally, during the run-in phase, shift tables will be produced for IGF-1 to show the change from baseline to the last assessment using the following categories (IGF-1 $\leq$1, IGF-1 between >1 and <1.3, IGF-1 $\geq$ 1.3, early terminated, missing). A shift table summarizing GH (<1.0, 1.0 – 2.5, >2.5, early terminated, missing) from baseline to the end of the run-in phase will also be presented.

The EQ-5D-5L will be summarized at baseline and the end of the run-in as follows:

- A summary of the frequency and proportion of reported problems for each level and dimension,
- A descriptive summary of the VAS,
- A descriptive summary of the index value.

No inferential statistics will be reported.

Each of the 4 WPAI scores will be summarized at baseline and the end of the run-in using descriptive statistics. No inferential statistics will be reported.

Analysis of the Acro-TSQ during the Run-in Phase will be conducted using the enrolled analysis set (EAS) for those subjects that have completed both Baseline and Week 26 assessments. Analyses will be based upon all available data, and missing scale data will not be imputed. We will include data from subjects that have completed the new versions of the Acro-TSQ, and will explore the possibility of including data from subjects using the old version where common items/scales are utilized. Descriptive statistics will be reported for all Acro-TSQ scale scores at Screening, Baseline and Week 26, including sample size, mean, median, standard deviation, minimum, maximum, and 95% confidence interval.

Descriptive statistics will be reported for the EAS who completed the updated version of the questionnaire at least on Screening/BL and Week 26, as well as separately for those randomized versus not randomized to the RCT phase. Descriptive statistics will also be reported for change from Baseline in Acro-TSQ scale scores at Week 26, including sample size, mean, median, standard deviation, minimum, maximum, and 95% confidence interval. As above, descriptive statistics for change scores will be reported overall, as well as separately for those entering versus not entering the RCT Phase.

For the three Acro-TSQ scales with established MID estimates (Symptom Interference: MID = 11; Treatment Convenience: MID=10; GI Interference: MID=9), subjects will be classified as Improved (scale scores increase by MID value or greater from Baseline to Week 26), Unchanged (scale scores do not increase or decrease by MID value from Baseline to Week 26), or Worsened (scale scores decrease by MID value or greater from Baseline to Week 26). In addition, for all six Acro-TSQ scales, subjects will be classified as Improved (scale scores increase by > 0.5 SD or greater from Baseline to Week 26), Unchanged (scale scores do not increase or decrease by 0.5 SD from Baseline to Week 26), or Worsened (scale scores decrease by < 0.5 SD or greater from Baseline to Week 26).

In order to identify characteristics of patients on SRL treatments that would be predictive for a successful switch to oral treatment, if such exist, exploratory analyses will be conducted using all patients enrolled into the run-in phase. Univariate and multivariate logistic regression models will be explored to identify baseline characteristics i.e., baseline IGF-1 level, GH1, dose of SRL injection, duration of disease, AIS score, gender, age, and BMI, associated with biochemical response at the end of the dose titration phase. A patient will be considered a responder (i.e., had a successful switch) if at the end of the Run-in phase their IGF-1 is <1.3 × ULN and mean integrated GH is

<2.5 ng/mL. Each of the above baseline characteristics will be included in univariate models. All baseline characteristics which are found to be statistically significant ($p < 0.05$) will be included in a multivariate logistic regression model to determine the final set of characteristics which are predictive of response based on stepwise approach using a 10% significance level. In addition, all baseline characteristics of those patients eligible to enter the RCT phase and those patients who were not, will be presented using descriptive statistics. Comparisons between the two groups (eligible vs not) will be made using two-sample t-tests and Chi-square tests, as appropriate. If any characteristics are found to be significant, which are not listed above, they will also be included in univariate and multivariate logistic regression models as described above.

Run-in + RCT Phase

Analysis of the exploratory endpoint(s) based on the Run-in and RCT phase will be summarized using the OAS population combined. The proportion of patients who maintain or improve their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score), compared to Baseline (i.e., prior to the Run-in phase) will be analyzed using the same approach as the primary endpoint.

Shifts from run-in baseline to week 62/EOT, in IGF-1 and GH, for the Run-In and RCT phase combined, will be presented using the OAS. Shift tables will be produced for IGF-1 using the following categories (IGF-1 ≤1, IGF-1 between >1 and <1.3, IGF-1 ≥ 1.3, early terminated, missing). Shift tables for GH will use the following categories (<1.0, 1.0 – 2.5, >2.5, early terminated, missing).

Shift tables showing the proportion of patients who worsened, maintained or improved their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score, worsened defined as an increase of at least 1 points and maintained defined as no change), compared to Baseline (i.e., prior to the Run-in phase) will be provided. If a patient terminates early, their last assessment will be used.

9.5 Combination Phase Sub-study (in selected sites)

Analysis of the combination phase endpoints will use the CAS population. The proportion and two-sided 95% CI of the proportion (based on the Clopper Pearson method) will be reported for each binomial endpoint. If a patient early terminates, they will be considered a non-responder. For all other patients, the LOCF approach will be used to impute any missing values, prior to determining the patients' response status.

Shifts from the combination baseline to the end of the combination phase, in IGF-1 and GH, for the combination phase, will be presented using the CAS. Shift tables will be produced for IGF-1 using the following categories (IGF-1 ≤1, IGF-1 between >1 and <1.3, IGF-1 ≥ 1.3, early terminated, missing). Shift tables for GH will use the following categories (<1.0, 1.0 – 2.5, >2.5, early terminated, missing).

Additionally, the rate of change for IGF-1 will be estimated using a repeated measures mixed effects model (without imputation of missing data). The model will contain fixed effects for baseline IGF-1, visit and the interaction between baseline IGF-1 and visit. Subject will be treated as random with and unstructured covariance matrix. If the model will not converge, alternative covariance structures will be evaluated with the best fit determined by the AIC and SBC criteria.

10 SAFETY ANALYSES

All safety endpoints will be summarized across each phase of the study separately using descriptive statistics. Safety endpoints will be also presented for all patients randomized to octreotide capsules throughout the run-in and RCT phase combined using the OAS.

For the Run-in phase, safety endpoints will be summarized for the EAS where table summaries will include treatment group columns for oral octreotide target doses of 40, 60, or 80 mg and a total column. For the RCT phase, safety endpoints will be summarized for the SAS where table summaries will include treatment group columns for oral octreotide total; oral octreotide target doses of 40, 60, or 80 mg; injection SRLs (total); and injection SRLs (low, middle or high doses).

For the Combination phase, safety endpoints will be summarized for the CAS where table summaries will include treatment group columns for the highest dose of cabergoline and overall.

For summaries of the Run-In + RCT phases combined, using the OAS, treatment group columns for oral octreotide target doses of 40, 60, or 80 mg and a total column will be presented.

10.1 Adverse Event

Adverse events (AEs) are assessed at all study visits from informed consent signing, however only treatment emergent adverse events (TEAEs) will be provided in summary tables. All adverse events will be provided in listings. A treatment emergent adverse event is defined as an AE with an onset on or after study drug initiation at Run-in (Day 0) or an AE that has worsened in severity after the first dose of study drug and prior to the last dose of study drug. Adverse events will be coded using the MedDRA Dictionary Version 18.1 or later.

All reported AEs will be summarized by system organ class (SOC) and preferred term. Additionally, AEs will be summarized by preferred term in descending order of frequency based on the total column of each table, and then alphabetically. If severity is missing, the maximum severity will be imputed. For analyses by relationship, all AEs defined as "possibly related" or "related" to study drug will be considered as related. If relationship is missing, the AE will be considered related.

For each study phase the following AE summaries will be provided:

- Overall AE summary
- All AEs by SOC and PT
- All AEs by SOC, PT and Severity
- All AEs by SOC, PT and Relationship
- All AEs resulting in Discontinuation by SOC, PT and Relationship
- All SAEs by SOC and PT

- All SAEs by SOC, PT and Relationship.

All AEs will be assigned to a study phase based on the start date of the AE in relation to the start and stop dates of each study phase. If the AE started in the run-in phase, it will be assigned to the run-in phase, if it started in the RCT phase it will be assigned to the RCT phase, if it started in the Combination phase it will be assigned to the combination phase. Summaries of the Run-In + RCT phase will include AEs which started in either phase.

10.2 Clinical Laboratory Tests

All clinical laboratory assessments will be performed by a central laboratory. Continuous data will be summarized at each time point using descriptive statistics. Both absolute and change from baseline will be provided for each continuous lab parameter.

Baseline values for each phase are defined in Section 4.1. These summary tables will also present the number and percentage of patients with laboratory values that fall outside the laboratory reference ranges. All categorical lab values will be summarized by presenting the number and percentage of patients by category.

Additional table summaries will present shifts from baseline to each post baseline visit, for each study phase separately. Shifts will be defined according to laboratory reference ranges, with values below the lower limit of normal, within the normal reference range and above upper limit of normal reported. Categorical lab data will not have shifts presented. A listing of patients with notable abnormalities at any visit occurring after treatment will be provided by phase.

The following lab data that will be summarized as continuous data:

- Hematology: red blood cell count, hemoglobin (Hb), hematocrit (Htc), white blood cell (WBC) count and differential, platelets
- Serum biochemistry: glucose, total bilirubin (in case that it is found elevated direct and indirect bilirubin), albumin, sodium, potassium, calcium, creatinine, BUN, phosphorous, uric acid, GOT (AST), GPT (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), total protein (for additional assessments in case of abnormal liver functions please refer to Protocol Section (6.2.4
- TSH, free T4
- HbA1c
- Lipid profile (total cholesterol, triglycerides, HDL, LDL)
- Urinalysis: glucose, pH

The following lab data that will be summarized as categorical data:

- Urinalysis: ketones, protein, specific gravity, and routine microscopy observations
- Serum pregnancy test, if applicable
- Urine pregnancy test, if applicable
- FPG; for diabetic patients only at Screening

10.3 Vital Signs

Vital signs will be summarized at each time point using descriptive statistics. Both absolute and change from baseline will be provided for each continuous lab parameter. Baseline values for each phase are defined in Section 4.1.

10.4 ECG

All 12-Lead ECGs will be read by a central lab. 12-Lead ECG parameters will be summarized at each time point using descriptive statistics. Both absolute and change from baseline will be provided for each continuous 12-Lead ECG parameter. Baseline values for each phase are defined in Section 4.1.

Additionally, the numbers and percentages of patients with ECG abnormalities (as determined by the central laboratory) at each visit will be presented. The parameters and abnormality criteria are specified in the table below:

Parameter	Abnormality Criterion
PR interval	<110 ms
	>300 ms
QRS interval	≥120 ms
QTcF	<350 ms
	Male >450 ms or Female >470 ms
	>500 ms
Heart rate	<50 bpm
	>110 bpm

Shift tables will be used to show the changes from baseline to each post baseline time point based on the above abnormality criteria.

A listing of patients with notable abnormalities at any visit occurring after treatment will be provided by phase

10.5 Echocardiogram

In selected sites participating in the Combination phase, cardiac ECHO is performed to assess the potential presence of valvular disease (valvular regurgitation, valvular restriction or valve leaflet thickening). It should be done as specified in the Protocol's Schedule of Assessments (Appendix B through Appendix D) in all patients receiving combination treatment of octreotide capsules + cabergoline. All ECHO data will be listed only.

10.6 Abdominal (Gall bladder) Ultrasound

Abdominal ultrasound is conducted to monitor gall bladder and biliary tract disease as specified in the Protocol's Schedule of Assessments (Appendix B through Appendix D). The following information was collected and will be summarized at each baseline and end of phase visit using standard descriptive statistics (i.e., numbers and percentages for categories of normal/abnormal results).

- Ultrasound Normality (Normal=Yes reported on eCRF; Abnormal = No)
- Biliary Sludge (Normal=No reported on eCRF; Abnormal =Yes)
- Wall Thickening (Normal=No reported on eCRF; Abnormal =Yes)
- Dilation of Common Bile Duct (Normal=No reported on eCRF; Abnormal =Yes)

Shifts from categories of Cholelithiasis (Single Stone, Multiple Stones, None, Number Not Reported) will also be summarized.

10.7 Physical Examination

Complete physical examination data are collected as specified in the Protocol's Schedule of Assessments (Appendix B through Appendix D in protocol).
Acromegaly directed and treatment directed physical examination in the RCT phase, will be conducted as specified in the Protocol's Schedule of Assessments (Appendix B through Appendix D in protocol).
All physical exam data and acromegaly directed, and treatment directed exam data will be listed.

11 INTERIM ANALYSIS

No interim analysis is planned, for the RCT phase and the Combination phase sub-study; however, data will be reviewed in phases by the IDMC for safety purposes. At the completion of the RCT and Combination phase sub-study the data base will be cleaned and locked and results of the study reported. An interim analysis of the Study Extension phase may be conducted for regulatory reporting purposes. This analysis will be conducted by the Sponsor, or its designee. As the Study Extension phase is an open label, single treatment phase of the study, to allow long-term safety data collection, no adjustments for multiplicity will be required.

12 SOFTWARE AND PROGRAMMING SPECIFICATIONS

12.1 Statistical Software

All analyses will be performed using SAS 9.4, or higher, in accordance with Pharm-Olam SOP 009-20- SAS Program Development and Change Control.

12.2 General Programming Specifications

All tables will include the sponsor name, protocol ID, "Page x of y" and "Draft" or "Final" in the header.

The last 2-footer lines will be:

1. Data Source: (a data set for listings, a listing reference for tables) left justified

2. "Program Location: P:\929Chiasma\Stats\Programs\xxx.sas" left justified and "Date-Time: DDMMMYYYY:HH:MM" right justified

13 REFERENCE LIST

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14 APPENDICIES

14.1 Changes to the Protocol Specified analyses

If different from statistical section of protocol, list here.